BIOSPECTRA
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GUANIDINE HYDROCHLORIDE 2024 LONG-TERM STABILITY REPORT

TABLE OF CONTENTS

1. OVERVIEW:

The purpose of this report is to analyze and conclude on the data obtained from the long-term stability study of a Guanidine Hydrochloride lot manufactured in 2024 at the Stroudsburg, PA BioSpectra facility. Testing intervals are designated by T_n, where n equals 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 long-term stability analysis will assess the stability of Guanidine Hydrochloride lot GHCL-0224-00010 that completed six (6) months of real-time stability in August 2024. This study includes the following analyses: Appearance and Color, Absorbance (6M) at 230 nm, Absorbance (6M) at 260 nm, Absorbance (6M) at 275 nm, Assay, Loss on Drying (LOD), Identification (IR) and Melting Range. Results from all analyses are summarized in Table 2 and 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. This study will be used to establish shelf life for all product codes under the intermediate code of GHCL-3200 for Guanidine Hydrochloride. The following product codes are commercially available:

- GHCL-3201
- GHCL-3202
- GHCL-3220
- GHCL-3221
- GHCL-3222
- GHCL-3224
- GHCL-3225
- GHCL-3250
- GHCL-3251
- GHCL-3253
- GHCL-4201
- GHCL-4202
- GHCL-4220
- GHCL-4221
- GHCL-4222
- GHCL-4250
- GHCL-5220
- GHCL-7201
- GHCL-7202
- GHCL-7203
- GHCL-7204
- GHCL-7210

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 Hydrochloride. Stability samples from this lot were put into P/F and Labline packaging configurations. The 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/Fiber (P/F)	Samples are individually placed into small polyethylene bags and are sealed with a zip tie. All individual bags are then placed into a fiber drum with a 4-unit desiccant.
Labline (HDPE Bottle)	Samples are packaged into a HDPE Lab Screw-Top Bottle.

4. STORAGE:

Samples were placed on stability in BioSpectra's Stroudsburg, PA facility stability area, located in the warehouse. The storage requirements for Guanidine Hydrochloride Bio Excipient Grade material is store below 30°C in a cool dry place. The storage conditions were continuously monitored and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (specification: 15- 30°C), humidity (specification: monitor) and Mean Kinetic Temperature at (specification: ≤ 25°C). The samples were stored in the Stroudsburg warehouse from February 2024 through August 2024. The maximum temperature of the warehouse was 24.85°C, the minimum temperature of the warehouse was 16.90°C and the average temperature was 21.71°C. The average mean kinetic temperature was 21.73°C. See Section 5 for the discrepancy investigations initiated for temperature excursions.

5. INVESTIGATIONS:

5.1. **None**

6. LOT EVALUATION:

TABLE 2: GHCL-0224-00010 P/F

Analysis	Specification	T_0	T_3	T_6
Absorbance (6M)	0.03 a.u. max @ 275 nm	0.0024 a.u.	0.0037 a.u.	0.0113 a.u.
	0.03 a.u. max @ 260 nm	0.0069 a.u.	0.0075 a.u.	0.0151 a.u.
	0.20 a.u. max @ 230 nm	0.1204 a.u.	0.0965 a.u.	0.1295 a.u.
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Assay	99.5-101.0%	100.13%	100.06%	100.17%
Identity (IR)	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying	0.5% max.	0.0547%	0.0691%	0.0749%
Melting Range	184-188°C	186.4 – 187.9°C	186.3 – 187.6°C	184.8 – 186.2°C

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 9; Scheduled for November 7, 2024
  - T = 12; Scheduled for February 7, 2025
  - T = 18; Scheduled for August 7, 2025
  - T = 24; Scheduled for February 7, 2026
  - T = 36; Scheduled for February 7, 2027
  - T = 48; Scheduled for February 7, 2028
  - T = 60; Scheduled for February 7, 2029

