BIOSPECTRA
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GUANIDINE HYDROCHLORIDE
REAL TIME STABILITY REPORT: 2022 LOT

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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 Hydrochloride lot manufactured in 2022 at the Stroudsburg, PA facility of BioSpectra. 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 real time stability analysis will assess the stability of Guanidine Hydrochloride lot GHCL-0222-00145 that completed eighteen (18) months of real-time stability in February 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 2A and 2B. 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 (≤ 25°C). The samples were stored in the Stroudsburg warehouse from September 2022 through February 2024. The maximum temperature of the warehouse was 29.75°C and the minimum temperature of the warehouse was 11.73°C. The average mean kinetic temperature was 20.68°C. See Section 5 for the discrepancy investigations initiated for temperature excursions.

5. INVESTIGATIONS:

5.1. **SDI22-184** was initiated due to an out of specification low temperature readings loggers recorded OOS low temperatures with the lowest reading of 13.40°C due to the AC being turned on instead of the heat and for the issue with heating unit number 3. This had no impact on the stability samples as because the excursions lasted only a few hours during the nights and early mornings.

5.2. **SDI23-07** was initiated because one of the MadgeTech data loggers fell from its bracket and stopped collecting data. This had no impact on the stability samples as the other six data loggers did not fall outside the specified temperature range of 15 – 30°C during the missing time frame.

5.3. **SDI23-76** was initiated for an out of specification low temperature on 3/29/23. The recorded temperature was 14.13°C which is below the minimum specification of 15°C. This was due to an empty propane tank. This had no impact on the Guanidine Hydrochloride stability samples as the excursion was brief lasting less than 12 hours.

5.4. **SDI23-128** was initiated for a MadgeTech logger that did not download its temperature and humidity data for the month of June 2023. This was due to damage on the logger itself. There was no impact of the stability samples as the other data loggers did not fall outside the specified temperature range of 15 – 30°C during the missing time.

5.5. **SDI23-159** was initiated for a MadgeTech logger that did not download its temperature and humidity data for the month of July 2023. This was due to a battery being dislodged from the logger. There was no impact to the stability samples as the other data loggers did not fall outside the specified temperature range of 15 – 30°C during the missing time.

5.6. **SDI24-17** was initiated due to missing data points from a logger from 1/17/24 to 1/30/24. The logger sustained damage when it fell from its bracket at the top of the racking. This had no impact on the stability samples as the other data loggers did not fall outside the specified temperature range of 15 – 30°C during the missing time.

