BIOSPECTRA
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CYSTEAMINE HCl (2-MEA) 2021 VALIDATION LOTS REAL TIME STABILITY REPORT:

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1. OVERVIEW:

The purpose of this report is to analyze and conclude on the data obtained from the real-time stability study of Cysteamine HCl (2-MEA). 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 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.

This Real Time Stability analysis will assess the stability of 2-MEA validation lots CSMH-0121-00003-PV, CSMH-0121-00006-PV, and CSMH-0121-00007-PV that completed twenty-four (24) months of real-time stability in April 2023 and is scheduled to finish at sixty (60) months in April 2026. This study includes the following analyses: Assay (HPLC Weight %), HPLC Minor Component 1 (Area %), Purity (HPLC Area %), Purity (Cysteamine (HPLC)), Appearance and Color, Chloride, Identification (IR), and Loss on Drying. Results from all analyses are summarized in Table 2A through 2C. 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 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. 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 2-MEA. The following Product Codes are commercially available.

- CSMH-3250

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 Q1

3. SAMPLE DESIGNATION:

3.1. Samples initially placed on the stability program consisted of three lots of 2-MEA. Stability samples from these lots were put into a 2P/P packaging configuration with a desiccant. The samples were packaged in accordance with the Stability Inventory SOP. Reference Table 1, below, for packaging configuration and description. The type of packaging utilized in this stability study was based on BioSpectra packaging offered to the customer.

TABLE 1: PACKAGING DETAILS	
Packaging Configuration	**Packaging Description**
2P/P with a desiccant and nitrogen purge of each poly liner	Samples are packaged into small polyethylene bags and goose neck sealed with a zip tie. All individual samples are then placed into a larger polyethylene bag, goose neck sealed with a zip tie, and then are placed into a poly drum. A desiccant pack is added between the small polyethylene bags and the larger polyethylene bag and each poly liner is purged with nitrogen before goose neck sealing.

4. STORAGE:

4.1. The Packaging and Storage requirements for 2-MEA are to be in tightly closed container, under nitrogen or argon blanket at 2-8°C, and stored in a dry, well-ventilated area away from incompatible substances. Samples were stored in refrigerated storage units A01RC02 and A01RC04 at the Bangor, PA facility. Storage conditions have been continuously measured and recorded utilizing Tempmate data loggers with regulated conditions for temperature (2-8°C). For the time period of April 2021 to May 2021, the samples were located in refrigeration unit A01RC02. The maximum temperature recorded was 25.7°C, the minimum temperature was 3.3°C, the average temperature was 8.8°C, and the Mean Kinetic Temperature was 11.2°C. In May 2021, the samples were moved to refrigeration unit A01RC04 due to temporary operating instruction BTOI21-84, which was a result of discrepancy investigation, BDI21-259. For this time period, the maximum temperature recorded was 29.8°C, the minimum temperature was -5.6°C, the average temperature was 5.8°C, and the Mean Kinetic Temperature was 5.9°C. Section 5 will include any excursions from the required temperature conditions.

5. INVESTIGATIONS:

5.1. BDI21-259: This discrepancy investigation documents several temperature excursions between the dates of 02/26/21 and 06/18/21 for refrigeration unit A01RC02. This investigation resulted in moving the stability samples from refrigeration unit A01RC02 to refrigeration unit A01RC04. This move was documented in Temporary Operating Instruction BTOI21-84. It was determined that there was no impact on the samples.

5.2. BLI22-04: This laboratory investigation covered the qualification and implementation of a new quality standard used to test for assay of T=9 samples from lots CSMH-0121-00003-PV, CSMH-0121-00006-PV, and CSMH-0121-00007-PV after obtaining OOS assay results.

