BIOSPECTRA
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L-HISTIDINE MONOCHLORIDE MONOHYDRATE 2024 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 the L-Histidine Monochloride Monohydrate. 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 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 product.

This long-term stability report assesses the stability of three lots of L- Histidine Monochloride Monohydrate; DMAT-0224-0042, DMAT-0224-0043 and DMAT-0224-0044 that completed twelve (12) months of long-term stability in April 2025. The study includes the analyses listed in Table 1 below. Results from all analyses are summarized in Tables 4 through 6.

TABLE 1: STABILITY SPECIFICATION

Analysis	Specification
Ammonium	≤0.02%
Appearance and Color	White Crystalline Powder or Crystals
Appearance of Solution	Passes Test
Assay (Anhydrous Basis)	99.0 – 101.0%
Assay (Dried Basis)	98.5 – 101.0%
Clarity and Color of Solution	Clear and Colorless
Identification (IR)	Passes Test
Loss on Drying	7.0 – 10.0%
pH (10%)	3.5 – 4.5

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 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 L-Histidine Monochloride Monohydrate. The following product codes are commercially available:

- LHMM-6250

2. REFERENCES

2.1. BSI-LST-0267, L-Histidine Monochloride Monohydrate Real Time Stability Data Card
2.2. BSI-PRL-0727, Stability Indicating Protocol: L-Histidine monohydrochloride, monohydrate
2.3. BSI-RPT-1753, Stability Indicating Report: L-Histidine monohydrochloride, monohydrate
2.4. BSI-SOP-0136, Stability Testing Program
2.5. BSI-SOP-0146, Stability Inventory
2.6. BSI-SOP-0289, Stability Indication Protocol
2.7. Current USP
2.8. ICH Q1E

3. SAMPLE DESIGNATION:

Samples placed on the Stability Testing Program consisted of three lots of L-Histidine Monochloride Monohydrate packaged into P/P packaging configurations. These samples were packaged in accordance with the Stability Inventory SOP, BSI-SOP-0146. Reference Table 1 below, for packaging configurations and descriptions. The types of packaging utilized in this stability study were based on BioSpectra final packaging.

TABLE 2: 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 HDPE pail and sealed.

4. STORAGE:

The Packaging and Storage requirements for L-Histidine Monochloride Monohydrate are to be stored at room temperature in a well-ventilated area. For this study, the samples were stored in the Long-Term Stability Chamber H03SC01 at the Bangor, PA facility from April 2024 through April 2025 and will continue until the end of the study in April 2029. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25°C ±2) and relative humidity (60% ±5). The storage conditions for the time period of this study are detailed in Table 3.

TABLE 3: STORAGE CONDITIONS

Condition	Specification	Value
Minimum Temperature	25°C ±2°C	21.81°C
Maximum Temperature		26.20°C
Average Temperature		25.30°C
Mean Kinetic Temperature	Monitor	25.30°C
Minimum Humidity	60%RH ±5%RH	50.3%
Maximum Humidity		63.4%
Average Humidity		61.5%

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. **BDI24-126;** Out of specification humidity and temperature for H03SC01 occurred on 8/15/24 with a humidity reading of 54.4% and a temperature of 21.81°C. It was discovered that a 20-amp fuse had blown. The fuse was replaced and the chamber went back into specification on 8/16/24 with a humidity reading of 62.3%. There is no impact on the stability samples as this excursion lasted less than 24 hours.