6. LOT EVALUATION:

TABLE 2A: GHCL-0222-00145 P/F

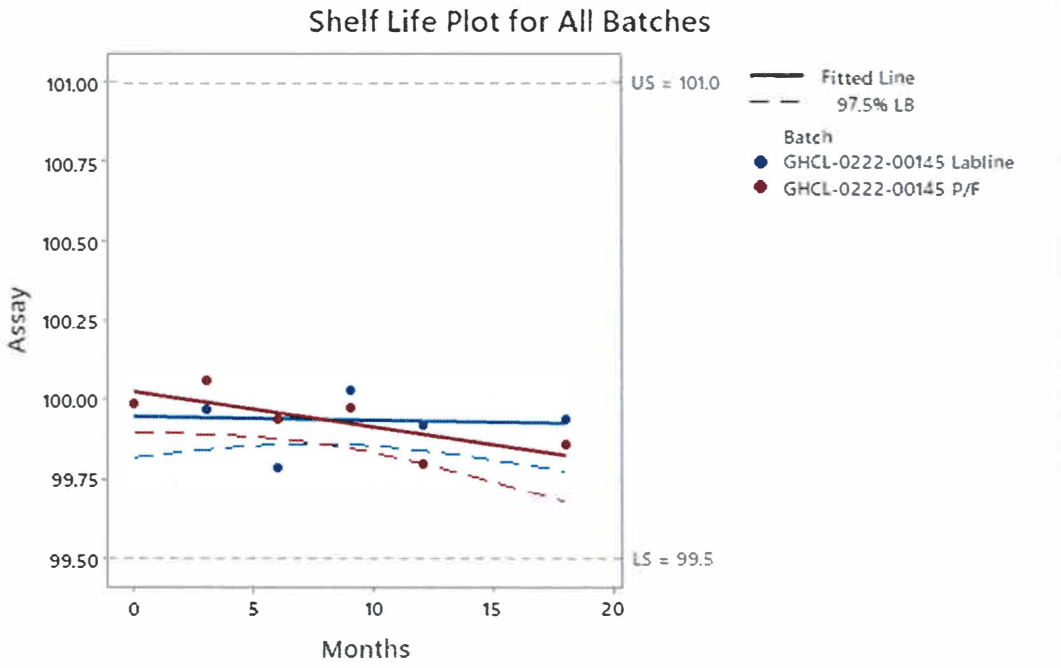
Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}
Absorbance (6M)	0.03 a.u. max @ 275 nm	0.0008 a.u.	0.0039 a.u.	0.0074 a.u.	0.0081 a.u.	0.0198 a.u.	0.0122 a.u.
	0.03 a.u. max @ 260 nm	0.0052 a.u.	0.0092 a.u.	0.0123 a.u.	0.0134 a.u.	0.0265 a.u.	0.0176 a.u.
	0.20 a.u. max @ 230 nm	0.1006 a.u.	0.1263 a.u.	0.1333 a.u.	0.1360 a.u.	0.1538 a.u.	0.1366 a.u.
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Assay	99.5-101.0%	99.99%	100.06%	99.94%	99.98%	99.80%	99.86%
Identity (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying	0.5% max.	0.0645%	0.1298%	0.0149%	0.1130%	0.1099%	0.0695%
Melting Range	184-188°C	185.2 – 187.1°C	185.6 – 187.4°C	185.8 – 187.4°C	186.4 - 187.4°C	185.0 – 186.1°C	185.6 – 187.4°C

- **Future pulls**
  - T = 24; Scheduled for September 1, 2024
  - T = 36; Scheduled for September 1, 2025

TABLE 2B: GHCL-0222-00145 LABLINE

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}
Absorbance (6M)	0.03 a.u. max @ 275 nm	0.0008 a.u.	0.0083 a.u.	0.0030 a.u.	0.0027 a.u.	0.0020 a.u.	0.0041 a.u.
	0.03 a.u. max @ 260 nm	0.0052 a.u.	0.0125 a.u.	0.0084 a.u.	0.0077 a.u.	0.0074 a.u.	0.0099 a.u.
	0.20 a.u. max @ 230 nm	0.1006 a.u.	0.1333 a.u.	0.1271 a.u.	0.1153 a.u.	0.1242 a.u.	0.1284a.u.
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Assay	99.5-101.0%	99.99%	99.97%	99.79%	100.03%	99.92%	99.94%
Identity (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying	0.5% max.	0.0645%	0.1046%	0.0700%	0.0746%	0.0743%	0.0796%
Melting Range	184-188°C	185.2 – 187.1°C	185.1 - 186.9°C	185.7 – 187.1°C	186.4 – 187.9°C	185.2 – 186.3°C	185.8 – 187.4°C