5.3. BDI22-26: Sample CSMH-0121-00003-PV 2P/P with a Desiccant T=9 Real Time did not have a valid Appearance and Color test completed as per test method BSI-ATM-0055 v. 2.2 by the 10-business day due date outlined in the Stability Test Program SOP (BSI-SOP-0136). This led to the investigation and resulting CAPA of a training for analysts on completing testing or notifying management of incompletion. The sample testing was performed late, and passed specification.

5.4. BDI22-40: Sample CSMH-0121-00007-PV 2P/P with a Desiccant T=9 Real Time did not have a valid Chloride test completed as per test method BSI-ATM-0055 v. 2.2 by the 10-business day due date outlined in the Stability Test Program SOP (BSI-SOP-0136). This led to the investigation and resulting CAPA to not issue discrepancies due to instrument maintenance, repair, troubleshooting, or OOS checklist. The sample testing was performed late, and passed specification.

5.5. BDI22-86: This discrepancy investigation documents several OOS temperature readings in A01RC04. These temperature excursions are described as brief, lasting approximately 20 minutes.

5.6. BLI22-19: Sample CSMH-0121-00003-PV 2P/P with a Desiccant T=12 Real Time had an OOS result for both Assay and Appearance and Color testing. The investigation concluded with a passing result for Assay, which was the cumulative result of 3x retests performed by 2 separate analysts with a reportable result of 98.5%. For Appearance and Color, the initial T=12 sample failed with a greenish-blue tint. A T=Extra sample was pulled and 3x retests were performed by 2 separate analysts. This initial testing failed as well, which resulted in further comparative analysis for the qualitative Appearance and Color testing. Two different color wheels were prepared to compare the CSMH-0121-00003-PV 2P/P with a Desiccant T=Extra sample with finished goods retains and the T=12 Stability samples from all three lots of 2-MEA in this study along with the Raw Material lot used to make all three lots. The final reportable conclusion was that the CSMH-0121-00003-PV 2P/P with a Desiccant T=12 sample had a contaminate present that distorted color and was not valid for use for Appearance and Color testing. The CSMH-0121-00003-PV 2P/P with Desiccant T=Extra sample was considered equivalent to the other 2-MEA samples, and would be considered passing for Appearance and Color for the T=12-time interval.

5.7. BDI23-09: This discrepancy covers one of the temperature data loggers being missing for the time period of 06/23/22 to 09/14/22, and not being able to retrieve data for that area of Cold Storage Container A01RC04. There were also out of specification (OOS) results obtained that could not be explained by container entrances. The root cause was determined to be the style of temperature data logger being used is easily knocked down and could possibly be removed on pallets stored in the unit. The OOS results were determined to be from entry into the unit that was not recorded in the log book. It was determined that there was no impact on samples stored in the unit.

5.8. BDI23-17: This discrepancy covers out of specification (OOS) temperatures for Cold Storage Container A01RC04 for the period of 03/07/22 to 06/23/22 that are not explained by container entrances. The root cause was determined to be entry into this storage unit that was not logged into the book, as the OOS results were recorded on the temperature data loggers closest to the door. It was determined that there was no impact on samples stored in this unit.

5.9. BDI23-18: This discrepancy covers out of specification (OOS) temperatures for Cold Storage Container A01RC04 for the period of 09/14/22 to 12/21/22 that are not explained by container entrances. The root cause was determined to be entry into this storage unit that was not logged into the book. It was determined that there was no impact on samples stored in this unit.

