BIOSPECTRA
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L-CYSTINE DIHYDROCHLORIDE 2023 LONG TERM STABILITY REPORT

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the long-term Stability of L- Cystine dihydrochloride. The long-term Stability Program consists of testing every three months for the first year, every six months for the second year and annually for each subsequent year, notated as T_n, where ***n*** represents the number of months on stability. Analysis has been conducted thus far for a total of eighteen months. At the end of the study, a total of sixty months of data will be analyzed to assure that the manufactured material 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 long-term stability report assesses the stability of L-Cystine dihydrochloride lots RMAT-0523-0109, RMAT-0523-0110 and RMAT-0523-0111 that completed eighteen (18) months of long-term stability in December 2024. The study includes the following analyses: Appearance and Color, Assay (Dried Basis), Chloride, Identification (IR), Loss on Drying (105°C), Solubility, and Specific Rotation (Free Basis) @ 20°C. Results from all analyses are summarized in Tables 2 through 7 and shelf-life plot determinations have been created for 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.

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 of L-Cystine dihydrochloride. The following product codes are commercially available:

- LCYS-4250
- LCYS-4252
- LCYS-4350
- LCYS-6250

2. REFERENCES:

2.1. BSI-PRL-0133, Stability Indicating Report: L-Cystine DiHCl Bio Contract Grade
2.2. BSI-RPT-0334, Stability Indicating Report: L-Cystine DiHCl Bio Contract Grade
2.3. BSI-SOP-0136, Stability Testing Program
2.4. BSI-SOP-0146, Stability Inventory
2.5. BSI-SOP-0289, Stability Indication Protocol
2.6. Current USP
2.7. ICH Q1E

3. SAMPLE DESIGNATION:

3.1. Samples initially placed on the stability program consisted of three lots of L-Cystine dihydrochloride. Stability samples from these batches were placed into P/P and Labline packaging configurations. The samples were packaged in accordance with Stability Inventory, BSI-SOP-0146. Reference Table 1 for packaging configuration and description. The type of packaging utilized in this stability study was based on BioSpectra packaging available for this product.

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	Samples are packaged into a HDPE Lab Screw-Top Bottle.

4. STORAGE:

4.1. The packaging and storage requirements for L-Cystine dihydrochloride are to be in tightly-closed containers stored in a dry well-ventilated place. For this study, the samples were stored in the long-term stability chamber H03SC01 at the Bangor, PA facility from June 2023 until December 2023. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25°C±2), relative humidity (60% RH ±5), mean kinetic temperature (monitor). For this period, the maximum temperature recorded was 25.73°C, the minimum temperature was 24.84°C, the average temperature was 25.41°C, and the average mean kinetic temperature was 25.41°C. The maximum humidity recorded was 80.5%, the minimum humidity was 46.1%, and average humidity for this period was 61.7%. In December 2023, the samples were moved into the long-term stability chamber, H02SC01, where it has been stored until December 2024. For this period, the maximum temperature recorded was 25.65°C, the minimum temperature was 22.09°C, the average temperature was 25.08°C, and the average mean kinetic temperature was 25.08°C. The maximum humidity recorded was 74.3%, the minimum humidity was 34.1%, and the average humidity for this period was 57.6%. All deviations were justified by confirming chamber entry with the Bangor Stability Chamber Entrance Log Book. Section 5 will include any excursions from these conditions that resulted in an investigation.

5. INVESTIGATIONS:

5.1. None

6. LOT EVALUATION:

TABLE 2: RMAT-0523-0109 P/P

Analysis	Specification	T0	T3	T6	T9	T12	T18
Appearance and Color	White to Slightly Yellow Crystalline Powder	White to Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder
Assay	98.0 – 102.0%	99.84%	99.91%	99.60%	99.50%	99.67%	99.82%
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Chloride	22.2 – 23.5%	22.60%	22.61%	22.55%	22.52%	22.56%	22.60%
Loss on Drying (105°C)	1.0% max	0.0236%	0.0717%	0.0485%	0.1192%	0.0247%	0.0264%
Solubility	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Specific Rotation (Free Basis) @ 20°C	-225.0° - -210.0°	-222.07°	-221.91°	-222.25°	-221.87°	-222.40°	-220.51°

