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100 Majestic Way, Bangor, PA 18013 / www.biospectra.us

CYSTEAMINE HCl (2-MEA) 2022 VALIDATION LOTS 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 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 Long-Term Stability analysis will assess the stability of 2-MEA validation lots CSMH-0122-00033-PV, CSMH-0122-00034-PV, and CSMH-0122-00038-PV that completed twenty-four (24) months of long-term stability in March 2024 for lots CSMH-0122-00033-PV and CSMH-0122-00034-PV, and April 2024 for lot CSMH-0122-00038-PV. Lots CSMH-0122-00033-PV and CSMH-0122-00034-PV are scheduled to finish at sixty (60) months in March 2027 and lot CSMH-0122-00038-PV in April 2027. 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 Tables 2 through 4. Refer to BSI-MEM-1162 regarding HPLC Assay (Weight %) data fluctuations due to internal 2-MEA Standard used for HPLC analysis up to T=12 timepoint.

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 code is commercially available:

- CSMH-3250

2. REFERENCES:

2.1. BSI-LST-0178, 2-MEA Stability Data Card
2.2. BSI-MEM-1162, Cysteamine Hydrochloride HPLC Standard Assessment
2.3. BSI-PRL-0381, Stability Indicating Protocol: 2-MEA
2.4. BSI-RPT-0588, Stability Indicating Report: 2-MEA
2.5. BSI-SOP-0136, Stability Testing Program
2.6. BSI-SOP-0146, Stability Inventory
2.7. BSI-SOP-0289, Stability Indication Protocol
2.8. Current USP
2.9. ICH Q1E

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 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 or pail. 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 a tightly closed container under nitrogen or argon blanket at 2-8°C, and stored in a dry, well-ventilated area away from incompatible substances. Section 5 will include any excursions from these required temperature conditions.

4.1.1. Samples were stored in refrigerated storage unit A01RC04 at the Bangor, PA facility from March 2022 until September 2023. Storage conditions have been continuously measured and recorded utilizing Tempmate data loggers with regulated conditions for temperature (2-8°C). the maximum temperature recorded was 48.3°C, the minimum temperature was -5.6°C, the average temperature was 6.8°C, and the average mean kinetic temperature was 8.6°C. Due to a failure of storage container A01RC04 (refer to discrepancy investigation BDI23-234) the samples were moved on 09/08/23 to storage container A01RC01 under temporary operating instructions, BTOI23-143.

4.1.2. Samples were stored in refrigerated storage unit A01RC01 at the Bangor, PA facility from September 2023 until the T_{24} pull date in March 2024. The maximum temperature recorded was 26.4°C, the minimum temperature was 3.3°C, the average temperature was 5.6°C, and the average mean kinetic temperature was 5.5°C.

5. INVESTIGATIONS:

5.1. **BDI22-198:** This discrepancy covers a 2-MEA stability sample, CSMH-0122-00038-PV 2P/P with desiccant T=3, that was pulled on 7/05/22 which was not tested within the 10 days from the pull. This occurrence was due to the HPLC instrument not functioning properly. The instrument was serviced and the stability samples were run 16 days past the scheduled due date. The stability sample passed the specification requirements and will be reported.

5.2. **BDI23-09**: This discrepancy covers one of the four temperature data loggers not being able to be located for the time period of 06/23/22 to 09/14/22. 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.

5.3. **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.

5.4. **BDI23-18**: This discrepancy covers out of specification (OOS) temperatures for Cold Storage Container A01RC04 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.

5.5. **BDI23-90**: This discrepancy covers out of specification (OOS) low temperatures for Cold Storage Container A01RC04 for the period of 12/21/22 to 03/31/23 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.

5.6. **BDI23-212**: This discrepancy covers out of specification (OOS) high temperatures for Cold Storage Container A01RC04 for the period from 3/31/23 to 7/13/23. The root cause is likely entry into the cold storage container and high ambient temperatures while the cold storage unit not being fully closed. It was determined that there was no impact on samples stored in this unit.

5.7. **BDI23-234**: The cold storage Trailer A01RC04 was observed to be 48.9°C on 8/28/23. It was determined that the cold storage unit compressor had failed. Review of the temperature data showed an increase in the temperature starting on 8/24/23. The stability samples were moved from A01RC04 to A01RC01 under BTOI23-143 on 9/8/23. Based on the 18-month stability pull data this excursion had no impact on the samples to date.