6. LOT EVALUATION:

TABLE 2A: RESULT OF REAL TIME STABILITY ANALYSES FOR CSMH-0121-00003-PV

Lot Number	Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
CSMH-0121-00003-PV	Assay (HPLC Weight %)	98.0 – 102.0%	100.0%	99.5%	100.2%	100.1%	98.5%	98.4%	99.1%
	HPLC Minor Component 1 (Area %)	Cystamine ≤ 2.0%	1.0%	1.0%	0.7%	0.9%	0.8%	0.8%	0.9%
	Purity (HPLC Area %)	≥ 98.0%	98.9%	99.0%	99.3%	99.1%	99.2%	99.2%	99.1%
	Purity (Cysteamine (HPLC))	≥ 92.0% Cysteamine	98.9%	99.0%	99.3%	99.1%	99.2%	99.2%	99.1%
	Purity (Cysteamine (HPLC))	≤ 8.0% Related Substances	1.1%	1.0%	0.7%	0.9%	0.8%	0.8%	0.9%
	[1]Appearance and Color	White or colorless crystals or powder, may contain lumps	WCP	WCP contains Lumps	WCP	WCP contains Lumps	WCCP contains Lumps	WCCP contains Lumps	WCCP contains Lumps
	Chloride	30.6 – 31.8%	31.3%	31.5%	30.8%	30.7%	30.9%	30.8%	31.0%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying	≤ 1.0%	0.4641%	0.1146%	0.1544%	0.2159%	0.1810%	0.1138%	0.1301%

[1]WCP = White Crystalline Powder; WCCP = White or Colorless Crystals of Powder

T=36: Scheduled to be pulled 04/23/24

T=48: Scheduled to be pulled 04/23/25

T=60: Scheduled to be pulled 04/23/26

TABLE 2B: RESULT OF REAL TIME STABILITY ANALYSES FOR CSMH-0121-00006-PV

Lot Number	Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
CSMH-0121-00006-PV	Assay (HPLC Weight %)	98.0 – 102.0%	100.5%	100.2%	100.7%	100.9%	98.3%	100.6%	99.5%
	HPLC Minor Component 1 (Area %)	Cystamine ≤ 2.0%	0.5%	0.6%	[2]<0.2%	0.9%	[2]<0.2%	[2]<0.2%	[2]<0.2%
	Purity (HPLC Area %)	≥ 98.0%	99.5%	99.4%	100.0%	99.1%	100.0%	100.0%	100.0%
	Purity (Cysteamine (HPLC))	≥ 92.0% Cysteamine	99.5%	99.4%	100.0%	99.1%	100.0%	100.0%	100.0%
	Purity (Cysteamine (HPLC))	≤ 8.0% Related Substances	0.5%	0.6%	[2]<0.2%	0.9	[2]<0.2%	[2]<0.2%	[2]<0.2%
	[1]Appearance and Color	White or colorless crystals or powder, may contain lumps	WCP	WCP contains Lumps	WCP	WCP contains Lumps	WCCP contains Lumps	WCCP contains Lumps	WCCP contains Lumps
	Chloride	30.6 – 31.8%	31.0%	30.7%	30.7%	30.7%	30.7%	30.9%	30.9%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying	≤ 1.0%	0.1563%	0.1516%	0.1116%	0.1693%	0.1483%	0.0713%	<0.0136%

[1]WCP = White Crystalline Powder; WCCP = White or Colorless Crystals of Powder

[2] Method LOQ is <0.2%. Result for HPLC Minor Component was <LOQ. Result will be reported as <LOQ.

