GUANIDINE HYDROCHLORIDE BIO EXCIPIENT GRADE REAL-TIME STABILITY REPORT: 2016 LOTS

GH3200-126-0816-PV

GH3200-127-0816-PV

GH3200-128-0816-PV

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the Real-Time Stability of Guanidine Hydrochloride Bio Excipient Grade material manufactured at BioSpectra's Stroudsburg, PA facility. Samples were placed on the Stability Testing Program in August of 2016 to fulfil the requirements of placing each Validation lot of manufactured material on the Stability Testing Program. Testing intervals are designated by T_n, where *n* represents 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 for a total of three years. Analysis has been conducted for a total of thirty-six months in order to assure that the manufactured product 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 Report assesses the stability of three lots of Guanidine Hydrochloride Bio Excipient Grade material. The study includes the following analyses: Absorbance (6M), Appearance and Color, Assay, Identity (IR), Loss on Drying, and Melting Range. Results from all analyses are summarized in Table 2, and Shelf-Life Plot determinations have been created for all 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 three lots of Guanidine Hydrochloride Bio Excipient Grade material. Stability samples from each of these batches were placed into one type of packaging configuration. These samples were packaged in accordance with the Stability Inventory SOP. Reference Table 1, below, for the packaging configuration and its description. The type of packaging utilized in this stability study was based on BioSpectra final packaging offered to the customer.

TABLE 1: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Poly/Fiber (P/F)	Samples are packaged into small poly bags and sealed with a ziptie. All individual samples are then placed into a fiber drum with a 4-unit desiccant.

4. STORAGE:

Samples were placed on stability in BioSpectra's Stroudsburg, PA facility Stability Area, located in the quarantine area of the Warehouse. Although there are no storage requirements for Guanidine Hydrochloride Bio Excipient Grade material, storage conditions were continuously monitored and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (specification: 15-30°C) and humidity (specification: monitor). The samples were stored in the Stroudsburg Warehouse from August 2016 through August 2019. The maximum temperature of the warehouse was 28.14°C and the minimum temperature of the warehouse was 12.63°C. See Section 5 for the discrepancy investigations initiated for temperature excursions.

5. INVESTIGATIONS:

5.1. SDI16-57 was initiated for temperatures dropping below the minimum storage temperature of 15°C. The temperature excursion had no impact on the Guanidine Hydrochloride stability samples, as the next time point, T_6, was pulled and tested, and all results met specification.

5.2. SDI18-01 was initiated for temperatures dropping below the minimum storage temperature of 15°C. The temperature excursion had no impact on the Guanidine Hydrochloride stability samples, as the next time point, T_{18}, was pulled and tested, and all results met specification.

5.3. SDI18-45 was initiated for MadgeTech data loggers not being replaced before the calibration due date. This had no impact on the Guanidine Hydrochloride stability samples, as the next time point, T_{36}, was pulled and tested, and all results met specification.

5.4. LI18-21 was initiated for Absorbance of GH3200-128-0816-PV T_{24} yielding negative results. It was determined that the negative results were due to analyst error. There is no impact to the quality of the material as these results were invalidated and the retests yielded passing results.

6. LOT EVALUATION:

TABLE 2: ALL INCLUSIVE STABILITY DATA

Guanidine Hydrochloride Stability Data										
Lot Number	**Analysis**	**Specification**	**T_0**	**T_3**	**T_6**	**T_9**	**T_{12}**	**T_{18}**	**T_{24}**	**T_{36}**
GH3200-126-0816-PV (P/F)	Absorbance (6M)	0.03 a.u. max @ 275 nm	0.0030	0.0147	0.0113	0.0137	0.0173	0.0131	0.0190	0.0079
		0.03 a.u. max @ 260 nm	0.0070	0.0185	0.0152	0.0190	0.0225	0.0178	0.0243	0.0124
		0.20 a.u. max @ 230 nm	0.1051	0.1163	0.1198	0.1053	0.1319	0.1237	0.1304	0.1132
	Appearance and Color	White/Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
	Assay	99.5-101.0%	99.93%	99.77%	99.84%	99.99%	99.67%	99.91%	99.86%	99.89%
	Identity (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying	0.5% max.	0.0540%	0.0399%	0.0697%	0.0398%	0.0448%	0.0449%	<0.0100 %	<0.0100 %
	Melting Range	184-188°C	185.0-185.9°C	185.5-186.4°C	185.5-187.0°C	185.2-186.5°C	185.5-186.9°C	185.7-187.1°C	185.3-186.5°C	184.7-186.2°C