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 24; Scheduled for June 8, 2025
  - T = 36; Scheduled for June 8, 2026
  - T = 48; Scheduled for June 8, 2027
  - T = 60; Scheduled for June 8, 2028

TABLE 3: RMAT-0523-0109 LABLINE

Analysis	Specification	T0	T3	T6	T9	T12	T18
Appearance and Color	White to Slightly Yellow Crystalline Powder	White to Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder
Assay	98.0 – 102.0%	99.84%	99.89%	99.84%	99.70%	99.75%	100.10%
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Chloride	22.2 – 23.5%	22.60%	22.61%	22.60%	22.57%	22.58%	22.66%
Loss on Drying (105°C)	1.0% max	0.0236%	0.0470%	0.0500%	0.0557%	0.0112%	0.0186%
Solubility	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Specific Rotation (Free Basis) @ 20°C	-225.0° - -210.0°	-222.07°	-221.58°	-222.05°	-221.43°	-221.94°	-220.45°

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 24; Scheduled for June 8, 2025
  - T = 36; Scheduled for June 8, 2026
  - T = 48; Scheduled for June 8, 2027
  - T = 60; Scheduled for June 8, 2028

TABLE 4: RMAT-0523-0110 P/P

Analysis	Specification	T0	T3	T6	T9	T12	T18
Appearance and Color	White to Slightly Yellow Crystalline Powder	White Crystalline Powder	White to Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder
Assay	98.0 – 102.0%	99.73%	99.33%	99.59%	99.66%	99.58%	99.84%
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Chloride	22.2 – 23.5%	22.58%	22.48%	22.54%	22.56%	22.54%	22.60%
Loss on Drying (105°C)	1.0% max	0.0410%	0.0738%	0.0310%	0.1113%	0.0203%	0.0514%
Solubility	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Specific Rotation (Free Basis) @ 20°C	-225.0° - -210.0°	-220.73°	-221.24°	-222.03°	-221.39°	-222.00°	-221.68°

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 24; Scheduled for June 8, 2025
  - T = 36; Scheduled for June 8, 2026
  - T = 48; Scheduled for June 8, 2027
  - T = 60; Scheduled for June 8, 2028

TABLE 5: RMAT-0523-0110 LABLINE

Analysis	Specification	T0	T3	T6	T9	T12	T18
Appearance and Color	White to Slightly Yellow Crystalline Powder	White Crystalline Powder	White to Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder
Assay	98.0 – 102.0%	99.73%	99.58%	99.99%	99.61%	99.57%	100.09%
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Chloride	22.2 – 23.5%	22.58%	22.54%	22.63%	22.55%	22.54%	22.66%
Loss on Drying (105°C)	1.0% max	0.0410%	0.0777%	0.0608%	0.1050%	0.0634%	0.0588%
Solubility	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Specific Rotation (Free Basis) @ 20°C	-225.0° - -210.0°	-220.73°	-221.61°	-222.22°	-221.49°	-222.25°	-222.20°

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 24; Scheduled for June 8, 2025
  - T = 36; Scheduled for June 8, 2026
  - T = 48; Scheduled for June 8, 2027
  - T = 60; Scheduled for June 8, 2028

