BIOSPECTRA
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L-CYSTINE DIHYDROCHLORIDE LONG-TERM STABILITY: 2018 VALIDATION LOTS

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the long-term stability study of L-Cystine dihydrochloride manufactured at BioSpectra's Bangor, PA facility. Samples were placed on the Stability Testing Program in May, and March of 2018 to fulfill the requirements of placing all validation batches manufactured on the Stability Testing Program. The real-time 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. Thirty-six (36) months of data have been 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 lot CY7202-001-0218-PV, CY7202-003-0518-PV and CY7202-004-0518-PV that completed thirty-six (36) months of long-term stability in May 2021. The study includes the analyses listed in Table 1 below.

Table 1: Stability Specifications

Analyses	Specification
Appearance and Color	White to Slightly Yellow Crystalline Powder
Assay (Dried Basis)	98.0 – 102.0%
Chloride	22.2 – 23.5%
Identification (IR)	Passes Test
Loss on Drying (105°C)	1.0% maximum
Solubility	Passes Test
Specific Rotation (Free Basis) @ 20°C	-225.0° to -210.0°

Results from all analyses are summarized in Tables 3 through 5 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 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 all product codes of L-Cystine dihydrochloride. The following product codes are commercially available:

- LCYS-4250
- LCYS-4350

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 Q1E

3. SAMPLE DESIGNATION:

3.1. Samples initially placed on the stability program consisted of three validation lots of L-Cystine dihydrochloride. Stability samples from these batches were put into a P/P packaging configuration. The samples were packaged in accordance with Stability Inventory, BSI-SOP-0146. Reference Table 2 for packaging configuration and description. The type of packaging utilized in this stability study was based on BioSpectra's packaging configuration offered to the customer.

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 poly pail and sealed.

4. STORAGE:

4.1. The packaging and storage requirements for L-Cystine dihydrochloride are to be in tightly-closed containers stored in a dry and well-ventilated place. For this study, the samples were stored in the Zone M warehouse from March 2018 until September 25, 2019. Storage conditions were continuously monitored and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (15-30°C until Q3 of 2018 when it was changed to 10-40°C), humidity (monitor) and Mean Kinetic Temperature (Monitor). The maximum temperature of the warehouse during the stability study was 33.67°C, the minimum temperature of the warehouse was 12.25°C, the average temperature was 23.59°C, the average mean kinetic temperature was 23.68°C and the average humidity was 37.8%. On September 28, 2019 all stability samples were moved from the Zone M Warehouse to the long-term stability chamber, H03SC01, at the Bangor, PA facility where they remained until May 2021. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25°C ±2), Mean Kinetic Temperature (≥25°C) and relative humidity (60% ±5). For this period, the maximum temperature recorded was 27.80°C, the minimum temperature was 21.75°C, the average temperature was 25.45°C, and the Average Mean Kinetic Temperature was 25.45°C. The maximum humidity was 68.8%, minimum humidity was 30.3% and the average humidity for this period was 61.7%. Section 5 will include any excursions from these conditions that resulted in an investigation.

5. INVESTIGATIONS:

5.1. BDI18-44: Contaminants were found within all three validation batches during laboratory packaging for outside testing. 100% inspections were performed on all three batches by manufacturing, and contaminants were isolated and analyzed. All three lots meet the requirements for finished good analysis.
5.2. BDI18-52: Between the dates of 7/3/18 through 8/7/18 the temperature in the Zone M Warehouse reached temperatures above 30°C with a high of 31.45°C on 7/3/18. Stability samples were pulled and tested at the next time point and all results were within specifications.

5.3. BDI18-92: Various days between 8/24/18 through 11/8/18 were not able to be downloaded from the data loggers. There were no temperature excursions out of the applicable specification between the dates. The root cause was determined to be due to the loggers being restarted, erasing the data prior to ensuring all data had been properly downloaded.