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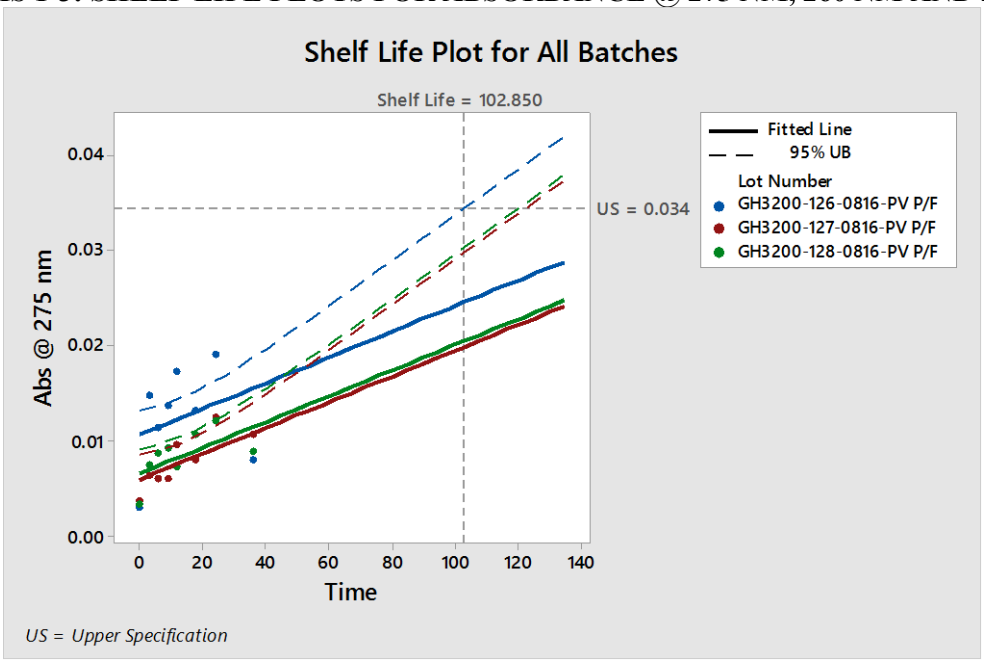
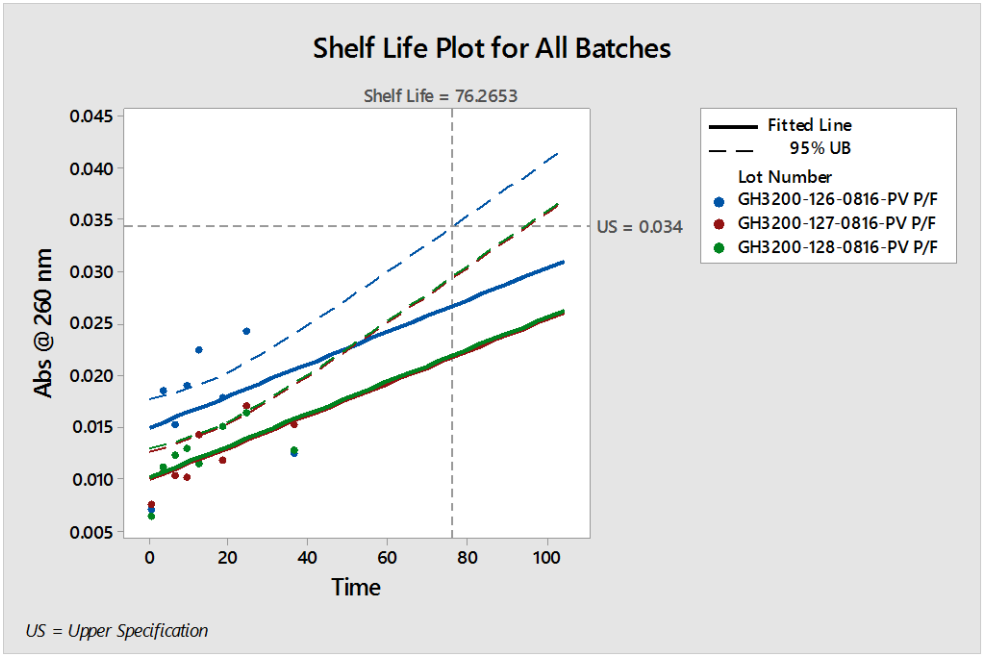
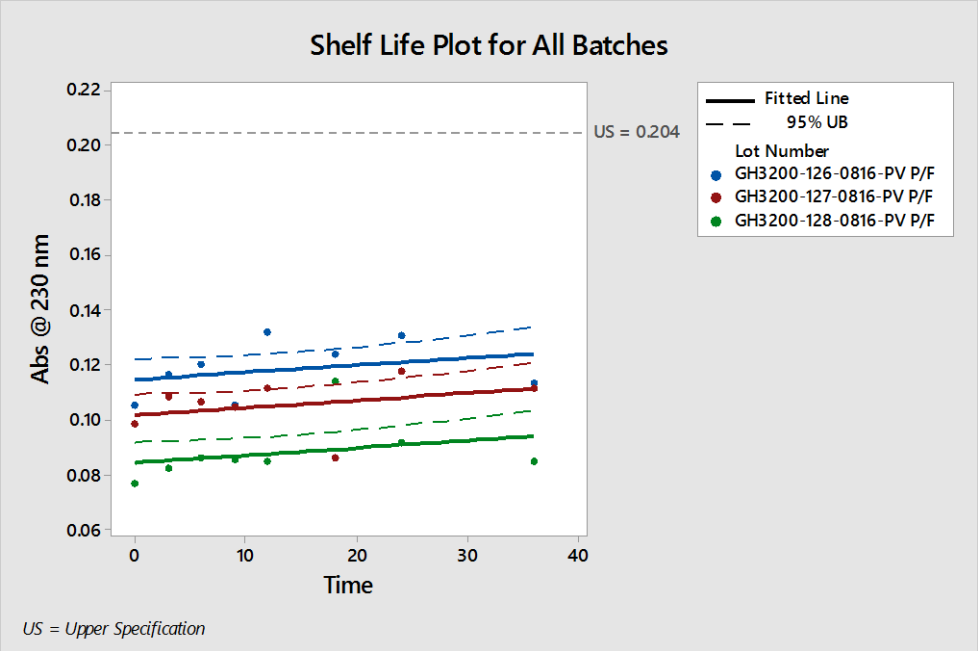
Lot Number	**Analysis**	**Specification**	**T_0**	**T_3**	**T_6**	**T_9**	**T_{12}**	**T_{18}**	**T_{24}**	**T_{36}**
GH3200-127-0816-PV (P/F)	Absorbance (6M)	0.03 a.u. max @ 275 nm	0.0036	0.0063	0.0060	0.0060	0.0095	0.0079	0.0124	0.0107
		0.03 a.u. max @ 260 nm	0.0076	0.0106	0.0103	0.0101	0.0143	0.0118	0.0170	0.0153
		0.20 a.u. max @ 230 nm	0.0984	0.1081	0.1062	0.1047	0.1114	0.0857	0.1172	0.1111
	Appearance and Color	White/Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
	Assay	99.5-101.0%	99.92%	99.85%	99.77%	100.27%	99.61%	99.74%	99.70%	100.13 %
	Identity (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying	0.5% max.	0.0891%	0.1196%	0.0942%	0.0499%	0.0597%	0.0488%	0.0399%	0.0446 %