TABLE 3: GHCL-0224-00010 LABLINE

Analysis	Specification	T_0	T_3	T_6
Absorbance (6M)	0.03 a.u. max @ 275 nm	0.0024 a.u.	0.0062 a.u.	0.0032 a.u.
	0.03 a.u. max @ 260 nm	0.0069 a.u.	0.0092 a.u.	0.0081 a.u.
	0.20 a.u. max @ 230 nm	0.1204 a.u.	0.1016 a.u.	0.1113 a.u.
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Assay	99.5-101.0%	100.13%	100.01%	100.14%
Identity (IR)	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying	0.5% max.	0.0547%	0.0687%	0.0847%
Melting Range	184-188°C	186.4 – 187.9°C	186.3 – 187.8°C	184.8 – 186.2°C

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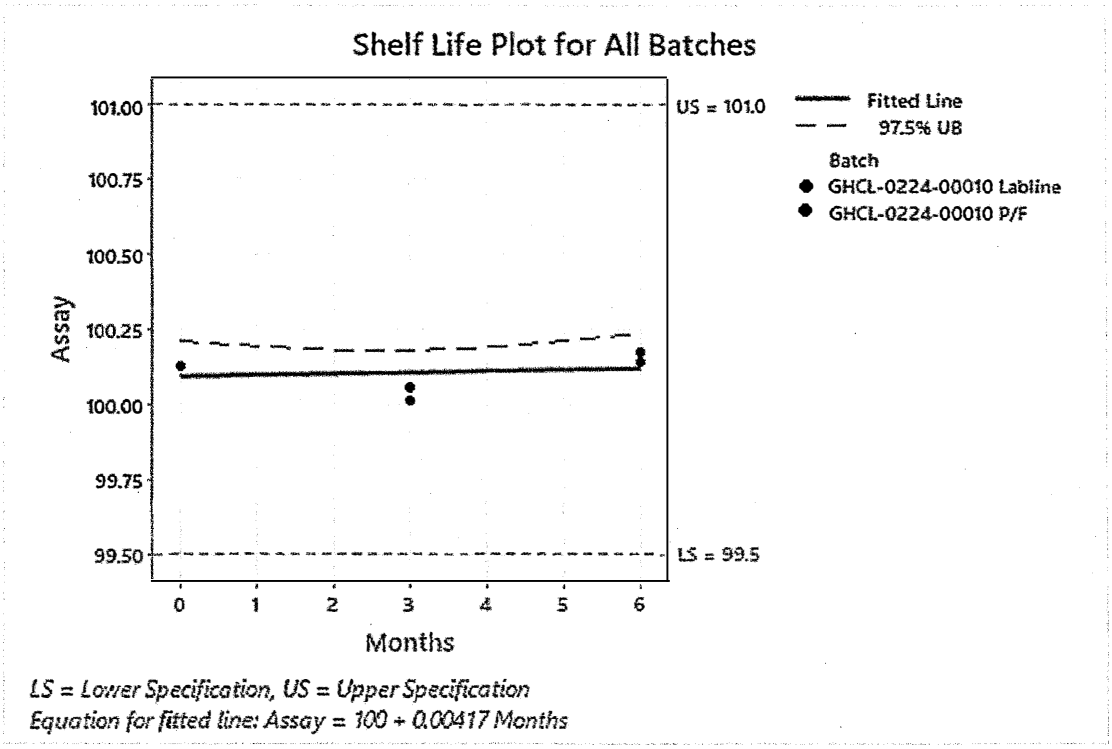
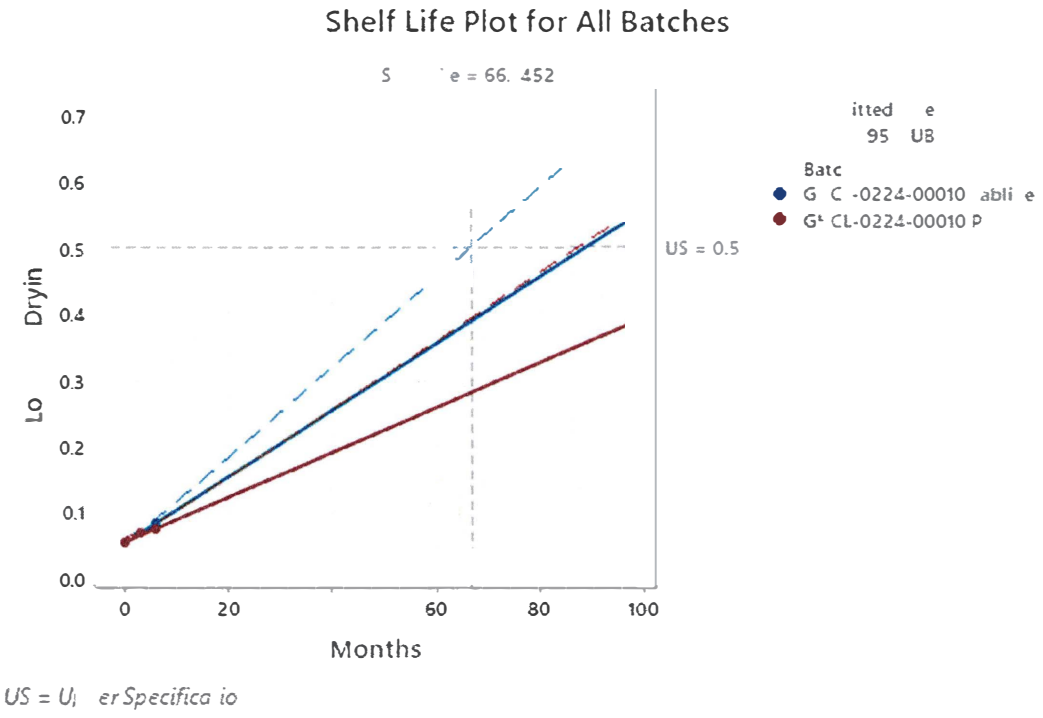
  - T = 48; Scheduled for February 7, 2028
  - T = 60; Scheduled for February 7, 2029