5.4. BDI18-97: MadgeTech data loggers located in the Zone J and M warehouse were not replaced before the calibration due date of 10/4/18. There were no temperature excursions during that period and all the data loggers were replaced on 11/15/18. All data loggers were found to be in tolerance for temperature.

5.5. BLI19-13: A failing UATR result was obtained for CY7202-003-0518-PV T=12 stability sample. It was concluded that the UATR was not functioning to a suitable standard. PerkinElmer was contacted and the instrument was removed from use.

5.6. BDI19-24: MadgeTech data logger S/N P57567 located in the Zone M warehouse and due for calibration on 3/23/19 was not removed until 3/27/19. There was no impact on the stability samples as this was one of fourteen loggers recording data in the Zone M warehouse from 3/23/19 until 3/27/19.

5.7. BLI19-46: An OOS result was obtained for CY7202-003-0518-PV T=18 solubility. The specification states the sample solution should be clear and colorless and comparable to the color and turbidity of water, visually. The sample solution was slightly yellow. It was concluded that the yellow color present in the solubility test is derived from the white to slightly yellow color allowed by the appearance and color analysis. BCC19-57 was issued to align the Appearance requirements with the Solubility requirements.

5.8. BDI19-77: Planned discrepancy for four MadgeTech loggers located in the Zone M Warehouse that could not be replaced before the due date of 7/3/19. The loggers were replaced upon receipt on 7/10/19 and the temperature and humidity assessment was completed.

5.9. BCC19-57: This change control was issued to revise the test methods after discovering that the critical quality attributes did not align between the way the solubility test was written and the explicitly stated color specifications as defined in appearance and color tests. Solubility test acceptance criteria now reflects the same attributes that are clearly defined by the specification.

5.10. BDI23-78: A temperature and humidity monitoring assessment was not completed and reviewed for the long-term stability chamber for December 2019. The root cause was employee oversight. There was no impact as the data was available and the assessment was completed and showed no deviations.

6. LOT EVALUATION:

Table 3: CY7202-001-0218-PV P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Appearance and Color	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder
Assay	98.0 – 102.0%	99.74%	99.73%	100.41%	99.77%	99.88%	100.08%	99.90%	98.58%
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Chloride	22.2 – 23.5%	22.58%	22.58%	22.73%	22.58%	22.61%	22.65%	22.61%	22.31%
Loss on Drying (105°C)	1.0% max	0.1256%	0.1002%	< 0.0300%	0.0268%	0.0252%	0.0399%	0.0316%	0.0291%
Solubility	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Specific Rotation (Free Basis) @ 20°C	-225.0° - -210.0°	-222.01°	-221.68°	-222.68°	-222.03°	-221.89°	-222.29°	-222.79°	-222.63°

Table 4: CY7202-003-0518-PV P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Appearance and Color	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White Crystalline Powder
Assay	98.0 – 102.0%	99.74%	99.92%	99.65%	99.98%	100.18%	99.87%	99.46%	99.72%
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Chloride	22.2 – 23.5%	22.58%	22.62%	22.56%	22.63%	22.68%	22.61%	22.51%	22.57%
Loss on Drying (105°C)	1.0% max	0.1024%	0.1129%	0.1002%	0.1106%	0.1326%	0.1084%	0.1765%	0.1327%
Solubility	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Specific Rotation (Free Basis) @ 20°C	-225.0° - -210.0°	-221.54°	-220.95°	-221.07°	-221.41°	-222.12°	-222.04°	-221.90°	-221.95°