	Melting Range	184-188°C	185.1-186.2°C	185.5-186.5°C	185.8-187.2°C	185.6-186.9°C	185.5-186.6°C	185.2-186.6°C	185.4-186.6°C	184.8-186.8°C
GH3200-128-0816-PV (P/F)	Absorbance (6M)	0.03 a.u. max @ 275 nm	0.0033	0.0075	0.0086	0.0092	0.0073	0.0106	0.0120	0.0089
		0.03 a.u. max @ 260 nm	0.0064	0.0111	0.0123	0.0130	0.0114	0.0150	0.0164	0.0128
		0.20 a.u. max @ 230 nm	0.0764	0.0820	0.0861	0.0854	0.0848	0.1139	0.0914	0.0846
	Appearance and Color	White/Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
	Assay	99.5-101.0%	99.86%	99.72%	99.98%	99.83%	99.62%	99.71%	99.69%	99.80%
	Identity (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying	0.5% max.	0.0636%	0.0700%	0.0450%	0.0694%	0.0545%	0.0342%	0.0347%	<0.0100 %
	Melting Range	184-188°C	185.2-186.7°C	185.7-186.7°C	185.5-187.0°C	185.7-187.0°C	185.2-186.1°C	185.6-186.8°C	185.3-186.6°C	184.8-186.8°C