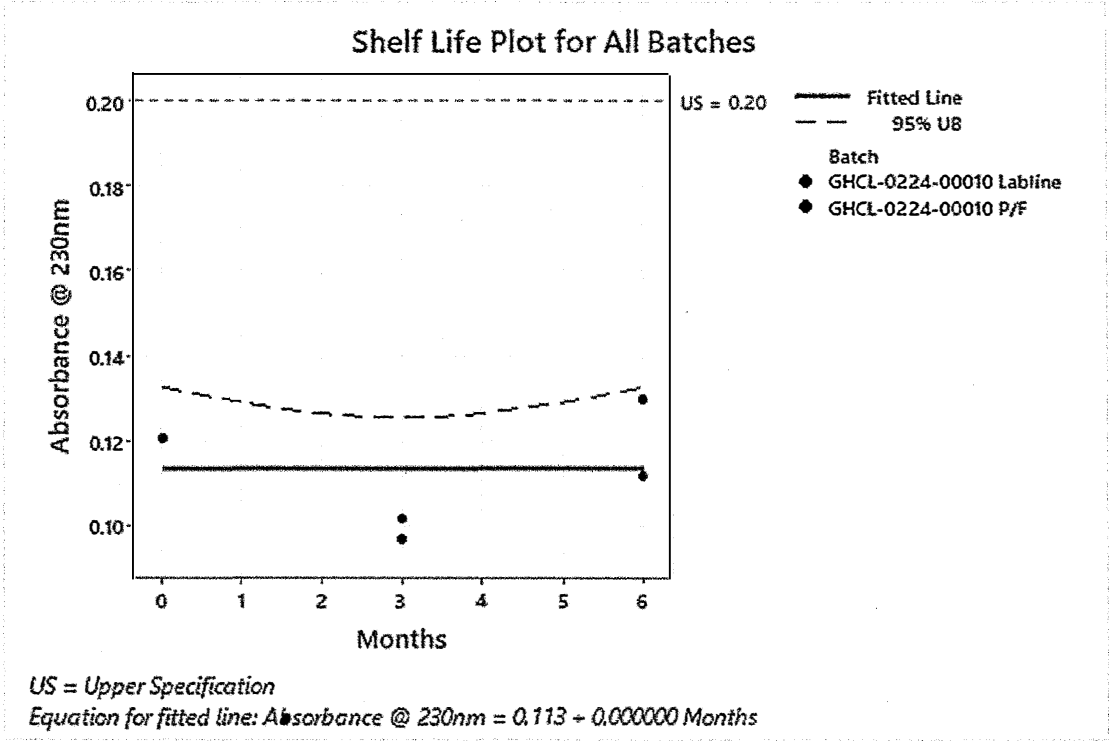
GRAPH 1: ASSAY

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 results met the predetermined specifications at T=6 months.