6. LOT EVALUATION:

TABLE 4: DMAT-0224-0042 P/P

Time Point	Analyses/Specifications								
	Ammonium	Appearance and Color	Appearance of Solution	Clarity and Color of Solution	Assay (Dried)	Assay (Anhydrous)	Identity (IR)	Loss on Drying	pH (1 in 10)
	≤0.02%	White Crystalline Powder or Crystals	Passes Test	Clear and Colorless	98.5 – 101.0%	99.0 – 101.0%	Passes Test	7.0 – 10.0%	3.5 – 4.5
T_0	<0.02%	White Crystalline Powder	Passes Test	Clear and Colorless	99.79%	99.87%	Passes Test	8.2700%	3.96
T_3	<0.01%	White Crystalline Powder	Passes Test	Clear and Colorless	100.14%	100.23%	Passes Test	8.6683%	3.96
T_6	<0.01%	White Crystalline Powder	Passes Test	Clear and Colorless	99.91%	99.90%	Passes Test	8.7682%	3.93
T_9	<0.02%	White Crystalline Powder	Passes Test	Clear and Colorless	100.02%	99.41%	Passes Test	8.7591%	3.93
T_{12}	<0.02%	White Crystalline Powder	Passes Test	Clear and Colorless	100.09%	99.89%	Passes Test	8.7682%	3.95

- **Remaining Testing Interval Pull Dates**
  - T = 18; Scheduled for October 10, 2025
  - T = 24; Scheduled for April 10, 2026
  - T = 36; Scheduled for April 10, 2027
  - T = 48; Scheduled for April 10, 2028
  - T = 60; Scheduled for April 10, 2029

TABLE 5: DMAT-0224-0043 P/P

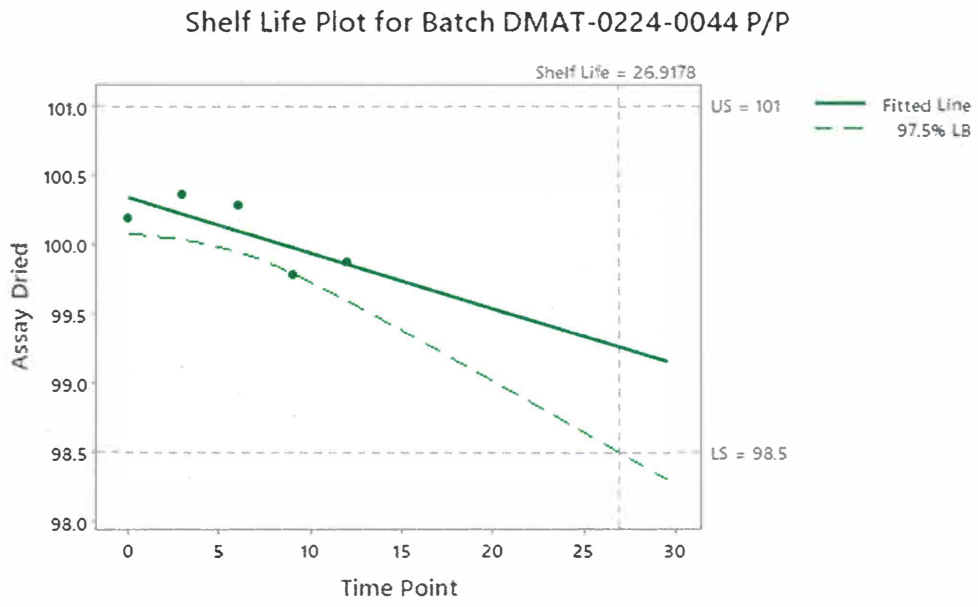
Time Point	Analyses/Specifications								
	Ammonium	Appearance and Color	Appearance of Solution	Clarity and Color of Solution	Assay (Dried)	Assay (Anhydrous)	Identity (IR)	Loss on Drying	pH (1 in 10)
	≤0.02%	White Crystalline Powder or Crystals	Passes Test	Clear and Colorless	98.5 – 101.0%	99.0 – 101.0%	Passes Test	7.0 – 10.0%	3.5 – 4.5
T_0	<0.02%	White Crystalline Powder	Passes Test	Clear and Colorless	100.27%	99.70%	Passes Test	8.7100%	3.95
T_3	<0.01%	White Crystalline Powder	Passes Test	Clear and Colorless	100.17%	100.35%	Passes Test	8.6974%	3.96
T_6	<0.01%	White Crystalline Powder	Passes Test	Clear and Colorless	100.08%	100.23%	Passes Test	8.7300%	3.93
T_9	<0.02%	White Crystalline Powder	Passes Test	Clear and Colorless	100.24%	99.98%	Passes Test	8.8600%	3.92
T_{12}	<0.02%	White Crystalline Powder	Passes Test	Clear and Colorless	100.01%	99.63%	Passes Test	8.7500%	3.94