T=36: Scheduled to be pulled 04/23/24

T=48: Scheduled to be pulled 04/23/25

T=60: Scheduled to be pulled 04/23/26

TABLE 2C: RESULT OF REAL TIME STABILITY ANALYSES FOR CSMH-0121-00007-PV

Lot Number	Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
CSMH-0121-00007-PV	Assay (HPLC Weight %)	98.0 – 102.0%	100.1%	100.0%	99.9%	99.9%	98.1%	99.6%	98.8%
	HPLC Minor Component 1 (Area %)	Cystamine ≤ 2.0%	1.2%	1.2%	1.1%	1.6%	1.2%	1.3%	1.3%
	Purity (HPLC Area %)	≥ 98.0%	98.8%	98.7%	98.9%	98.4%	98.8%	98.7%	98.7%
	Purity (Cysteamine (HPLC))	≥ 92.0% Cysteamine	98.8%	98.7%	98.9%	98.4%	98.8%	98.7%	98.7%
	Purity (Cysteamine (HPLC))	≤ 8.0% Related Substances	1.2%	1.3%	1.1%	1.6%	1.2%	1.3%	1.3%
	[1]Appearance and Color	White or colorless crystals or powder, may contain lumps	WCCP contains Lumps	WCP contains Lumps	WCP	WCP contains Lumps	WCCP contains Lumps	WCCP contains Lumps	WCCP contains Lumps
	Chloride	30.6 – 31.8%	31.1%	31.4%	31.0%	30.7%	30.7%	31.0%	31.1%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying	≤ 1.0%	0.0795%	0.0209%	[2] 0.0117%	0.1212%	0.0848%	0.0761%	0.1888%

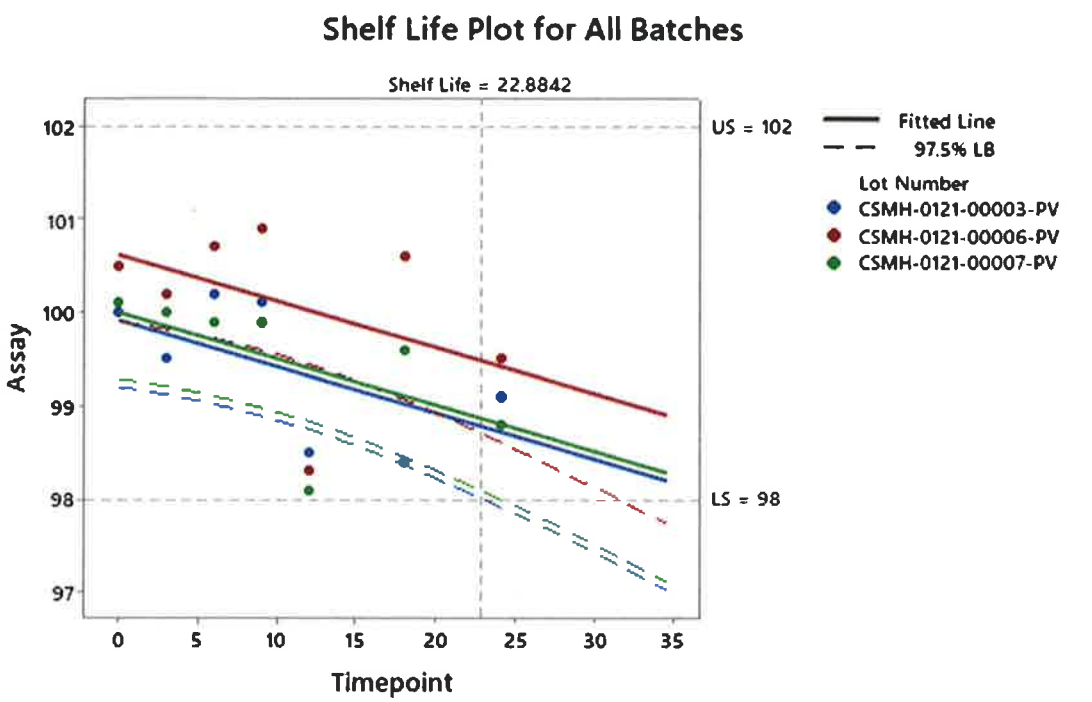
[1]WCP = White Crystalline Powder; WCCP = White or Colorless Crystals of Powder

[2]Sample gained mass after heating resulting in calculated LOD as (balance error/sample mass) * 100