TABLE 6: RMAT-0523-0111 P/P

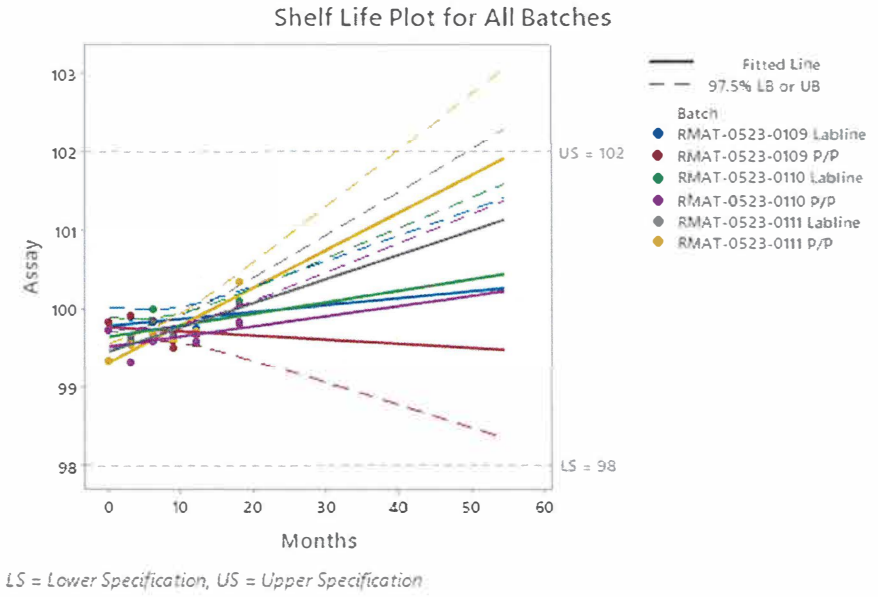
Analysis	Specification	T0	T3	T6	T9	T12	T18
Appearance and Color	White to Slightly Yellow Crystalline Powder	White Crystalline Powder	White to Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder
Assay	98.0 – 102.0%	99.35%	99.54%	99.66%	99.60%	99.70%	100.34%
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Chloride	22.2 – 23.5%	22.49%	22.53%	22.56%	22.54%	22.57%	22.71%
Loss on Drying (105°C)	1.0% max	0.0351%	0.0656%	0.0362%	0.1056%	0.0929%	0.0444%
Solubility	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Specific Rotation (Free Basis) @20°C	-225.0° - -210.0°	-221.95°	-221.39°	-221.84°	-221.44°	-222.00°	-221.89°

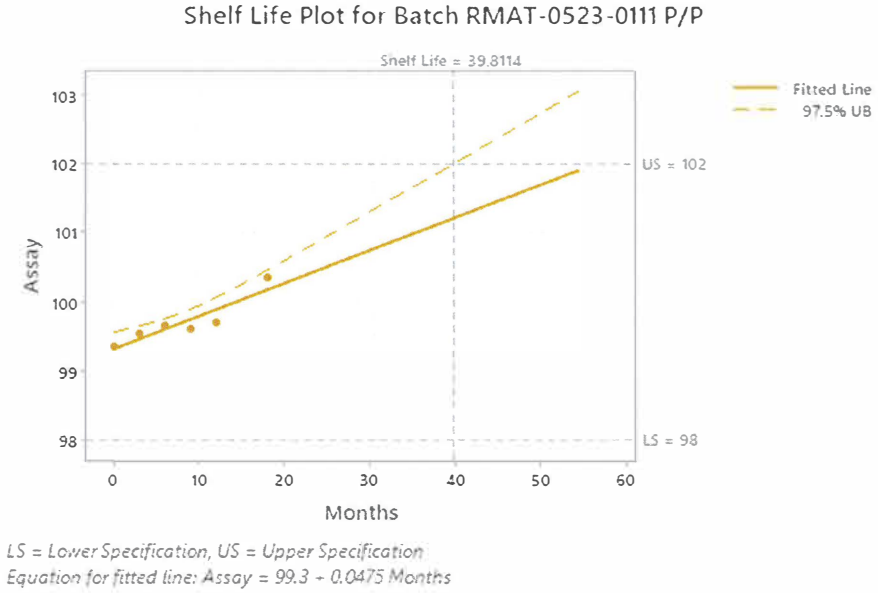
- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 24; Scheduled for June 8, 2025
  - T = 36; Scheduled for June 8, 2026
  - T = 48; Scheduled for June 8, 2027
  - T = 60; Scheduled for June 8, 2028

TABLE 7: RMAT-0523-0111 LABLINE

Analysis	Specification	T0	T3	T6	T9	T12	T18
Appearance and Color	White to Slightly Yellow Crystalline Powder	White Crystalline Powder	White to Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder	Slightly Yellow Crystalline Powder
Assay	98.0 – 102.0%	99.35%	99.62%	99.85%	99.64%	99.70%	100.06%
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Chloride	22.2 – 23.5%	22.49%	22.55%	22.60%	22.55%	22.57%	22.65%
Loss on Drying (105°C)	1.0% max	0.0351%	0.0588%	0.0349%	0.0872%	0.0134%	0.0174%
Solubility	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Specific Rotation (Free Basis) @20°C	-225.0° - -210.0°	-221.95°	-221.63°	-221.54°	-221.55°	-221.87°	-221.67°