- **Remaining Testing Interval Pull Dates**
  - T = 18; Scheduled for October 10, 2025
  - T = 24; Scheduled for April 10, 2026
  - T = 36; Scheduled for April 10, 2027
  - T = 48; Scheduled for April 10, 2028
  - T = 60; Scheduled for April 10, 2029

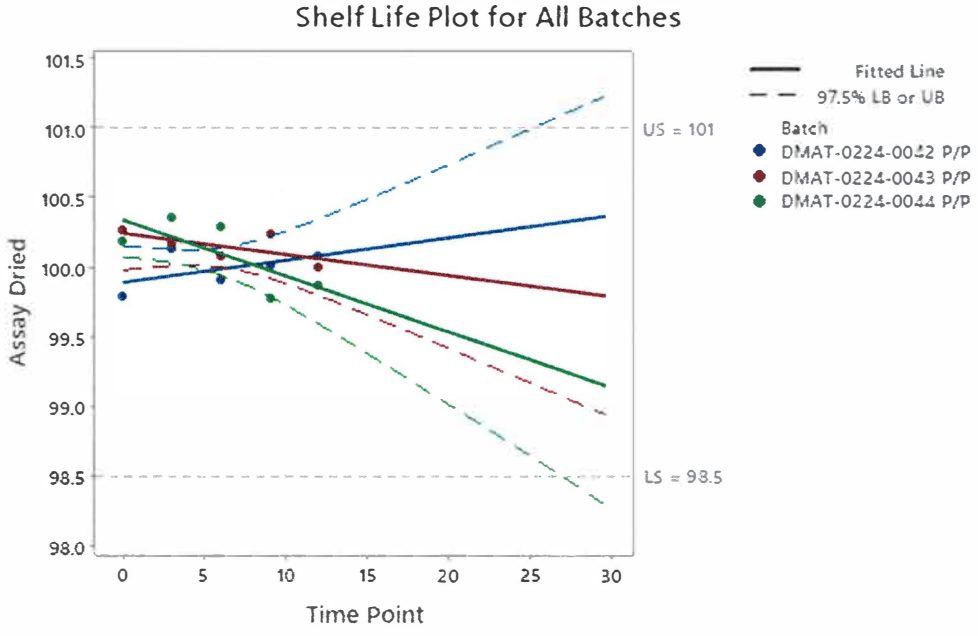
TABLE 6: DMAT-0224-0044 P/P

Time Point	Analyses/Specifications								
	Ammonium	Appearance and Color	Appearance of Solution	Clarity and Color of Solution	Assay (Dried)	Assay (Anhydrous)	Identity (IR)	Loss on Drying	pH (1 in 10)
	≤0.02%	White Crystalline Powder or Crystals	Passes Test	Clear and Colorless	98.5 – 101.0%	99.0 – 101.0%	Passes Test	7.0 – 10.0%	3.5 – 4.5
T_0	<0.02%	White Crystalline Powder	Passes Test	Clear and Colorless	100.19%	99.86%	Passes Test	8.7100%	3.95
T_3	<0.01%	White Crystalline Powder	Passes Test	Clear and Colorless	100.36%	100.57%	Passes Test	8.6883%	3.95
T_6	<0.01%	White Crystalline Powder	Passes Test	Clear and Colorless	100.29%	100.42%	Passes Test	8.7391%	3.92
T_9	<0.02%	White Crystalline Powder	Passes Test	Clear and Colorless	99.78%	99.47%	Passes Test	8.6857%	3.89
T_{12}	<0.02%	White Crystalline Powder	Passes Test	Clear and Colorless	99.88%	99.28%	Passes Test	8.7565%	3.96