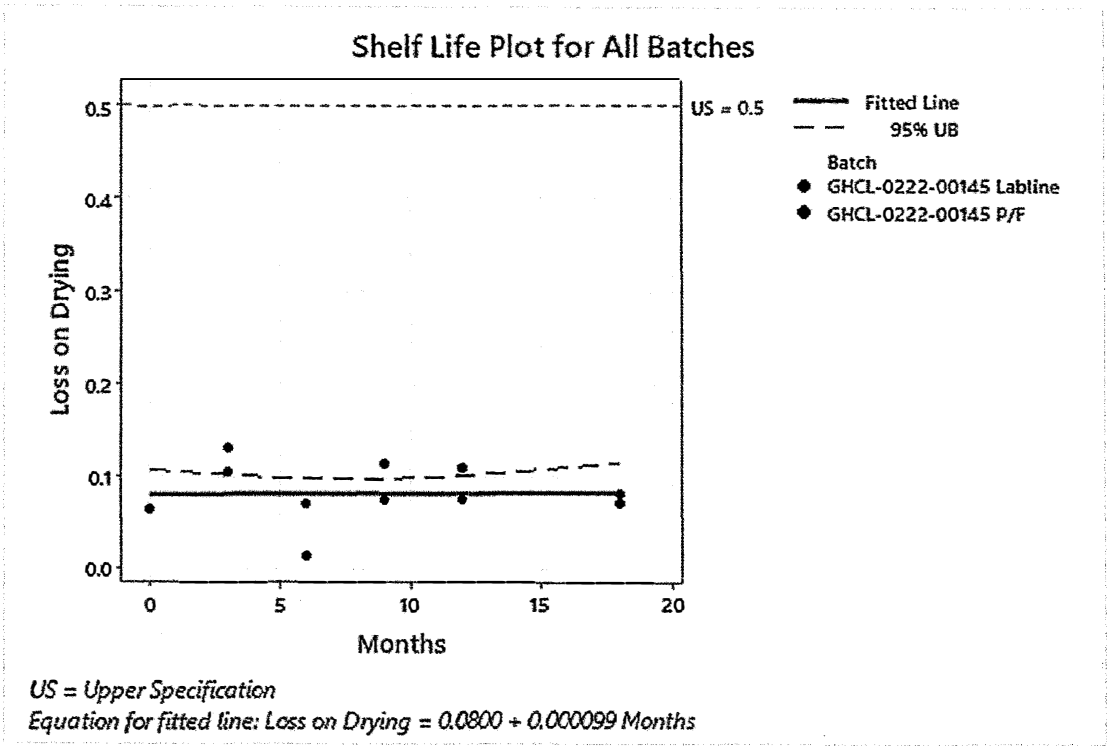
- **Future pulls**
  - T = 24; Scheduled for September 1, 2024
  - T = 36; Scheduled for September 1, 2025



LS = Lower Specification, US = Upper Specification

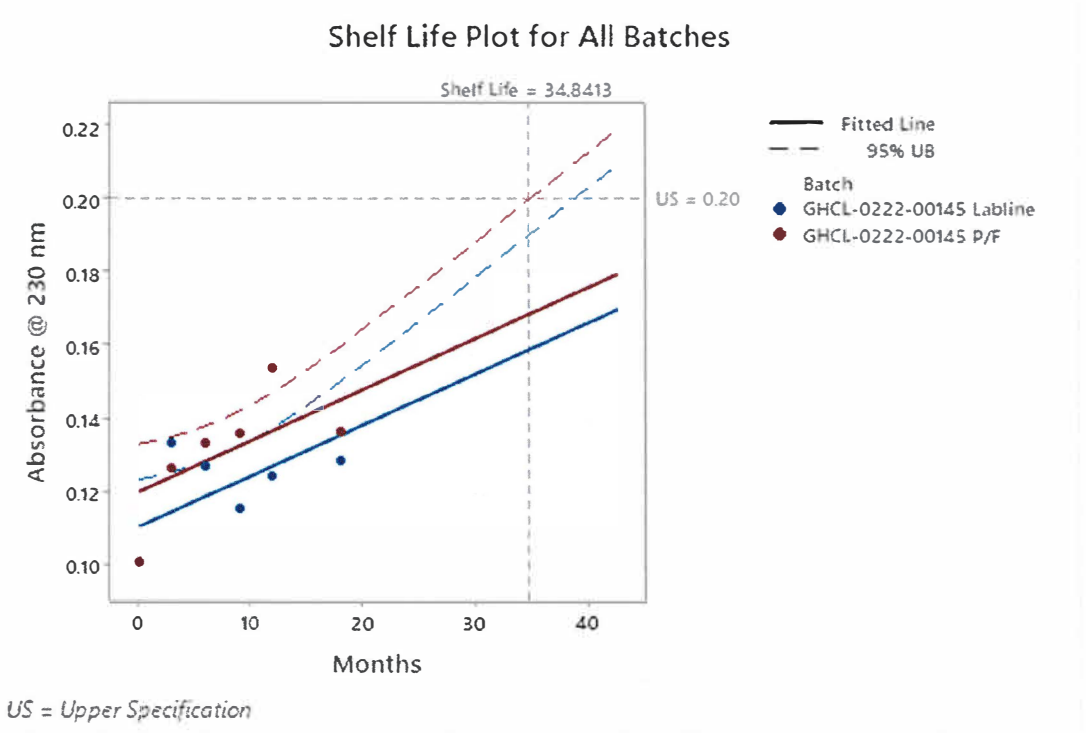
GRAPH 1: ASSAY

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=18 months.



