

L-CYSTINE diHCl  
ACCELERATED STABILITY REPORT 2018

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## 1. OVERVIEW:

The purpose of this Report is to analyze the data obtained from the Accelerated Stability of L-Cystine Dihydrochloride manufactured in Process Room N02 of BioSpectra's Bangor, PA facility. Samples were placed on the Stability Testing Program in March and May of 2018 consisting of three Process Validation batches. The Accelerated Stability Program consists of testing every month for six months, notated as T<sub>0</sub>, T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>, T<sub>4</sub>, T<sub>5</sub>, and T<sub>6</sub>. Analysis has been conducted for a total of six months for the each of the process validation lots 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 also aid in a re-evaluation of the retest date for the finished good product.

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 data can be found in the L-Cystine diHCl Accelerated Stability Program binder.

## 2. REFERENCES:

- 2.1. Current USP
- 2.2. ICH Q1
- 2.3. [Stability Testing Program](#)
- 2.4. [L-Cystine diHCl Bio Contract Grade Stability Indicating Profile Report](#)

## 3. DEFINITIONS:

- 3.1. CL: Control Limit, the average
- 3.2. UCL: Upper control limit, 3 sigma above the CL
- 3.3. LCL: Lower control limit, 3 sigma below the CL
- 3.4. OOL: Point(s) that fall outside the UCL or LCL
- 3.5. OOT: Out Of Trend, this means that the material still meets control limits but was not in trend with the rest of the material.
- 3.6. OOS: Out of Specification.
- 3.7. T: Time in months.

## 4. SAMPLE DESIGNATION:

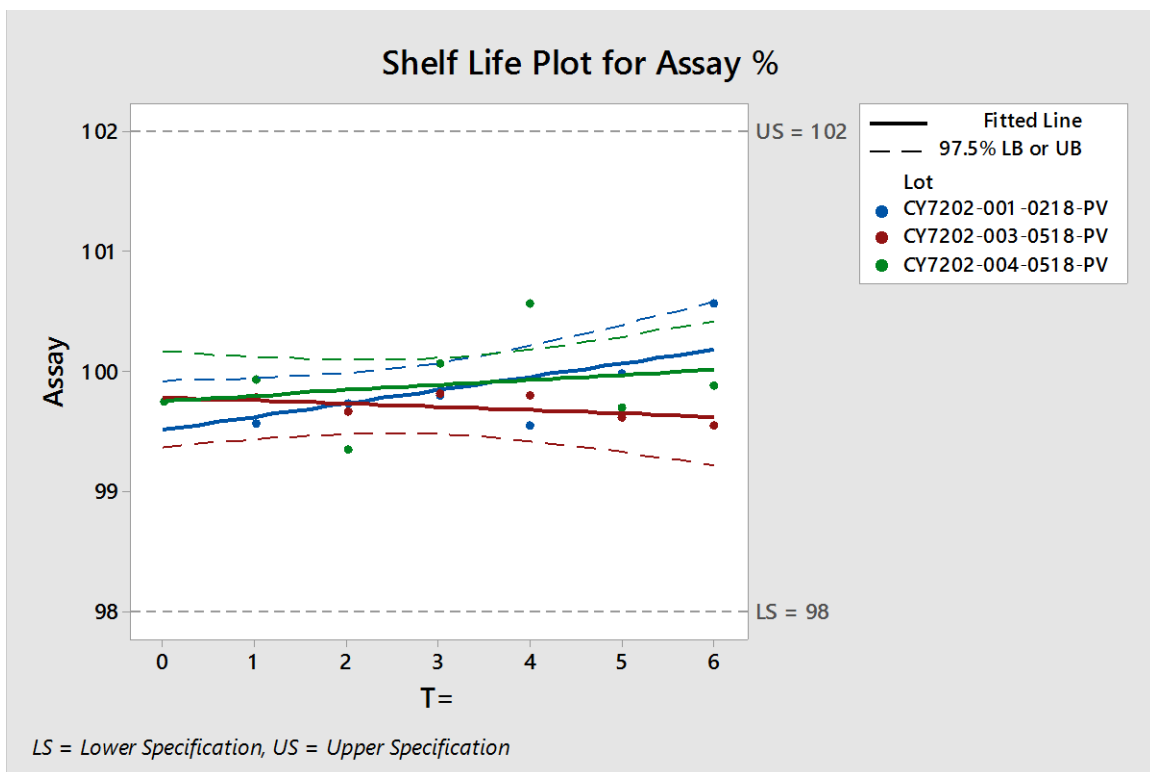
Samples placed on the Stability Testing Program consisted of three L-Cystine diHCl Bio Contract Grade Process Validation batches. Stability samples from each of the batches were put into a round poly pail (with a green lid) lined with a poly liner (P/P), with the liner being goose-neck tied closed. These