Table 5: CY7202-004-0518-PV P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Appearance and Color	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White to Slightly Yellow Crystalline Powder	White Powder	White Powder
Assay	98.0 – 102.0%	99.74%	100.09%	99.86%	99.74%	99.85%	99.89%	99.90%	99.94%
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Chloride	22.2 – 23.5%	22.58%	22.66%	22.60%	22.58%	22.60%	22.61%	22.62%	22.62%
Loss on Drying (105°C)	1.0% max	0.0571%	0.1171%	0.0776%	0.0758%	0.0774%	0.0732%	0.0819%	0.0616%
Solubility	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Specific Rotation (Free Basis) @ 20°C	-225.0° - -210.0°	-221.33°	-221.61°	-220.57°	-221.47°	-222.02°	-221.98°	-221.67	-221.04°

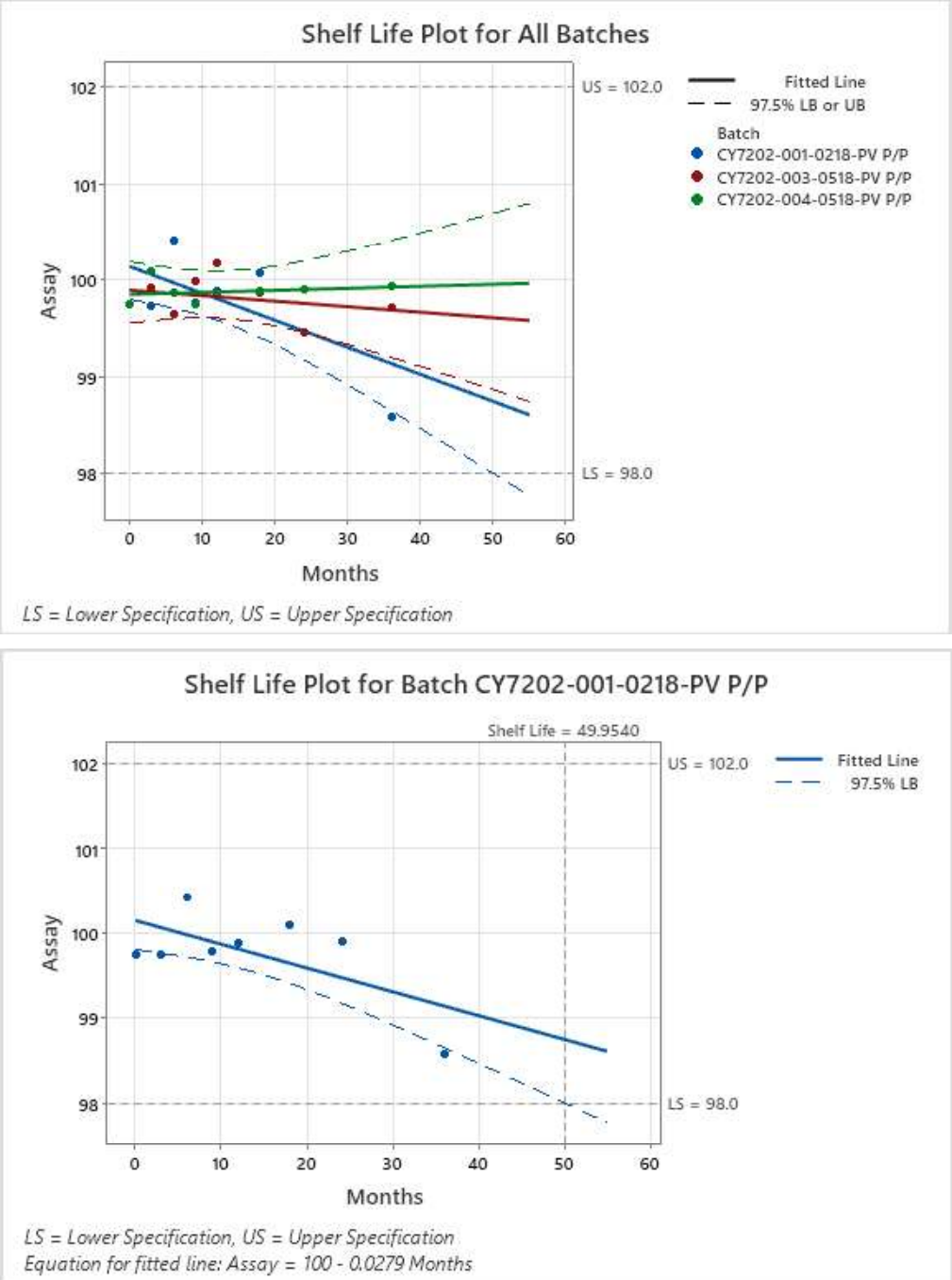
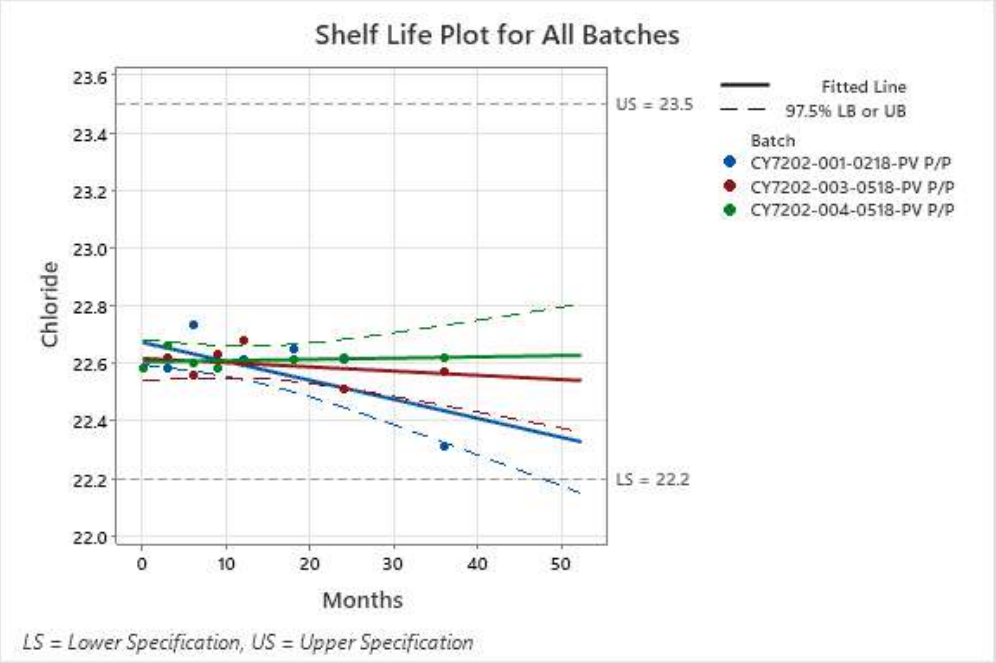