- **Remaining Testing Interval Pull Dates**
  - T = 18; Scheduled for October 10, 2025
  - T = 24; Scheduled for April 10, 2026
  - T = 36; Scheduled for April 10, 2027
  - T = 48; Scheduled for April 10, 2028
  - T = 60; Scheduled for April 10, 2029



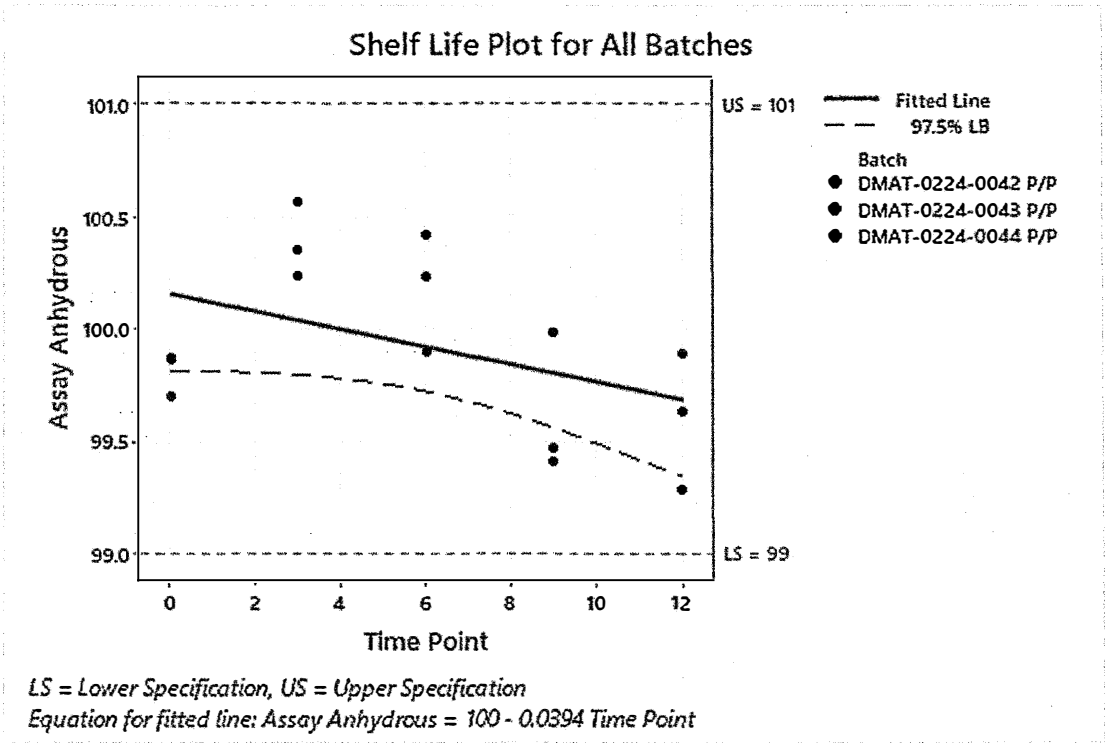
LS = Lower Specification, US = Upper Specification
Equation for fitted line: Assay Dried = 100 - 0.0400 Time Point