batches were placed on stability in the Accelerated Stability Chamber located in the BioSpectra Bangor, PA facility. The type of packaging utilized in the stability study was based on BioSpectra packaging.

## 5. STORAGE:

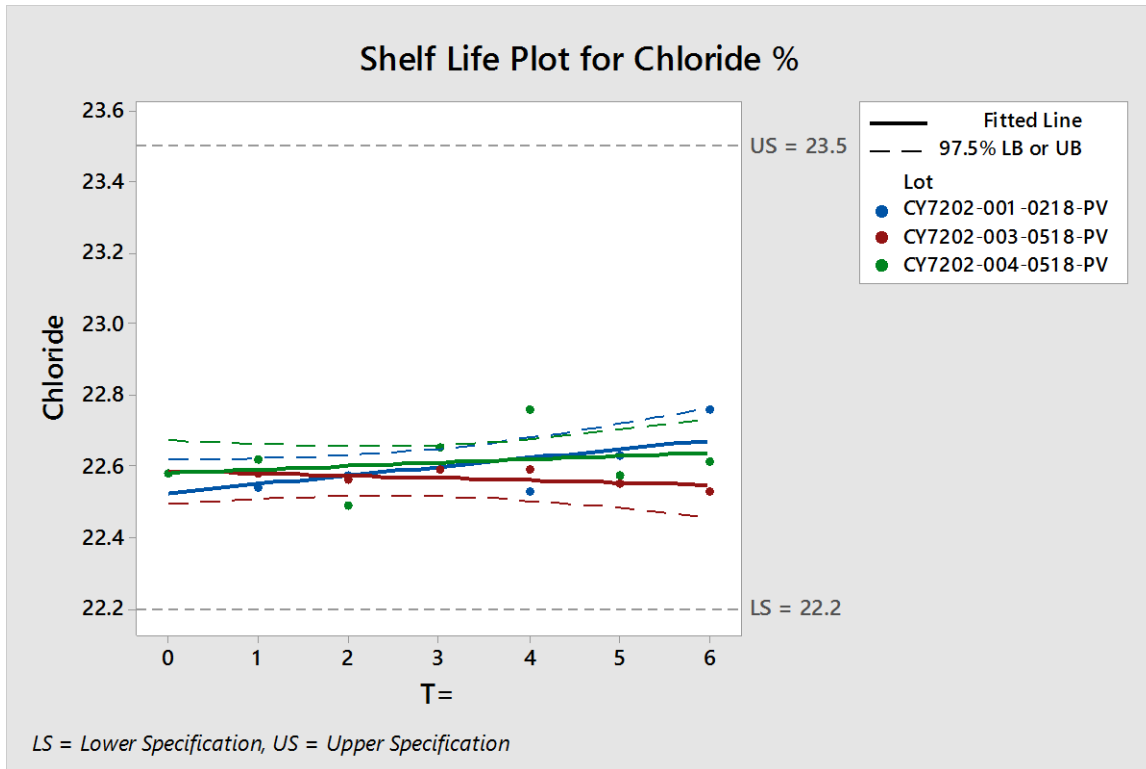
Storage conditions have been continuously monitored and recorded. The temperature and humidity was monitored continuously utilizing a chart recorder and MadgeTech data loggers located on the Darwin Accelerated Stability Chamber. The temperature is set to 40°C + 2°C and 75% Relative Humidity + 5% Relative Humidity. There was one discrepancy associated with the storage of CY7202-001-0218-PV as it was delayed being placed on accelerated stability due to lack of available pails, this is detailed in BDI18-22.