T=36: Scheduled to be pulled 04/28/24

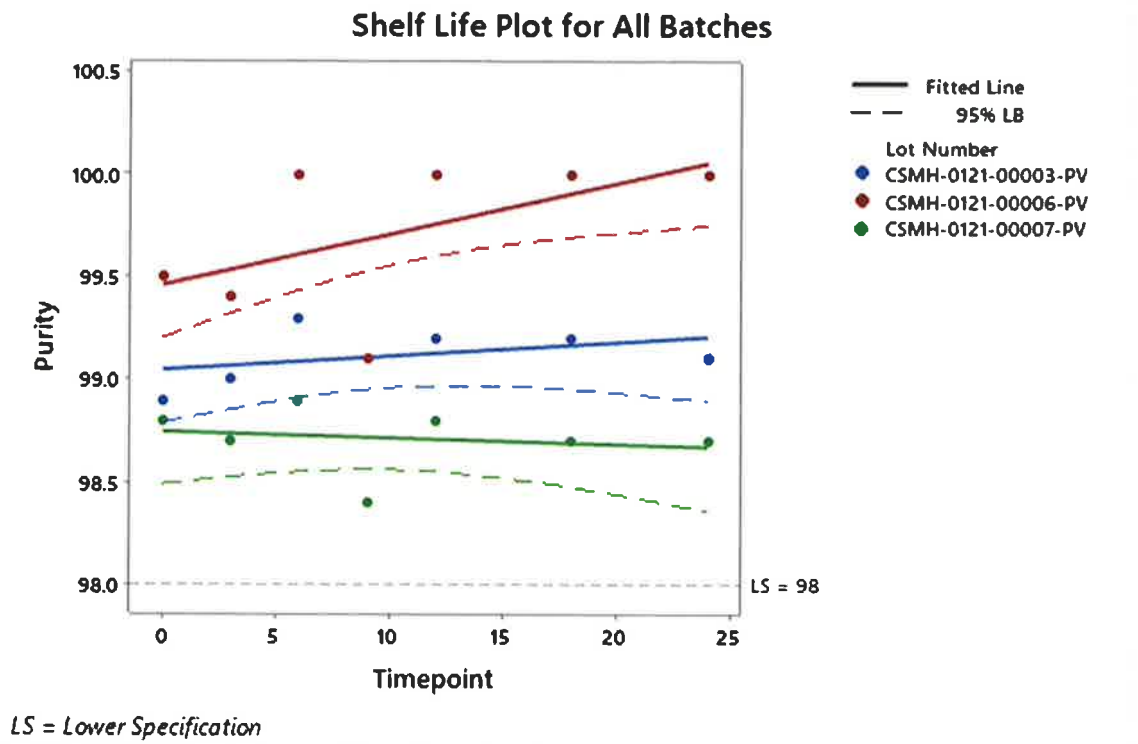
T=48: Scheduled to be pulled 04/28/25

T=60: Scheduled to be pulled 04/28/26



GRAPH 1: ASSAY

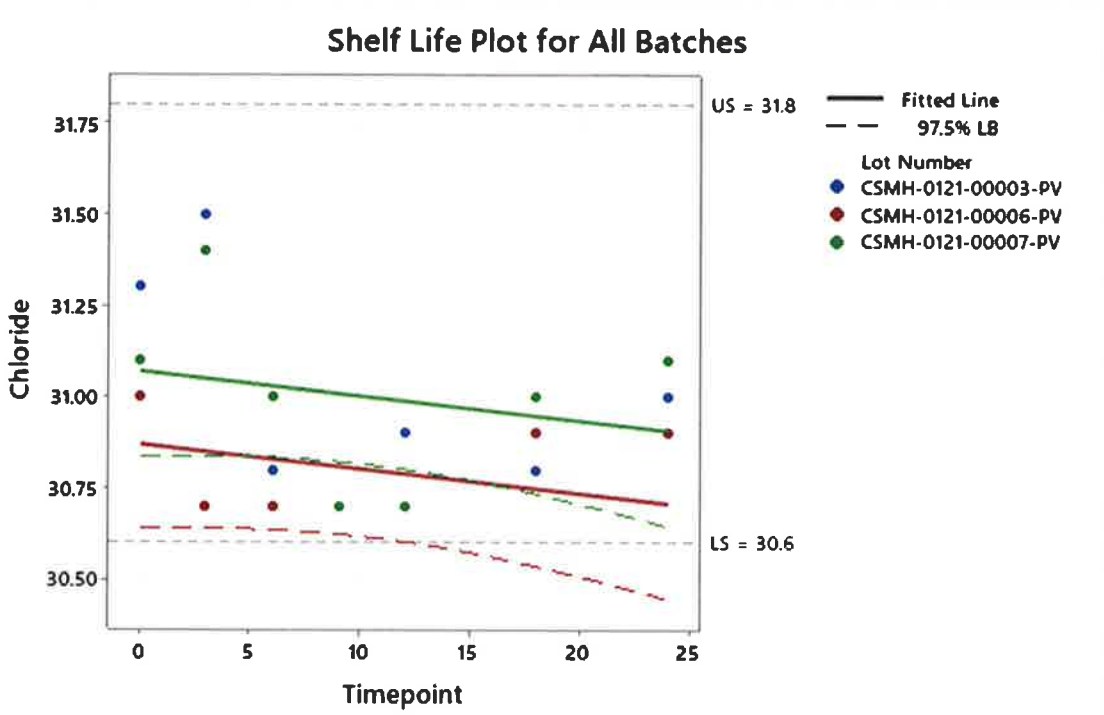
The predictive shelf-life for Assay was 22.8842 months. The shelf-life is defined as the time period in which you may be 95% confident that at least 50% of the response is within the required limits of