LS = Lower Specification, US = Upper Specification

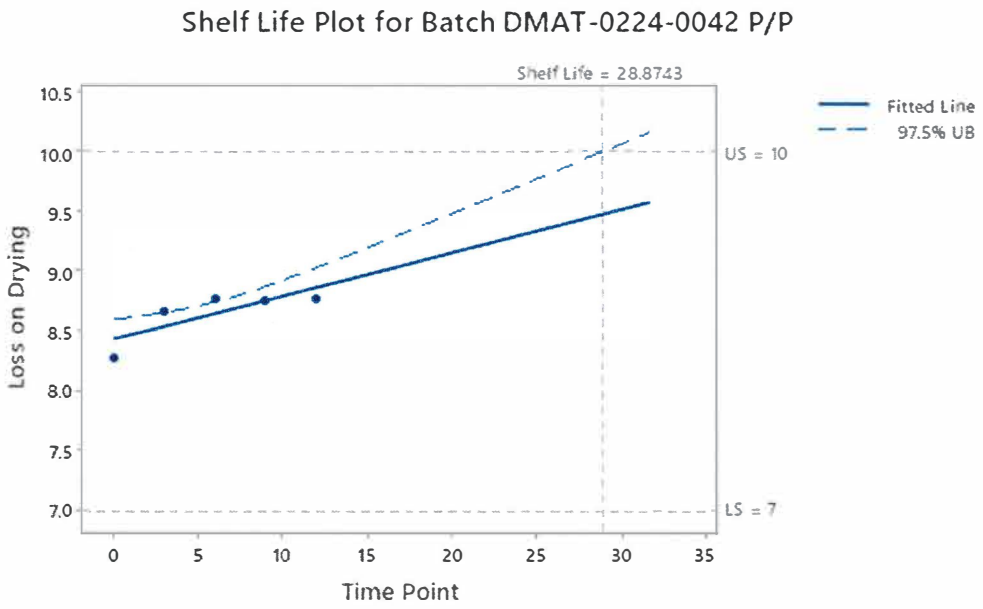
GRAPH 1 SHELF LIFE PLOTS FOR ASSAY (DRIED BASIS)

The predicted Shelf-Life for Assay (Dried Basis) was determined to be 26.9178 months as of the 12-month time interval. There is no impact to the product or currently assigned retest period of this material.

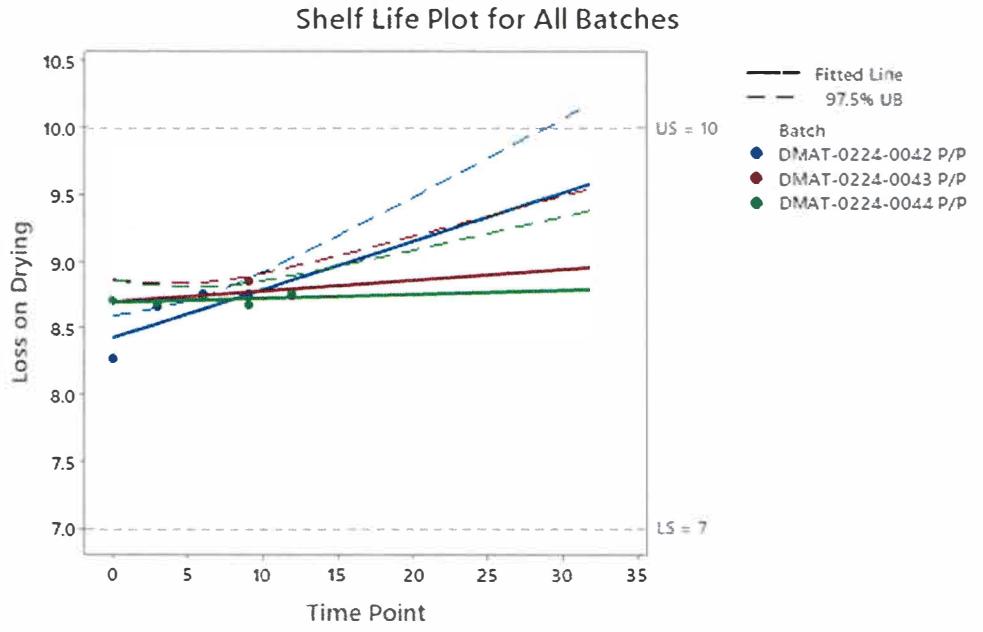


GRAPH 2 SHELF LIFE PLOTS FOR SHELF LIFE PLOTS FOR ASSAY (ANHYDROUS BASIS)

No Shelf-Life was able to be determined for Assay (Anhydrous Basis), 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.