## 6. LOT EVALUATION:



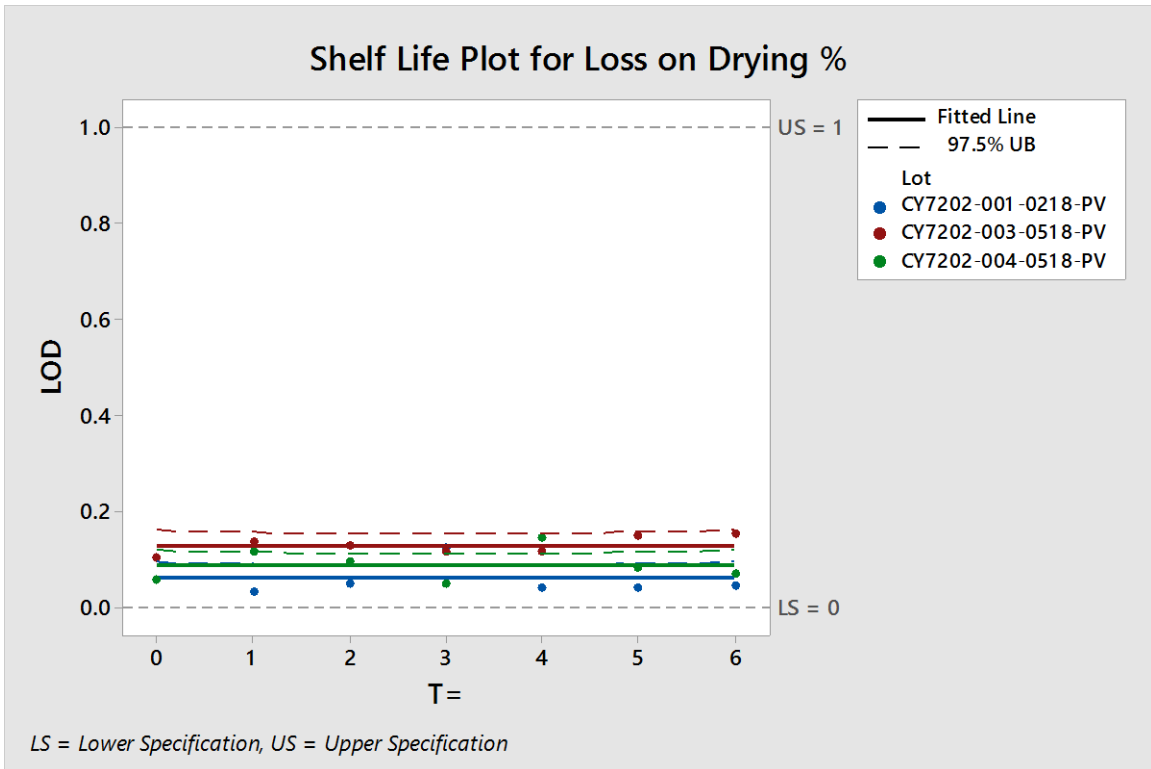
**GRAPH 1 – ASSAY %**

Results for assay showed no predictable shelf life, as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from this analysis in the 6 month analysis time frame.