GRAPHS 1-3: SHELF LIFE PLOTS FOR ABSORBANCE @ 275 NM, 260 NM AND 230NM.

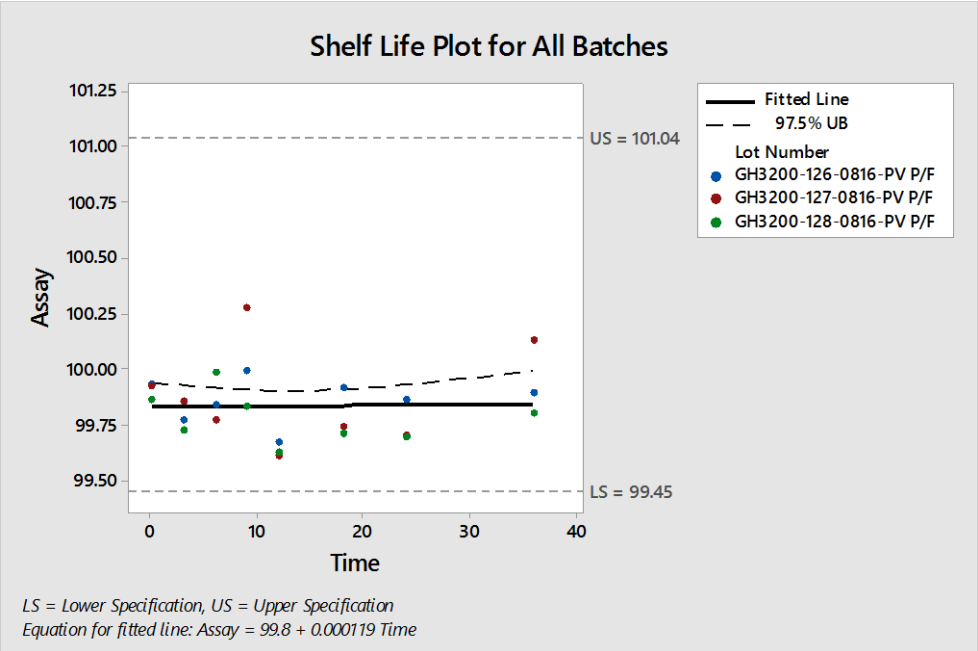






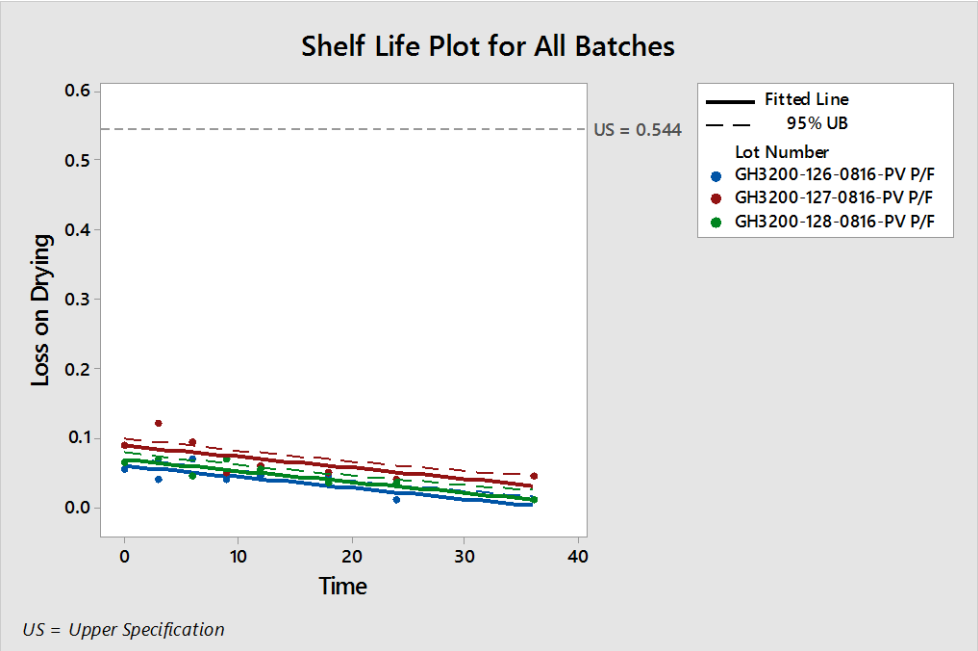
No predicted Shelf-Life is able to be determined for Absorbance @ 230 nm, as the mean response slope is not significantly different from zero. However, the predicted Shelf-Life of Absorbance at 275 nm, and 260 nm were determined to be 102.850 months and 76.2653 months, respectively. Based