Figure 1: Graph Shelf Life Plot for Assay

The predicted shelf-life for Assay was determined to be 49.9540 months as of the T=36-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.



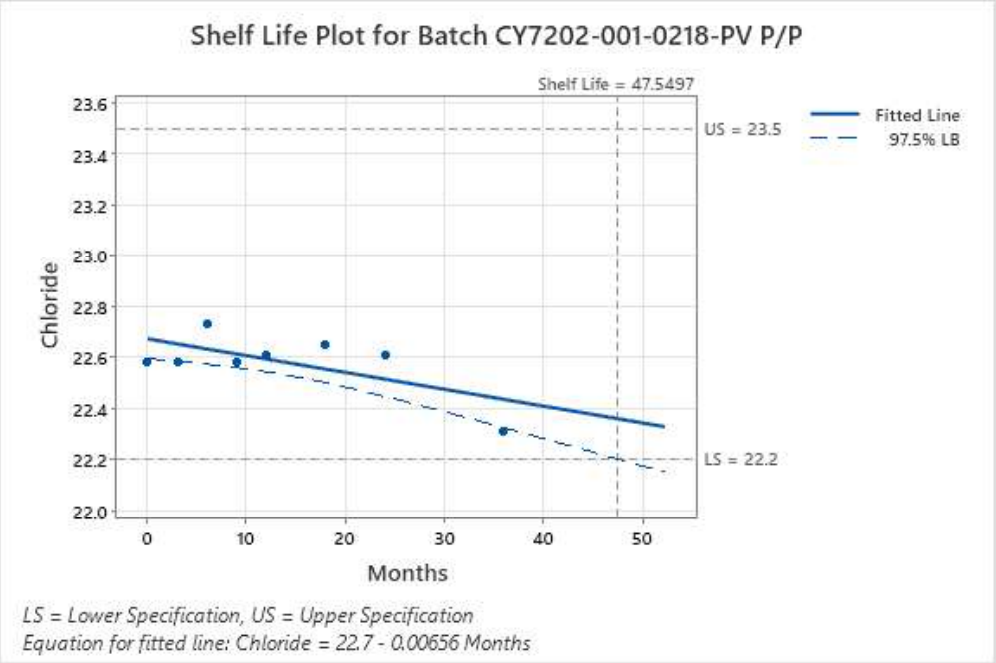


Figure 2: Graph Shelf Life Lot for Chloride

The predicted shelf-life for Chloride was determined to be 47.5497 months as of the T=36-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.

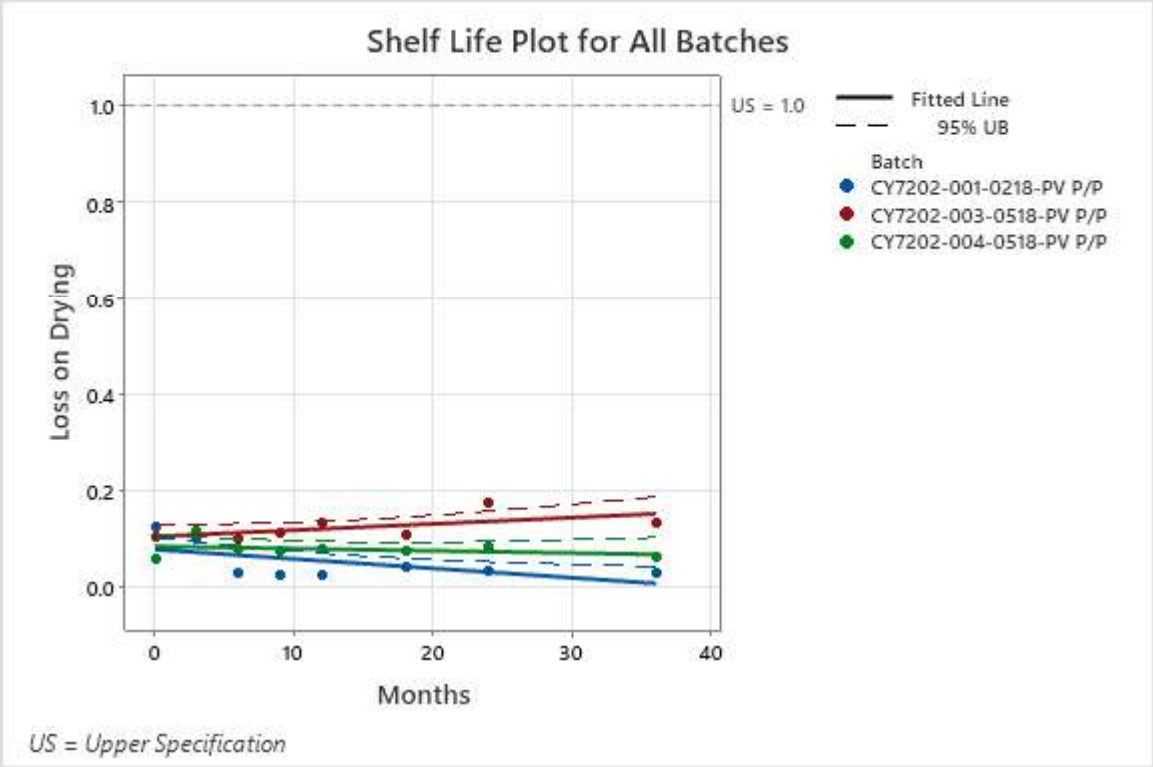


Figure 3: Graph Shelf Life Plot for Loss on Drying

No 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 the lots.