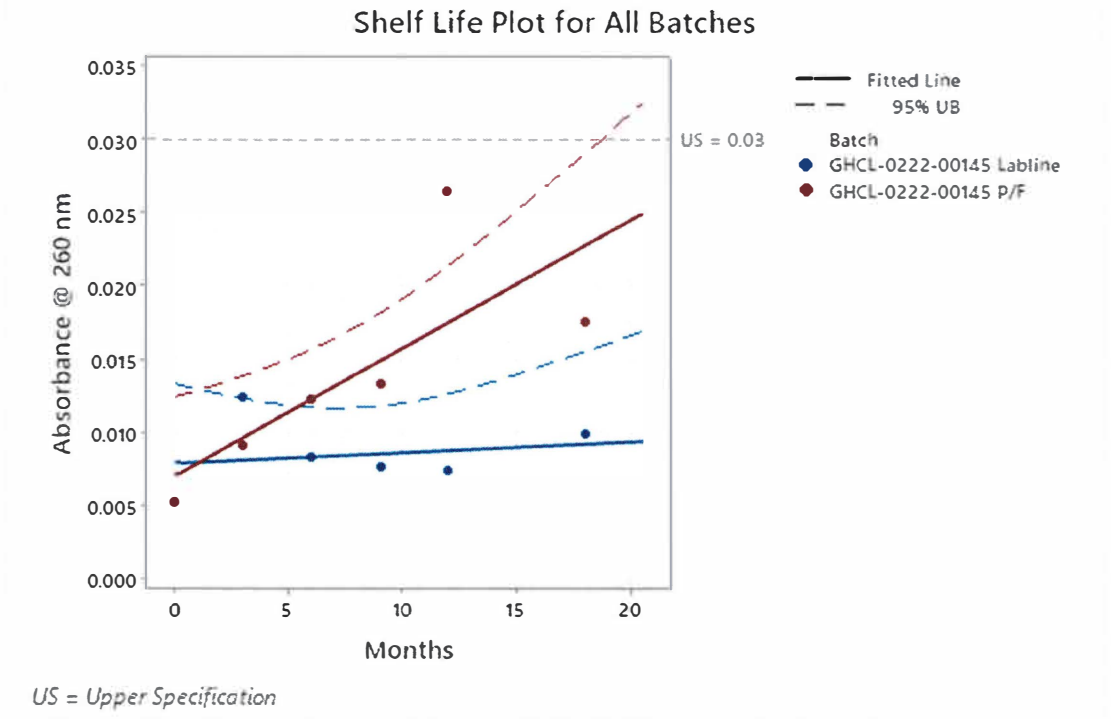
GRAPH 2: LOSS ON DRYING (LOD)

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 results met the predetermined specifications at T=18 months.