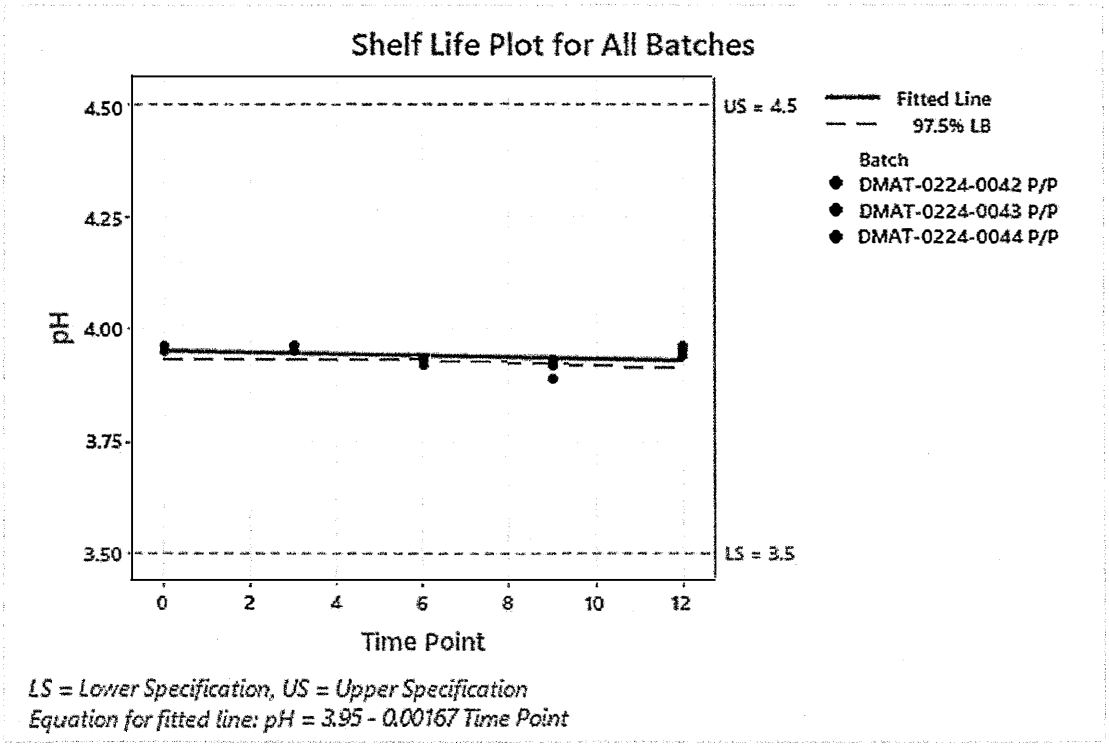
LS = Lower Specification, US = Upper Specification
Equation for fitted line: Loss on Drying = 8.43 + 0.0362 Time Point



LS = Lower Specification, US = Upper Specification

GRAPH 3 SHELF LIFE PLOTS LOSS ON DRYING

The predicted Shelf-Life for Loss on Drying was determined to be 28.8743 months as of the 12-month time interval. There is no impact to the product or currently assigned retest period of this material.



GRAPH 4: SHELF LIFE PLOT FOR PH (10% SOLUTION)

No Shelf-Life was able to be determined for pH (10% Solution), 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.

7. CONCLUSION:

In regards to the long-term stability study for L-Histidine Monochloride Monohydrate, all data met the specifications set forth in the Stability Testing Program for the lots stored at the 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, temperature (25°C ±2) and relative humidity (60% ±5). The long-term stability study data, along with the predicted shelf-life plots, supports a retest date of 24 months for lots of L-Histidine Monochloride Monohydrate.

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.