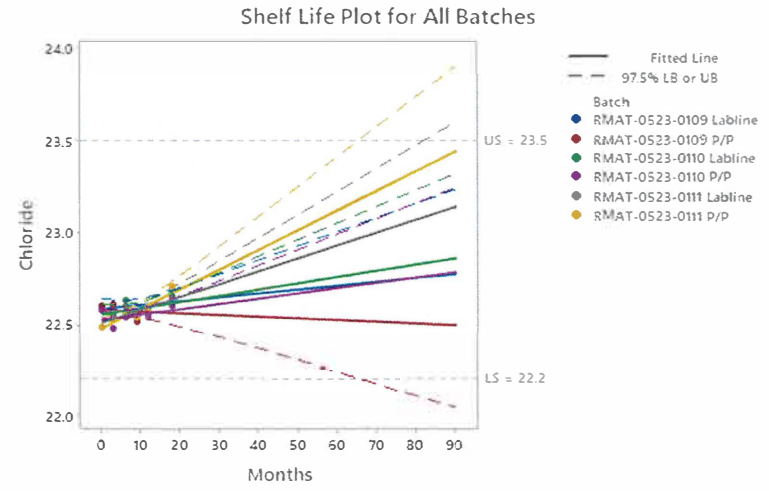
- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 24; Scheduled for June 8, 2025
  - T = 36; Scheduled for June 8, 2026
  - T = 48; Scheduled for June 8, 2027
  - T = 60; Scheduled for June 8, 2028

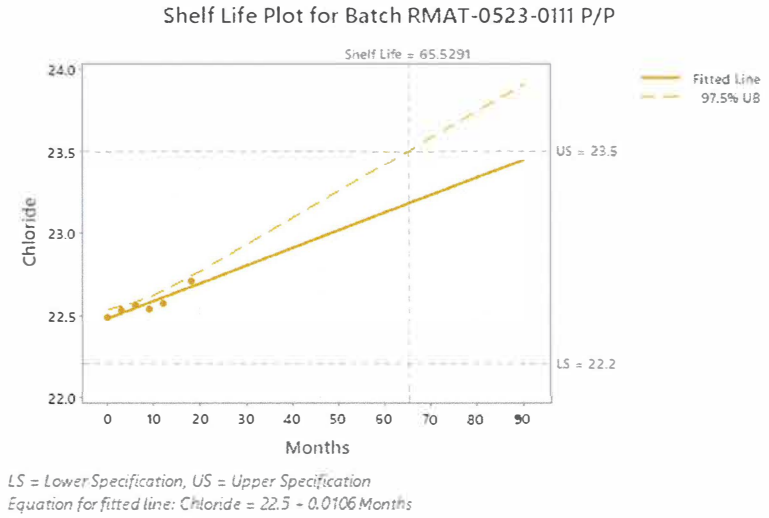




GRAPH 1 SHELF LIFE PLOT FOR ASSAY

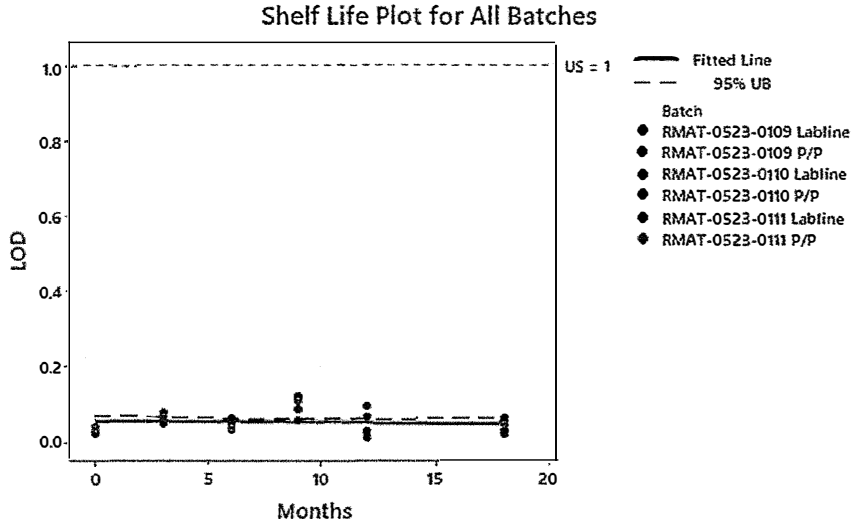
No shelf-life was able to be determined for Assay, as the mean response slope is not significantly different from zero using 95% confidence at the T=18-month time interval for all batches. However, the predicted shelf-life for Assay of lot RMAT-0523-0111 P/P was determined to be 39.8114 months at the T=18-month time interval. There is no impact to the product or currently assigned retest period of this material.