on this data, the predicted Shelf-Life for Absorbance is 76.2653 months. This is well beyond the thirty-six-month stability study, and shows no indication of issue to the product or the currently assigned expiration.

GRAPH 4: SHELF LIFE PLOT FOR ASSAY



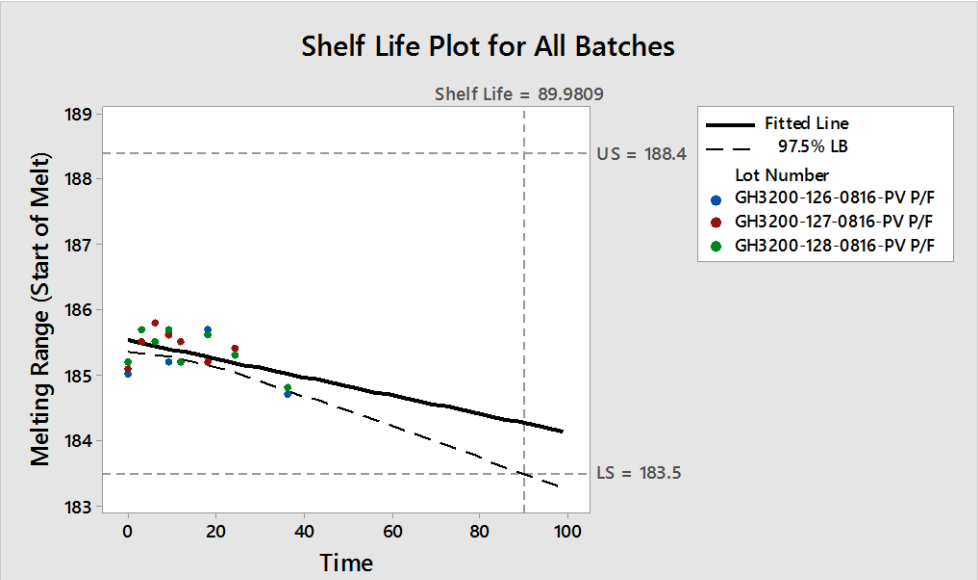
No predicted Shelf-Life is able to be determined for Assay, as the mean response slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