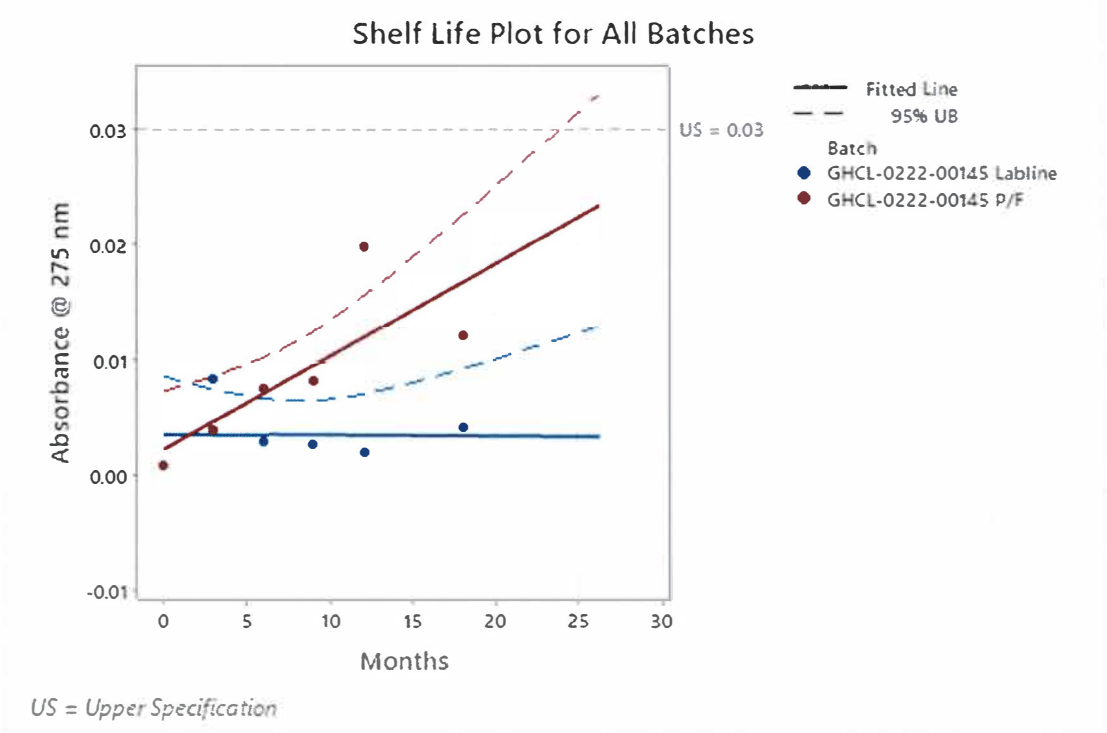
GRAPH 3: ABSORBANCE AT 230 NM

The predicted Shelf-Life for Absorbance at 230 nm was determined to be 34.8413 months as of the T=18-month time interval. There is no impact to the product or currently assigned retest period of this material, as this is significantly beyond the end of the study.