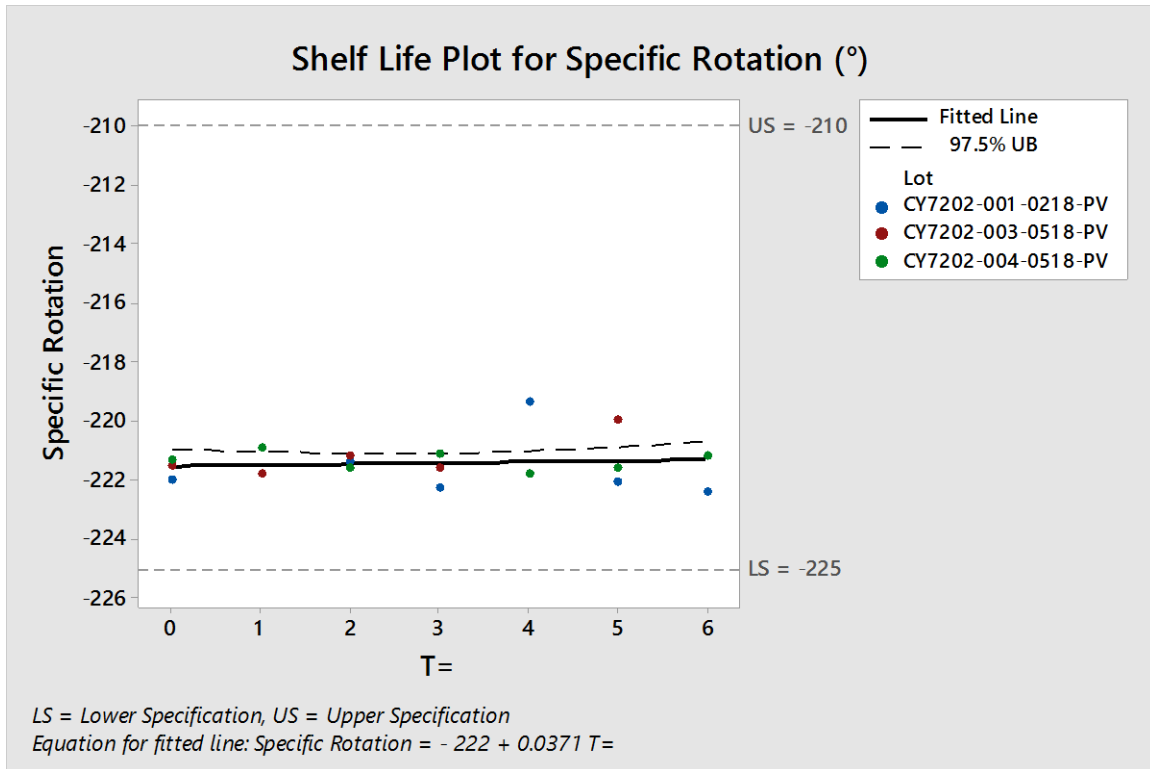
**GRAPH 2 – CHLORIDE %**

Results for chloride showed no predictable shelf life, as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from this analysis in the 6 month analysis time frame.



**GRAPH 3 – LOSS ON DRYING %**

Results for loss on drying showed no predictable shelf life, as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from this analysis in the 6 month analysis time frame.



**GRAPH 4 – SPECIFIC ROTATION (°)**

Results for specific rotation showed no predictable shelf life, as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from this analysis in the 6 month analysis time frame.

## 7. CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. The Accelerated Stability data shows little to no change over time and little to no variation. Based on the successful completion of the stability study under accelerated conditions a proposed retest date may be assigned to L-Cystine Dihydrochloride. In accordance with ICH Q1E, the retest date may be proposed for up to 2X, where X is the period covered by long term data, but not exceeding X + 12 months.

## 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.



## L-Cystine diHCl Long Term Stability Study through T=18 Testing Interval

**Objective:** This stability study is being performed to evaluate product quality attributes over time in the appropriate storage conditions to facilitate the assignment of appropriate retest or expiration dates.

**Packaging used for stability study:** P/P

**Selection of Batches:** Process Validation Batches

**Storage Conditions:** Zone M Warehouse. There are currently no storage conditions for L-Cystine dihydrochloride, storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (10-40°C) and humidity (monitor).