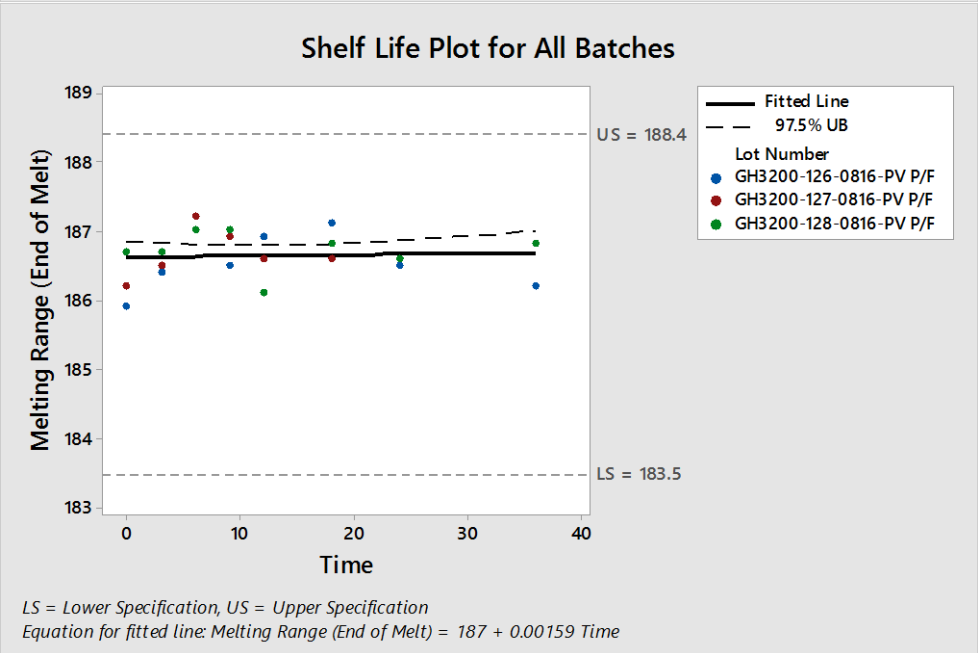
GRAPH 5: SHELF LIFE PLOT FOR LOSS ON DRYING



No predicted 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 currently assigned expiration of this material.

GRAPHS 6-7: SHELF LIFE PLOTS FOR MELTING RANGE





No predicted Shelf-Life is able to be determined based on the End of Melt data for Melting Range, as the mean response slope is not significantly different from zero. However, the predicted Shelf-Life for the Start of Melt data for Melting Range was determined to be 89.9809 months. Based on this data, the overall predicted Shelf-Life for Melting Range is 89.9809 months. This is well beyond the thirty-six-month stability study, and shows no indication of issue to the product or the current assigned expiration.

7. CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. In accordance with ICH Q1E, 2.4.2.1, the retest date may be proposed for up to 2*x*, 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 Guanidine Hydrochloride Bio Excipient material packaged in a Poly/Fiber Packaging configuration is stable for thirty-six months. The retest date of this material will remain at twenty-four months unless requested to be extended on a lot-by-lot basis.

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.