specifications. All data regardless of the predicted model up to the 24-month time point has met the required specification. The shelf-life will be continued to be monitored at the 36-month timepoint.



LS = Lower Specification

GRAPH 2: PURITY (HPLC AREA %)

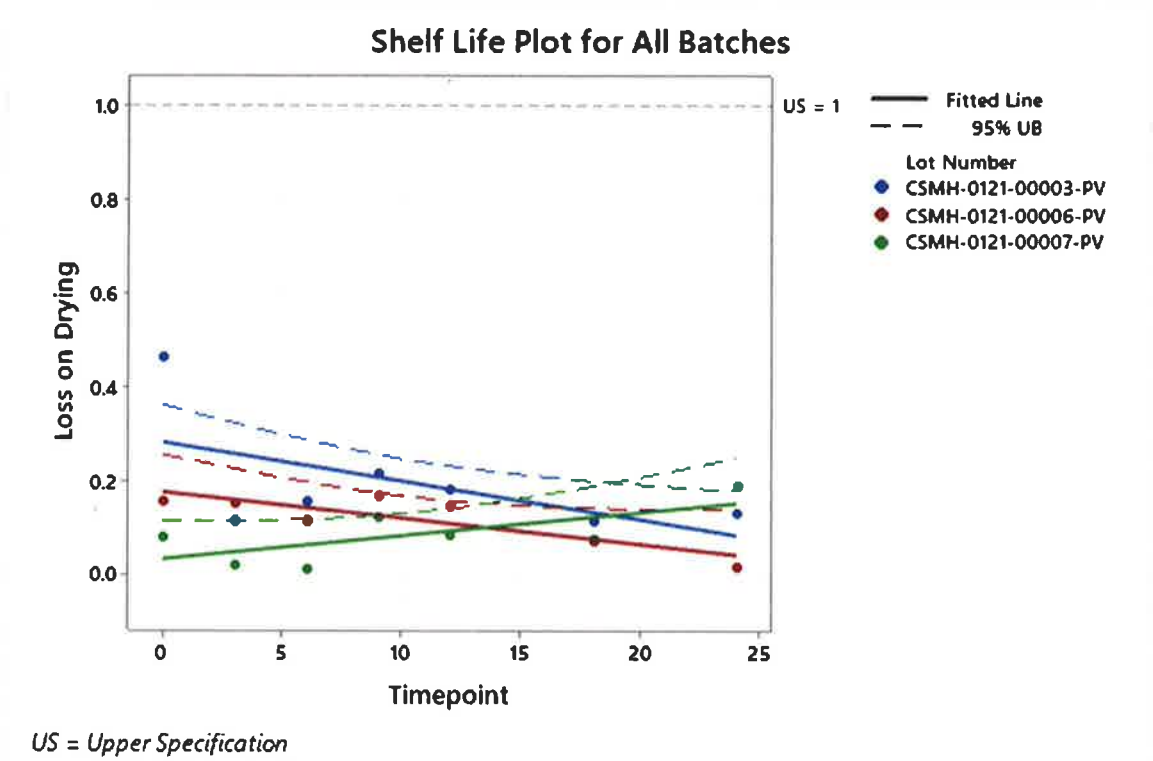
No Shelf-Life was able to be determined for Purity (HPLC Area %), as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material.