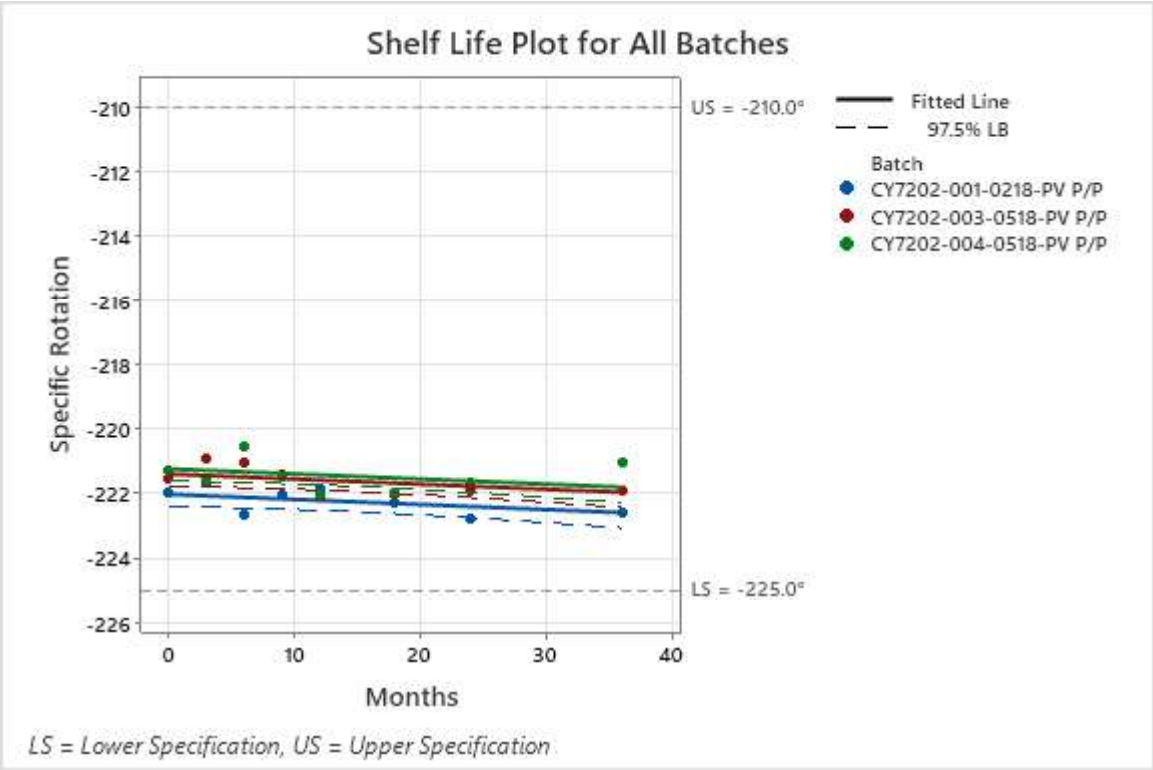


Figure 4:Graph Shelf Life Plot for Specific Rotation

No shelf life is able to be determined for Specific Rotation, as the mean response slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of the lots.

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 the lots stored at the recommended long-term condition. In accordance with ICH Q1, 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 long-term stability study data, along with the predicted shelf-life plots, supports a retest date of 24 months and expiration date of 36 months for L-Cystine Dihydrochloride manufactured at BioSpectra in the Bangor, PA facility.

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.