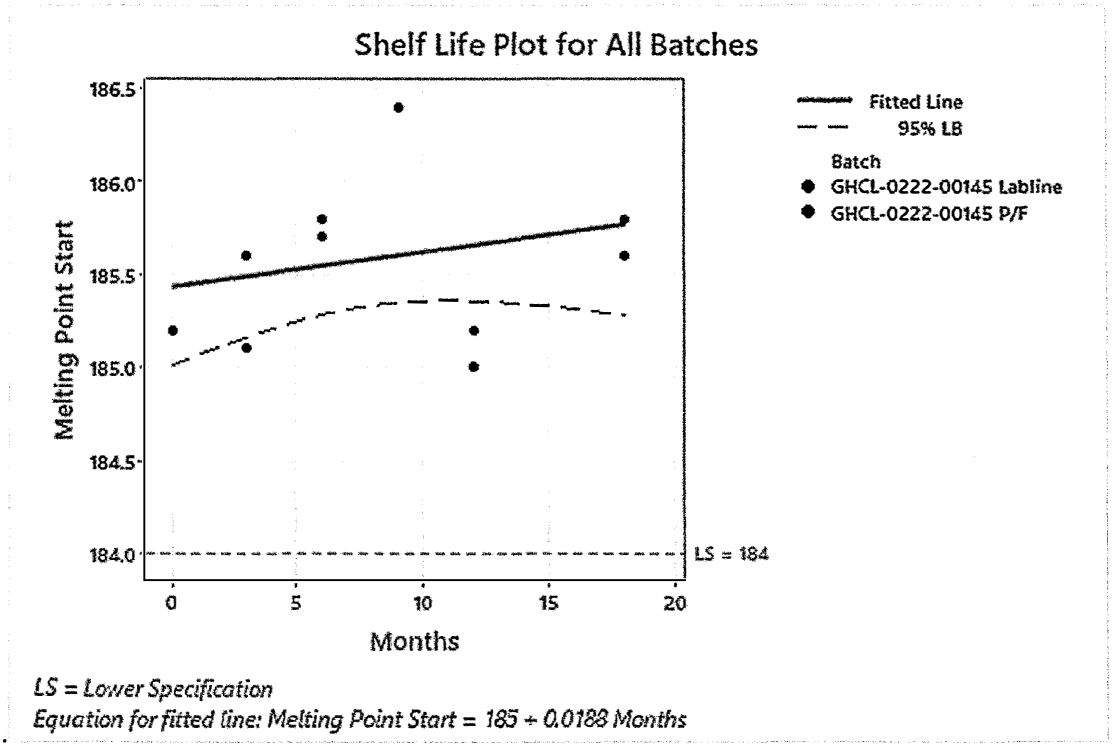
GRAPH 4: ABSORBANCE AT 260 NM

The predicted Shelf-Life for Absorbance at 260 nm was determined to be 18.705 months as of the T=18-month time interval. There is no impact to the product or currently assigned retest period of this material, as this is significantly beyond the end of the study.



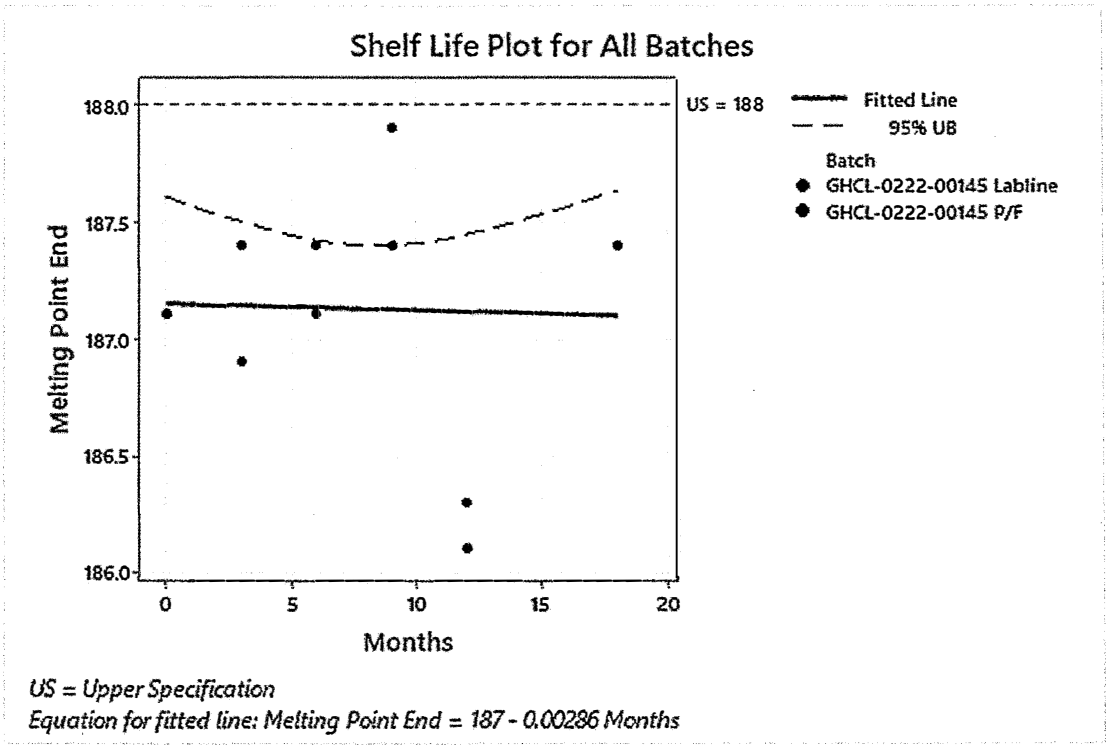
GRAPH 5: ABSORBANCE AT 275 NM

The predicted Shelf-Life for Absorbance at 275 nm was determined to be 23.943 months as of the T=18-month time interval. There is no impact to the product or currently assigned retest period of this material, as this is significantly beyond the end of the study.



GRAPH 6: MELTING POINT START

No Shelf-Life was able to be determined for Melting Point 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 results met the predetermined specifications at T=18 months.



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=18 months.

7. CONCLUSION:

In regards to the real time stability study for Guanidine Hydrochloride 2022 lot, all data met the specifications set forth in the stability testing program for the lot stored at the recommended real time 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 real time conditions (warehouse conditions of 15 – 30°C). The real time stability study data, along with the predicted shelf-life plots, supports a retest date of 18 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.