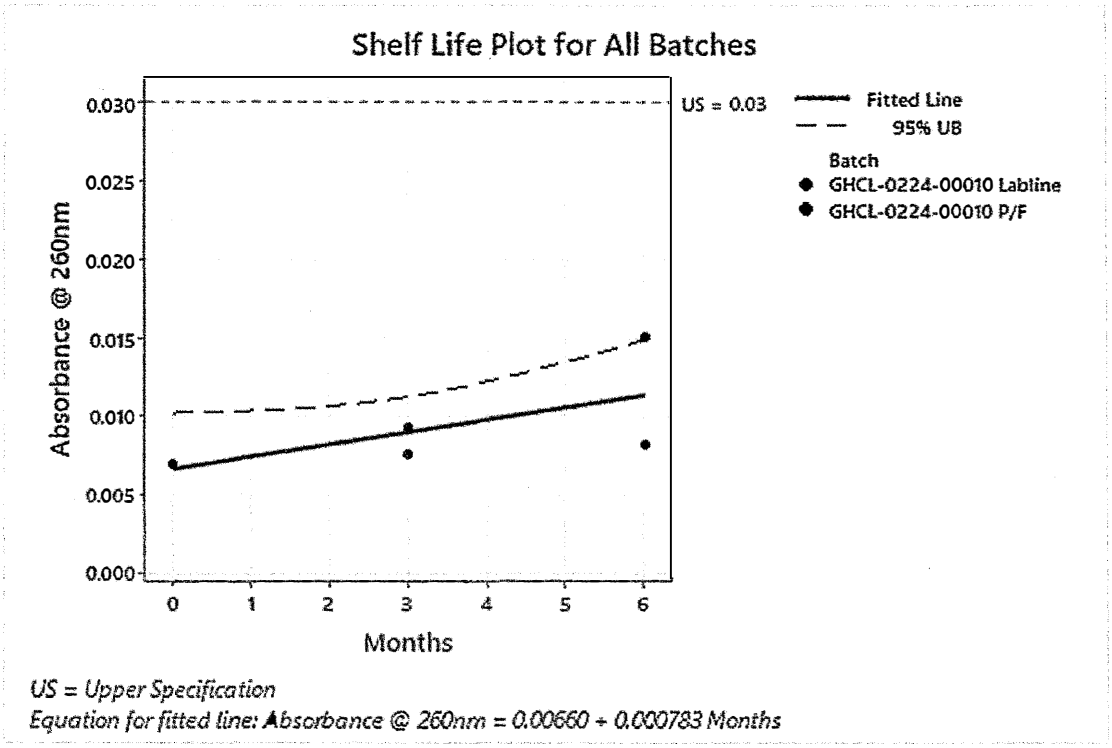
GRAPH 2: LOSS ON DRYING (LOD)

The predicted Shelf-Life for Loss on Drying was determined to be 66.7452 months as of the T=6-month time interval. There is no impact to the product or currently assigned retest period of this material since all results are within the current specification requirement.