**Sampling Plan:** Sampling intervals will be (in months): zero, three, six, nine, twelve, eighteen, twenty-four and thirty-six. The container(s) will be pulled at each testing interval and the material is then tested with appropriate test methods.

**Stability Indicating Test Methods:** The following tests are performed:

Test	Specification
Appearance and Color	White to Slightly Yellow Crystalline Powder
<sup>1</sup> Assay (dried basis)	98.0-102.0%
<sup>1</sup> Chloride	22.2-23.5%
Identity (IR)	Passes Test
<sup>1</sup> Loss on Drying (LOD)	1.0% max.
Solubility	Passes Test
<sup>1</sup> Specific Rotation (Free Basis) at 20°C	-225.0 to -210.0°

**Data:** <sup>1</sup> The following data sets are the quantitative results used to determine the new proposed retest date.

Data Set 1: First Process Validation lot CY7202-001-0218-PV has been tested for T=0 through T=18 month testing.

Data Set 2: Second Process Validation lot CY7202-003-0518-PV has been tested for T=0 though T=18 month testing.

Data Set 3: Third Process Validation lot CY7202-004-0518-PV has been tested for T=0 through T=18 month testing.

**Data Set 1:****Batch: CY7202-001-0218-PV****Package: P/P**

<b>Test</b>	<b>Specification</b> Testing Method: DCN 17-002319	T=0 Results	T=3 Month Results	T=6 Month Results	T=9 Month Results	T=12 Month Results	T=18 Month Results
Assay (dried basis)	98.0-102.0%	99.74	99.73	100.41	99.77	99.88	100.08
Chloride	22.2-23.5%	22.58	22.58	22.73	22.58	22.61	22.65
Loss on Drying	1.0% max	0.1256	0.1002	<0.0300	0.0268	0.0252	0.0399
Specific Rotation (Free Basis) @20°C	-225.0-210.0°	-222.0	-221.7	-222.7	-222.0	-221.9	-222.29

**Data Set 2:****Batch: CY7202-003-0518-PV****Package: P/P**

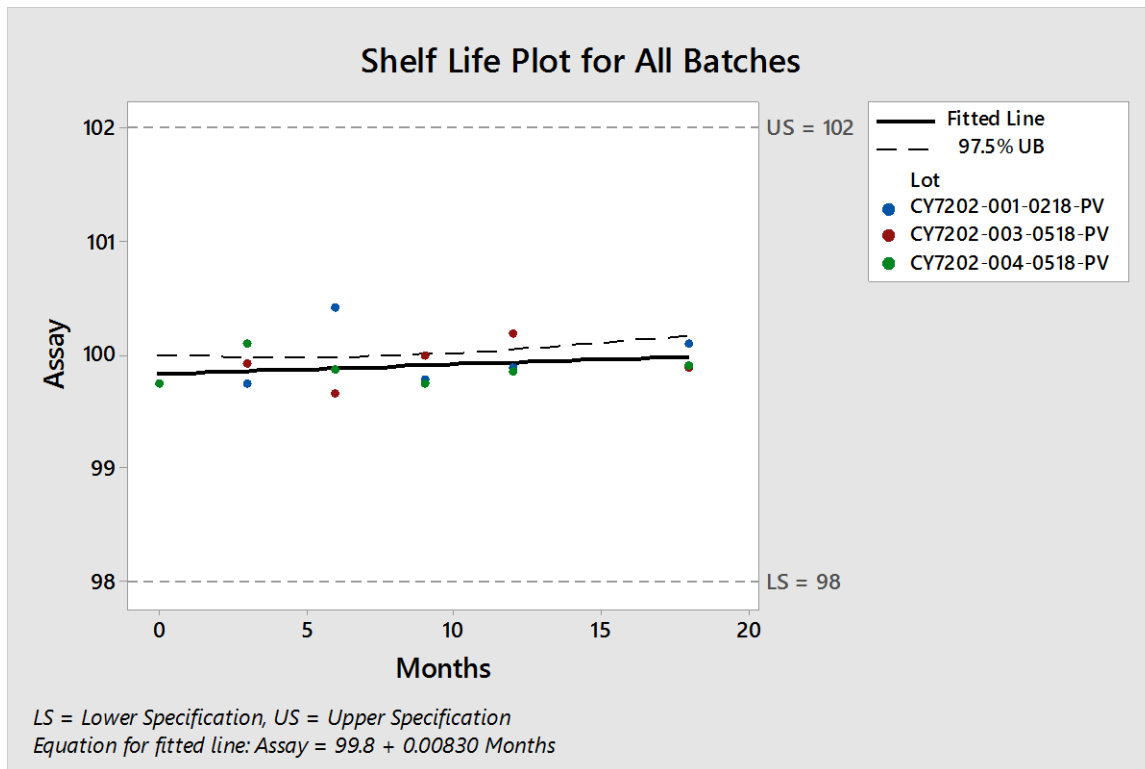
<b>Test</b>	<b>Specification</b> Testing Method: DCN 17-002319	T=0 Results	T=3 Month Results	T=6 Month Results	T=9 Month Results	T=12 Month Results	T=18 Month Results
Assay (dried basis)	98.0-102.0%	99.74	99.92	99.65	99.98	100.18	99.87
Chloride	22.2-23.5%	22.58	22.62	22.56	22.63	22.68	22.61
Loss on Drying	1.0% max	0.1024	0.1129	0.1002	0.1106	0.1326	0.1084
Specific Rotation (Free Basis) @20°C	-225.0-210.0°	-221.5	-221.0	-221.1	-221.4	-222.1	-222.04