5.8. **BLI24-10**: Cysteamine HCl stability sample CSMH-0122-00038-PV T=24 2P/P with desiccant obtained an OOS result for Assay. The specification is 98.0-102.0% and the original result was 97.0%. Six retests from CSMH-0122-00038-PV T=Extra were analyzed on the Waters Alliance HPLC to confirm or refute the original result and investigate the material. All retests were found to be passing and therefore, the original result was refuted. The average of the six retests will be reported as the official result.

5.9. **BDI24-33**: This discrepancy covers out of specification (OOS) high temperatures for the period of 9/1/23 to 12/13/23 for Cold Storage Container A01RC01 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.

5.10. **BDI24-50**: During the download and review of the Tempmate data loggers in A01RC01 for the period 12/13/23 to 3/28/24 high OOS temperatures that are not explained by container entries were recorded from 3/17/24 to 3/19/24. The root cause was due to a malfunctioning compressor. Based on the 24-month stability pull data this excursion had no impact on the samples to date.

5.11. **BDI24-56**: High out of specification OOS temperatures recorded by all four loggers for Cold Storage Container A01RC01 were recorded on 7/17/23, 7/26/23, and 8/24/23-8/28/23. Additionally, logger S/N S122122089-12 recorded high OOS temperatures on 7/14/23, 7/15/23, 7/28/23, 7/29/23 and 8/6/23. The main root cause was due to a malfunctioning compressor or chamber entrance. The stability of the 2-MEA samples was not impacted as the last time point met the specification requirements.

6. LOT EVALUATION:

TABLE 2: RESULT OF LONG-TERM STABILITY ANALYSES FOR CSMH-0122-00033-PV

Lot Number	Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
CSMH-0122-00033-PV	Assay (HPLC Weight %)	98.0 – 102.0%	98.70%	100.12%	99.39%	100.52%	98.40%	99.81%	100.00%
	HPLC Minor Component 1 (Area %)[1]	Cystamine ≤ 2.0%	<0.2%	0.6%	<0.2%	0.5%	<0.2%	<0.2%	<0.2%
	Purity (HPLC Area %)	≥ 98.0%	100.0%	99.4%	100.0%	99.5%	100.0%	100.0%	100.0%
	Purity (Cysteamine (HPLC))	≥ 92.0% Cysteamine	100.0%	99.4%	100.0%	99.5%	100.0%	100.0%	100.0%
	Purity (Cysteamine (HPLC))[1]	≤ 8.0% Related Substances	<0.2%	0.6%	<0.2%	0.5%	<0.2%	<0.2%	<0.2%
	Appearance and Color	White or colorless crystals or powder, may contain lumps	White or Colorless Crystals or Powder, may contain lumps	White or colorless Crystals or powder	white powder contains Lumps	White Powder	White Powder	White Crystals	White Powder
	Chloride	30.6 – 31.8%	30.9%	30.92%	30.83%	30.97%	31.11%	31.02%	30.94%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying	≤ 1.0%	0.1343%	0.0197%	<0.0165%	0.2988%	0.0439%	0.0161%	0.0323%

[1]Method LOQ is <0.2%. Results for HPLC Minor Component and Purity Cysteamine HPLC that were <LOQ, will be reported as <LOQ.

Future pull dates

T=36: Scheduled to be pulled 03/14/25

T=48: Scheduled to be pulled 03/14/26

T=60: Scheduled to be pulled 03/14/27

TABLE 3: RESULT OF LONG-TERM STABILITY ANALYSES FOR CSMH-0122-00034-PV

Lot Number	Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
CSMH-0122-00034-PV	Assay (HPLC Weight %)	98.0 – 102.0%	98.70%	100.09%	99.16%	100.23%	98.25%	98.36%	98.89%
	HPLC Minor Component 1 (Area %)[1]	Cystamine ≤ 2.0%	0.5%	<0.2%	0.6%	0.8%	0.7%	0.84%	0.83%
	Purity (HPLC Area %)	≥ 98.0%	99.5%	100.0%	99.4%	99.2%	99.3%	99.2%	99.2%
	Purity (Cysteamine (HPLC))	≥ 92.0% Cysteamine	99.5%	100.0%	99.4%	99.2%	99.3%	99.2%	99.2%
	Purity (Cysteamine (HPLC))[1]	≤ 8.0% Related Substances	0.5%	<0.2%	0.6%	0.8%	0.7%	0.84%	0.83%
	Appearance and Color	White or colorless crystals or powder, may contain lumps	White or Colorless Crystals or Powder, may contain lumps	White or colorless crystals or powder	White Powder contains lumps	White Powder	White Powder	White Crystals	White Powder
	Chloride	30.6 – 31.8%	30.8%	30.90%	30.82%	30.90%	30.84%	31.11%	30.93%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying	≤ 1.0%	0.1281%	0.0380%	0.0807%	0.0772%	0.0182%	0.0276%	0.0271%

[1]Method LOQ is <0.2%. Results for HPLC Minor Component and Purity Cysteamine HPLC that were <LOQ, will be reported as <LOQ.