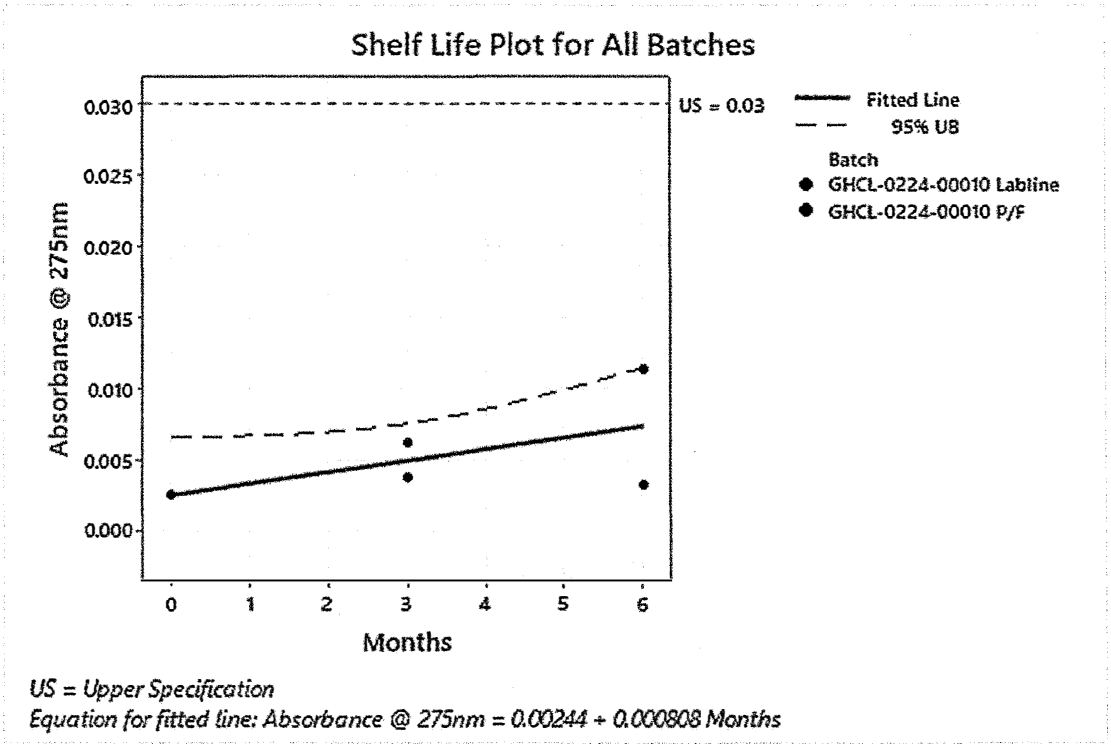
GRAPH 3: ABSORBANCE AT 230 NM

No Shelf-Life was able to be determined for Absorbance at 230 nm, 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 results met the predetermined specifications at T=6 months.



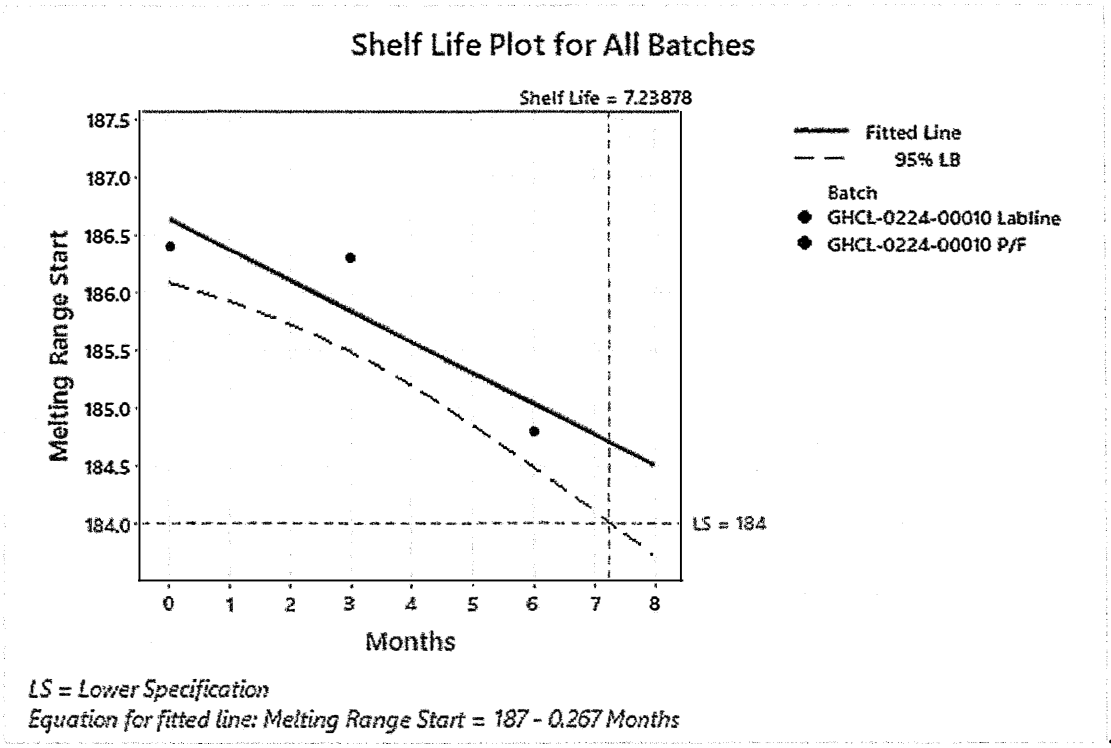
GRAPH 4: ABSORBANCE AT 260 NM

No Shelf-Life was able to be determined for Absorbance at 260 nm, 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 results met the predetermined specifications at T=6 months.