**Data Set 3:**

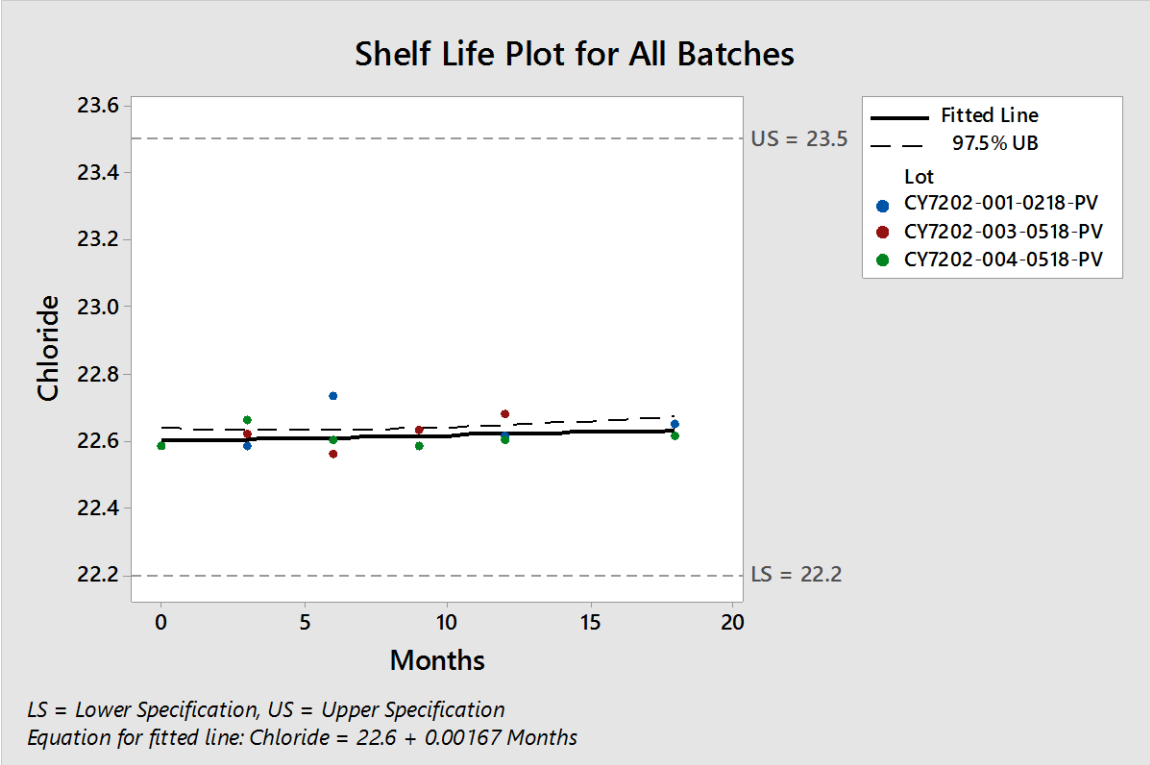
**Batch: CY7202-004-0518-PV**

**Package: P/P**

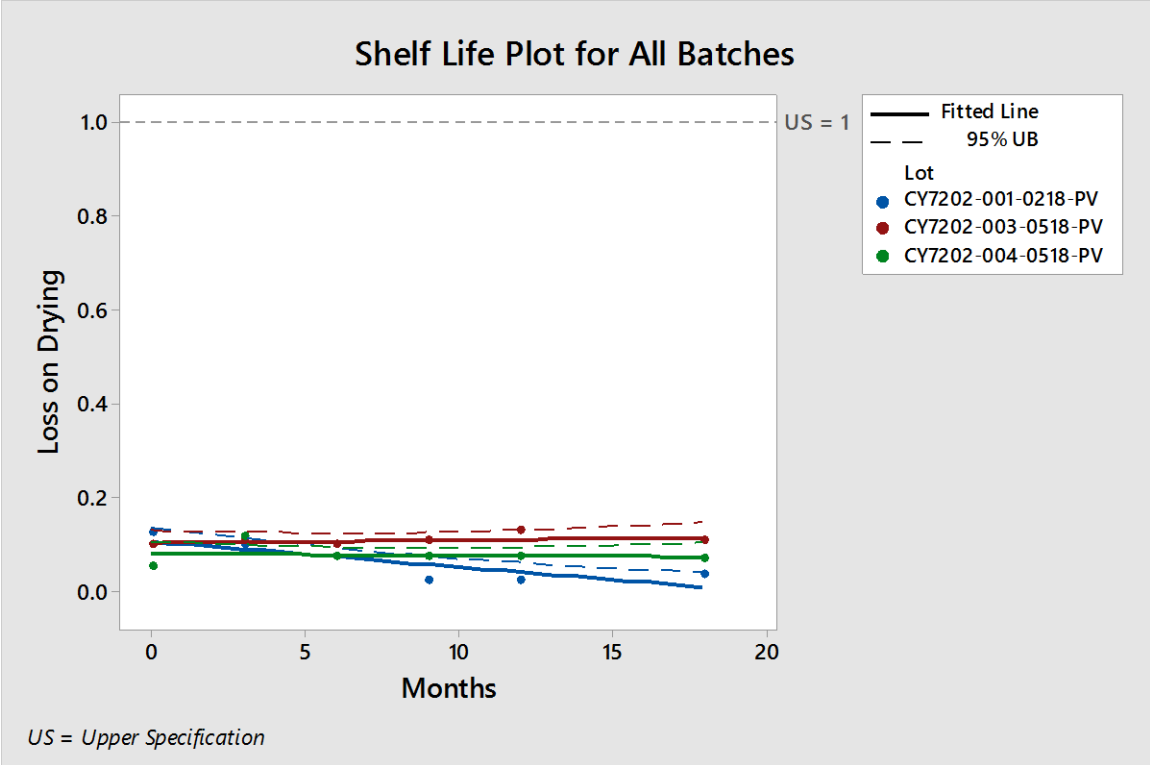
Test	Specification Testing Method: DCN 17-002319	T=0 Results	T=3 Month Results	T=6 Month Results	T=9 Month Results	T=12 Month Results	T=18 Month Results
Assay (dried basis)	98.0-102.0%	99.74	100.09	99.86	99.74	99.85	99.89
Chloride	22.2-23.5%	22.58	22.66	22.60	22.58	22.60	22.61
Loss on Drying	1.0% max	0.0571	0.1171	0.0776	0.0758	0.0774	0.0732
Specific Rotation (Free Basis) @20°C	-225.0-210.0°	-221.3	-221.6	-220.6	-221.5	-222.0	-221.98