Future pull dates

T=36: Scheduled to be pulled 03/14/25

T=48: Scheduled to be pulled 03/14/26

T=60: Scheduled to be pulled 03/14/27

TABLE 4: RESULT OF LONG-TERM STABILITY ANALYSES FOR CSMH-0122-00038-PV

Lot Number	Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
CSMH-0122-00038-PV	Assay (HPLC Weight %)	98.0 – 102.0%	100.29%	101.40%	98.54%	100.89%	100.65%	99.29%	99.6%
	HPLC Minor Component 1 (Area %)[1]	Cystamine ≤ 2.0%	<0.2%	<0.2%	<0.2%	<0.2%	<0.2%	<0.2%	0.79%
	Purity (HPLC Area %)	≥ 98.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.71%
	Purity (Cysteamine (HPLC))	≥ 92.0% Cysteamine	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.71%
	Purity (Cysteamine (HPLC))[1]	≤ 8.0% Related Substances	<0.2%	<0.2%	<0.2%	<0.2%	<0.2%	<0.2%	0.79%
	Appearance and Color	White or colorless crystals or powder, may contain lumps	White or Colorless Crystals or Powder, may contain lumps	White Powder contains lumps	White Powder contains lumps	White Powder contains lumps	White Powder contains lumps	White Crystals	White Powder contains lumps
	Chloride	30.6 – 31.8%	30.7%	30.71%	31.60%	31.18%	31.04%	31.09%	30.92%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying	≤ 1.0%	0.0242%	<0.0136%	0.1168%	0.0121%	0.1024%	0.0641%	0.0354%

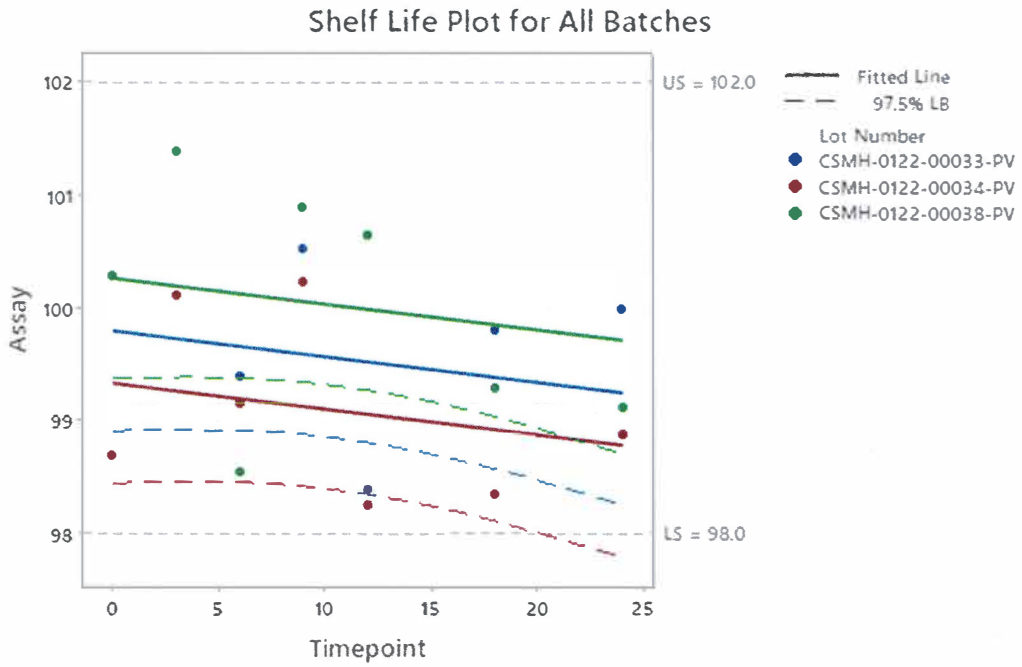
[1]Method LOQ is <0.2%. Results for HPLC Minor Component and Purity Cysteamine HPLC that were <LOQ, will be reported as <LOQ.