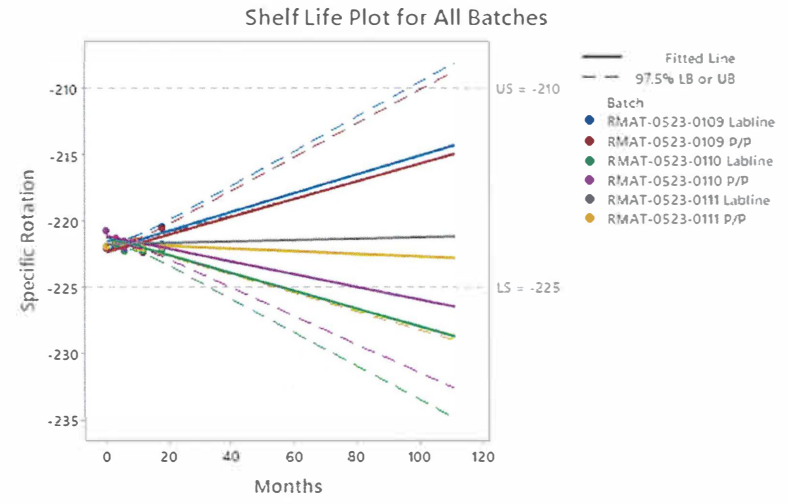
GRAPH 2 SHELF LIFE PLOT FOR CHLORIDE

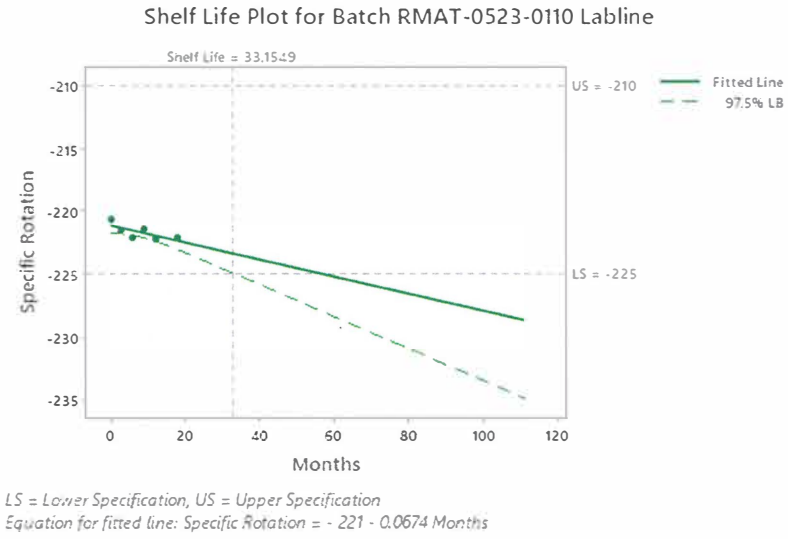
No shelf-life was able to be determined for Chloride, as the mean response slope is not significantly different from zero using 95% confidence at the T=18-month time interval for all batches. However, the predicted shelf-life for Chloride of lot RMAT-0523-0111 P/P was determined to be 65.5291 months at the T=18-month time interval. There is no impact to the product or currently assigned retest period of this material.



GRAPH 3 SHELF LIFE PLOT FOR 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 at the T=18-month time interval. There is no impact to the product or currently assigned retest period of this material.





GRAPH 4: SHELF LIFE PLOT FOR SPECIFIC ROTATION

No shelf-life was able to be determined for Specific Rotation, as the mean response slope is not significantly different from zero using 95% confidence at the T=18-month time interval for all batches. However, the predicted shelf-life for Specific Rotation was determined to be 33.1549 months at the T=18-month time interval for lot RMAT-0523-0110 Labline. 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-Cystine dihydrochloride, all data met the specifications set forth in the Stability Testing Program for lots 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. The long-term stability study data, along with the predicted shelf-life plots, supports a retest date of 30 months for L-Cystine Dihydrochloride.

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 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.

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