LS = Lower Specification, US = Upper Specification

GRAPH 3: 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. There is no impact to the product or currently assigned retest period of this material.



US = Upper Specification

GRAPH 4: 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. There is no impact to the product or currently assigned retest period of this material.

7. CONCLUSION:

7.1. 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 1.5x, where x is the period covered by long-term stability data, but should be no more than 6 months beyond for refrigerated conditions. Real-Time Stability Data up to 24 months displayed in this report along with the predicted shelf-life plots would support a retest date of 24 months. This stability report supports a retest date of 24 months for 2-MEA manufactured at BioSpectra in the Bangor, PA facility, and will continued to be monitored.

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.

8.2. 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.

8.2.1. 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.

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

Signature Manifest

Document Number: BSI-RPT-0940 **Revision:** 1.5
Title: 2-MEA 2021 Validation Lots Stability Report
Effective Date: 15 Jan 2024

All dates and times are in US/Eastern.

BSI-RPT-0940, 2-MEA 2021 Validation Lots Stability Report

Change Request

Name/Signature	Title	Date	Meaning/Reason
Virginia Pena (VIRGINIA.PENA)	Document Control Specialist	13 Dec 2023, 09:41:13 AM	Approved
Amy Yencho (AMY.YENCHO)	Vice President, Laboratory Services	13 Dec 2023, 10:22:21 AM	Approved

Originator and Peer Review Collaboration Workspace

Name/Signature	Title	Date	Meaning/Reason
Stephen Hrizuk (STEPHEN.HRIZUK)	Stability Manager	14 Dec 2023, 10:54:49 AM	Complete & Quit
Emily Gibbons (EMILY.GIBBONS)	Laboratory Systems Supervisor	12 Jan 2024, 03:16:37 PM	Complete & Quit
Hannah Kuchmas (HANNAH.KUCHMAS)	Associate Director of Quality, Stroudsburg	15 Jan 2024, 08:37:37 AM	Complete & Quit
Wayne Talamonti (WAYNE.TALAMONTI)	Director of Laboratory Services	15 Jan 2024, 08:44:57 AM	Complete

Departmental Approval

Name/Signature	Title	Date	Meaning/Reason
Amy Yencho (AMY.YENCHO)	Vice President, Laboratory Services	15 Jan 2024, 10:10:17 AM	Approved

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Wayne Talamonti (WAYNE.TALAMONTI)	Director of Laboratory Services	15 Jan 2024, 10:34:05 AM	Approved

Quality Approval

Name/Signature	Title	Date	Meaning/Reason
Hannah Kuchmas (HANNAH.KUCHMAS)	Associate Director of Quality, Stroudsburg	15 Jan 2024, 11:31:13 AM	Approved

Set Date

Name/Signature	Title	Date	Meaning/Reason
Virginia Pena (VIRGINIA.PENA)	Document Control Specialist	15 Jan 2024, 11:50:15 AM	Approved