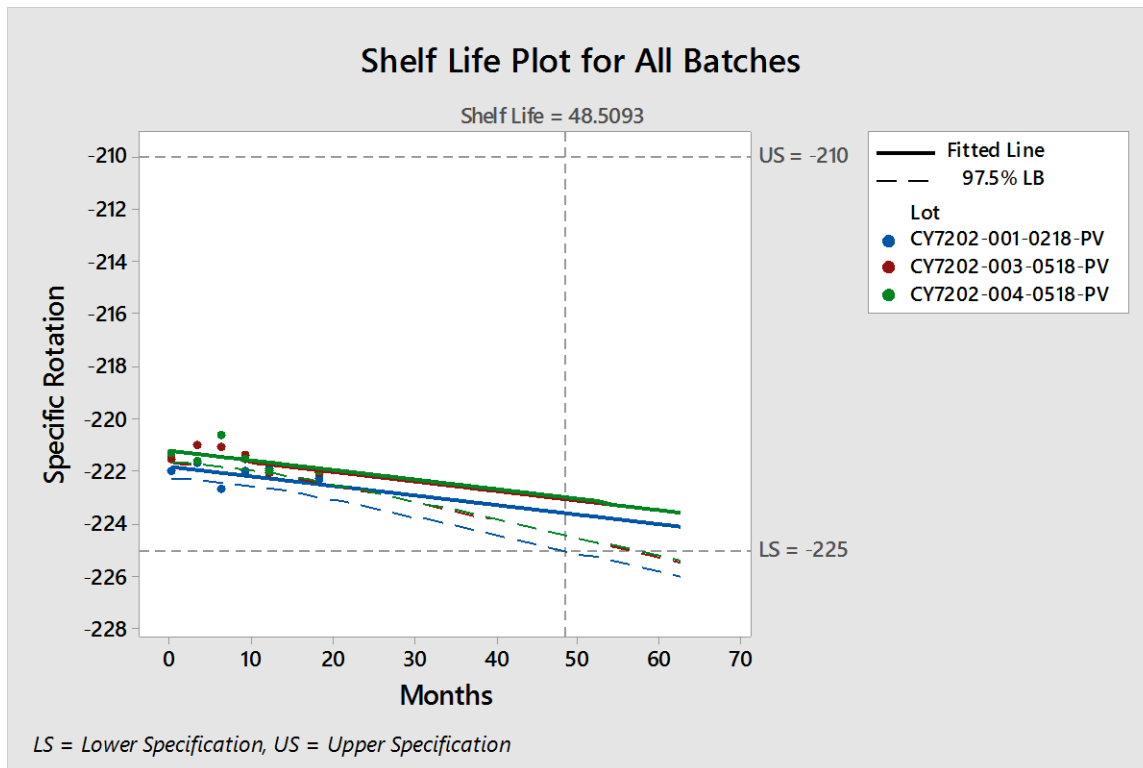
The mean response slope is not significantly different from zero. No shelf life estimate is available for Assay.



The mean response slope is not significantly different from zero. No shelf life estimate is available for Chloride.



The mean response slope is not significantly different from zero. No shelf life estimate is available for Loss on Drying.



Overall proposed shelf life for Specific Rotation is 48 months.

**Conclusion:** Based on the stability studies performed, L-Cystine diHCl packaged in P/P has shown to be stable for a minimum of 18 months. Even though the Specific Rotation proposed shelf life well exceeds the current and new recommended retest date, the decision to extend the retest date to 30 months is based on the ICH guidelines. The recommended retest interval is 30 months. Further evaluation of the shelf life will be performed once the stability study is complete.