Future pull dates

T=36: Scheduled to be pulled 04/05/25

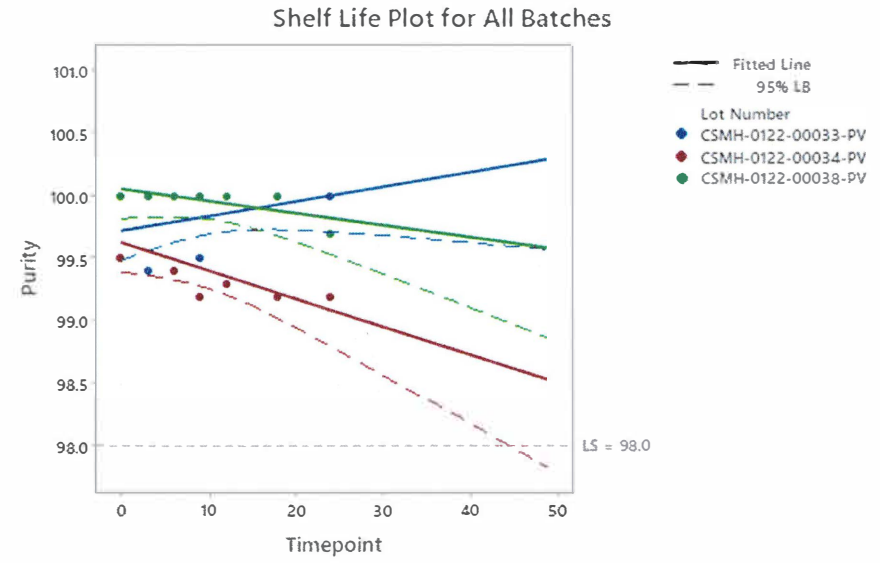
T=48: Scheduled to be pulled 04/05/26

T=60: Scheduled to be pulled 04/05/27

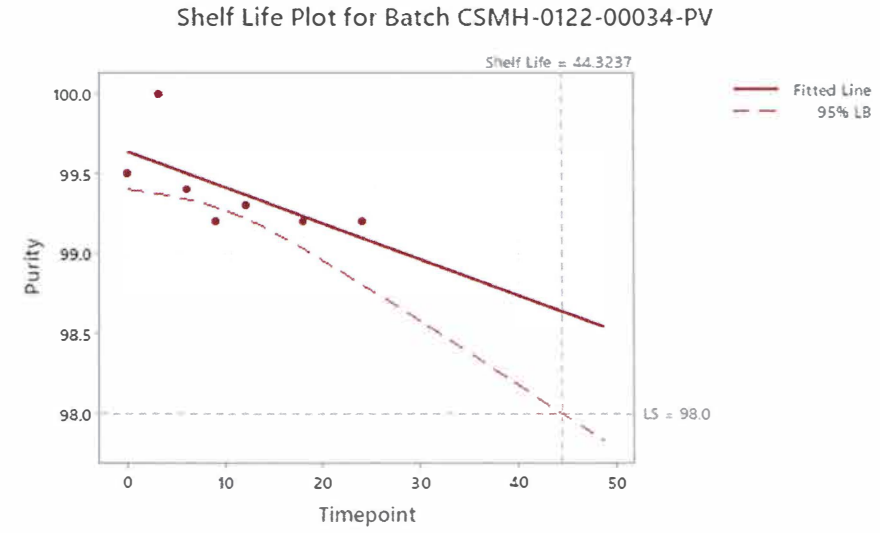


GRAPH 1: ASSAY

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



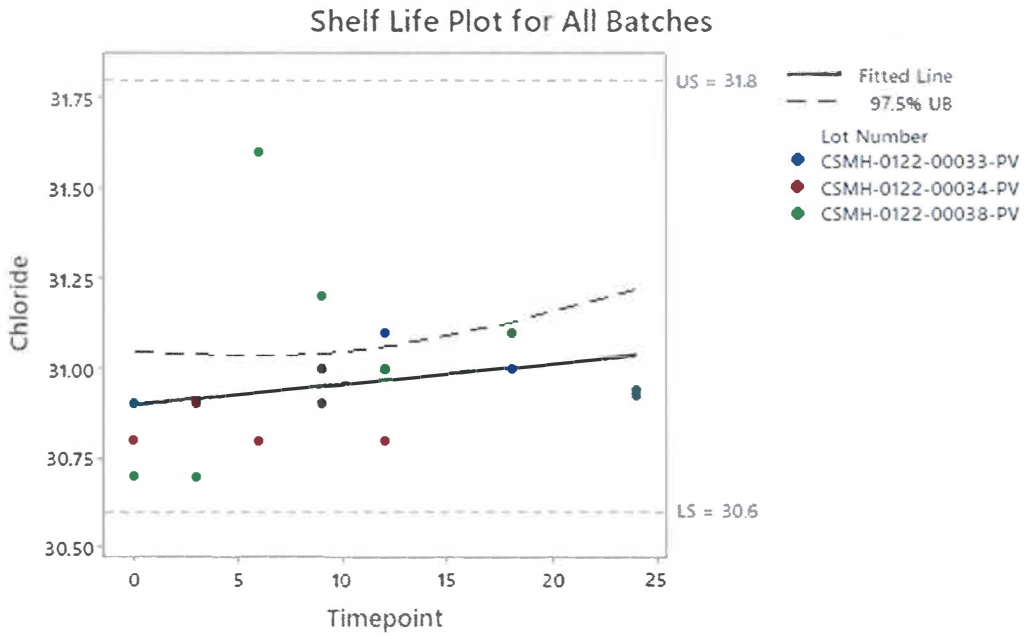
LS = Lower Specification



LS = Lower Specification
Equation for fitted line: Purity = 99.6 - 0.0224 Timepoint

GRAPH 2: PURITY (HPLC AREA %)

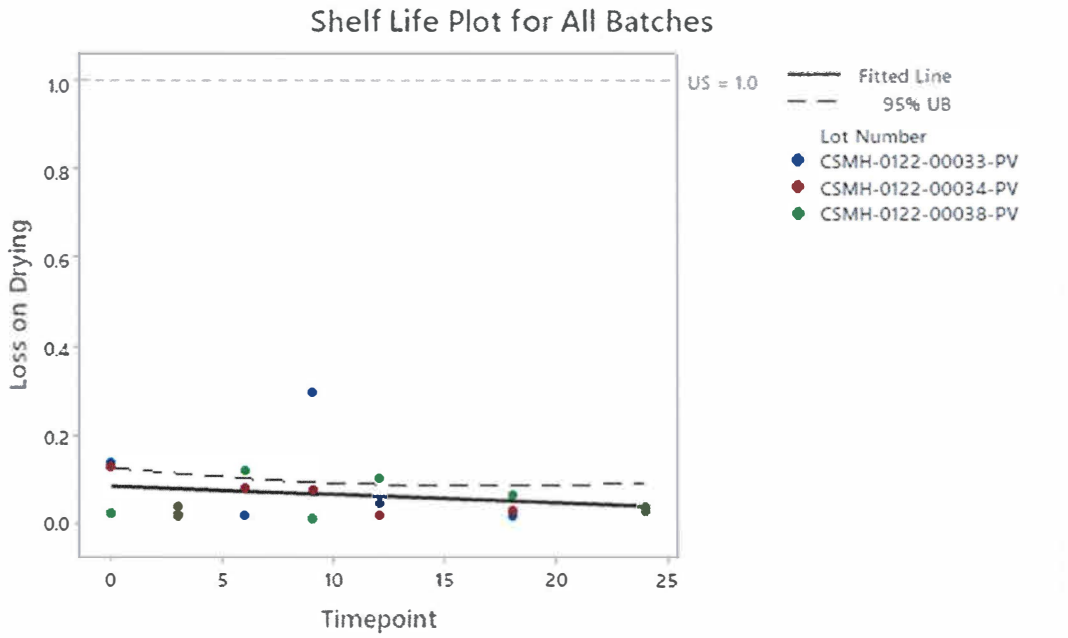
The predicted Shelf-Life for Purity (HPLC Area%) was determined to be 44.3237 months as of the T=24-month time interval. There is no impact to the product or currently assigned retest period of this material.



LS = Lower Specification, US = Upper Specification
Equation for fitted line: Chloride = 30.9 + 0.00568 Timepoint

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
Equation for fitted line: Loss on Drying = 0.0829 - 0.00192 Timepoint

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, 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. Long-Term Stability Data displayed in this report up to T=24 (24 months) of testing for 2022 lots of 2-MEA manufactured at BioSpectra in the Bangor, PA facility, along with the predicted shelf-life plots, would support a retest date of 24 months, an extension to a retest date of 30 months upon request is acceptable and will continued to be monitored. The current retest date of 24 months based on previous stability data will continue to be assigned to all 2-MEA lots released to product code CSMH-3250.

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.