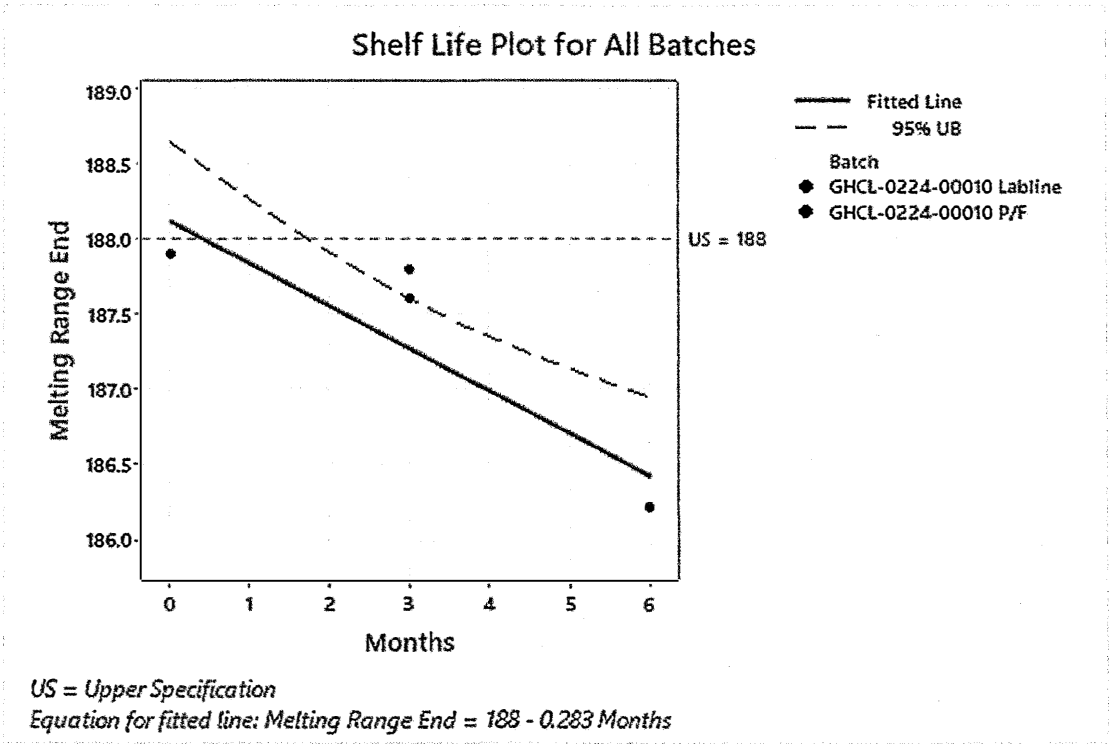
GRAPH 5: ABSORBANCE AT 275 NM

No Shelf-Life was able to be determined for Absorbance at 275 nm, 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 results met the predetermined specifications at T=6 months.



GRAPH 6: MELTING POINT START

The predicted Shelf-Life for Melting Point Start was determined to be 7.23878 months as of the T=6-month time interval. There is no impact to the product or currently assigned retest period of this material since all results are within the current specification requirement.



GRAPH 7: MELTING POINT END

No Shelf-Life was able to be determined for Melting Point 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 results met the predetermined specifications at T=6 months.

7. CONCLUSION:

In regards to the real time stability study for Guanidine Hydrochloride 2024 lot, all data met the specifications set forth in the stability testing program for the lot stored at the recommended long-term condition. In accordance with ICH Q1E, 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 for long-term conditions (warehouse conditions of 15 – 30°C). The long-term stability study data, along with the predicted shelf-life plots and historical data from older batches, continue to support a retest date of 24 months for lot of Guanidine Hydrochloride manufactured at BioSpectra in the Stroudsburg, PA facility. BioSpectra will continue to release Guanidine Hydrochloride with a 2-year retest date.

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.