BIOSPECTRA

MES MONOHYDRATE 2018 AND 2019 LOTS REAL TIME STABILITY REPORT:

TABLE OF CONTENTS

1. OVERVIEW:

The purpose of this report is to analyze and conclude on the data obtained from the real time stability study of MES Monohydrate (MES). 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 analysis will assess the stability of MES lots ME3200-104-0318 that completed 36 months of real time stability in April 2021 and ME3200-134-0319 that completed 36 months of real time stability in March 2022. This study includes the following analyses: Absorbance (1M) @ 280nm, Absorbance (1M) @ 260nm, Assay (As Is), Appearance and Color, Identification (IR), and Loss on Drying (LOD). Results from all analyses are summarized in Table 2. 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 MES, Monohydrate. The following Product Codes are commercially available.

- MESM-3220
- MESM-3221
- MESM-3222
- MESM-3223
- MESM-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 for real time testing consisted of two lots of MES. Stability samples from these lots were put into multiple packaging configurations. 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**
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.
2 Poly/Poly (2P/P)	Samples are individually placed into small polyethylene bags and are sealed with a zip tie. All individual bags are then placed into a single large poly bag, the bag is sealed with a zip tie, then placed in a poly pail and sealed.
2 Poly/Fiber (2P/F)	Samples are individually placed into small polyethylene bags and are sealed with a zip tie. All individual bags are then placed into a single large poly bag, the bag is sealed with a zip tie, then placed in a fiber drum and sealed.
Labline (HDPE Bottle)	Samples are packaged into a HDPE Lab Screw-Top Bottle

4. STORAGE:

4.1. The Packaging and Storage requirements for MES are to be in a tightly closed container and stored in a dry, well-ventilated area. For the real time study, the samples were stored in either the L05 Warehouse or the Real Time Stability Chamber at the Bangor, PA facility depending on the time interval.

4.2. For lot ME3200-104-0318, the samples were stored in the L05 Warehouse from April 2018 until August 2019. For L05, storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature $(15 - 30°C)$ and relative humidity (monitored). For this time period, the maximum temperature recorded was 25.92°C, the minimum temperature recorded was 14.27°C, the average temperature recorded was 22.91°C, and the average kinetic temperature recorded was 22.93°C. Humidity is only monitored in this area. In September 2019, the samples were moved to the Real Time Stability Chamber where they remained until April 2021, which was the final time interval of T=36 for this study. For the Real Time Stability Chamber, storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature $(25°C \pm2)$ and relative humidity $(60\%RH \pm5)$. For this time period, the maximum temperature recorded was 27.80°C, the minimum temperature recorded was 21.75°C, the average temperature recorded was 25.45°C, and the average kinetic temperature recorded was 25.45°C. The maximum relative humidity recorded was 68.8%, the minimum relative humidity recorded was 30.3%, and the average relative humidity recorded was 61.6%. Maximum and minimum values that are outside the limits for temperature and humidity are due to opening the door of the chamber as explained in the Temperature and Humidity Monitoring Assessments. Section 5 will include any excursions from these conditions that resulted in an investigation.

4.3. For lot ME3200-134-0319, the samples were stored in the L05 Warehouse from March 2019 until August 2019. For L05, storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature $(15 - 30°C)$ and relative humidity (monitored).

For this time period, the maximum temperature recorded was 25.12°C, the minimum temperature recorded was 21.51°C, the average temperature recorded was 23.18°C, and the average kinetic temperature recorded was 23.19°C. Humidity is only monitored in this area. In September 2019, the samples were moved to the Real Time Stability Chamber where they remained until March 2022, which was the final time interval of T=36 for this study. For the Real Time Stability Chamber, storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25°C ±2) and relative humidity (60% RH ±5). For this time period, the maximum temperature recorded was 27.80°C, the minimum temperature recorded was 21.75°C, the average temperature recorded was 25.46°C, and the average kinetic temperature recorded was 25.46°C. The maximum relative humidity recorded was 72.4%, the minimum relative humidity recorded was 30.3%, and the average relative humidity recorded was 61.4%. Maximum and minimum values that are outside the limits for temperature and humidity are due to opening the door of the chamber as explained in the Temperature and Humidity Monitoring Assessments. Section 5 will include any excursions from these conditions that resulted in an investigation.

5. INVESTIGATIONS:

5.1. BLI18-10: This laboratory investigation covers the improper documentation of an invalid assay result for lot ME3200-104-0318 T=0. It was determined that the original assay result was OOS (out of specification) due to loss of material during the preparation step, however this loss was not documented correctly and the retest was done before any investigation was performed. The original OOS result and the retest were invalidated, and as part of the investigation a single retest for assay was performed, which was within specification for this product. This result was used as the final reportable value.

5.2. BDI19-01: This discrepancy investigation covers several temperature and humidity assessments not being complete on a quarterly basis for multiple monitored locations, including the L05 Warehouse. The data was collected and downloaded via the MadgeTech data loggers, but the assessment was not completed and any discrepancies were not addressed in a timely manner. It was determined that there was no negative effect on the samples at this time.

5.3. BDI22-61: This discrepancy investigation covers missing data points for the MadgeTech data loggers located in the Real Time Stability Chamber from 01/28/22 until 02/09/22. The loggers were reset on 02/09/22, and functioned normally for the rest of the monitoring period. The backup Analog chart recorders were inspected, and it was determined that there were no temperature and humidity excursion outside the specification ranges for that time.

5.4. BDI22-143: This discrepancy investigation covers missing data points for the MadgeTech data loggers located in the Real Time Stability Chamber from 11/20/21 until 12/03/21, which was the end of this data collection time period. The backup Analog chart recorders were inspected, and it was determined that there were no temperature and humidity excursion outside the specification ranges for that time.

5.5. BDI23-78: This discrepancy investigation was issued in March 2023 for a missing temperature and humidity assessment for the Real Time Stability Chamber for December 2019. The assessment could not be located, and it could not be determined if it was never completed or was not scanned and filed. The data for this time period was available, so the assessment was written at this time and the discrepancy was initiated for the missing document.

6. LOT EVALUATION:

TABLE 2A: REAL TIME STABILITY RESULTS FOR ME3200-104-0318 P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0032 a.u.	0.0054 a.u.	0.0044 a.u.	0.0064 a.u.	0.0061 a.u.	0.0080 a.u.	0.0064 a.u.	0.0123 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0042 a.u.	0.0067 a.u.	0.0054 a.u.	0.0077 a.u.	0.0074 a.u.	0.0085 a.u.	0.0072 a.u.	0.0146 a.u.
Assay (As Is)	99.0% min.	100.1%	99.5%	99.9%	100.2%	100.2%	100.4%	100.1%	100.6%
Appearance and Color	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying (105°C)	7.0 – 10.0%	8.8%	8.6%	8.5%	8.5%	8.5%	8.5%	8.5%	8.5%

TABLE 2B: REAL TIME STABILITY RESULTS FOR ME3200-104-0318 2P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0032 a.u.	0.0057 a.u.	0.0051 a.u.	0.0061 a.u.	0.0068 a.u.	0.0070 a.u.	0.0079 a.u.	0.0113 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0042 a.u.	0.0065 a.u.	0.0060 a.u.	0.0073 a.u.	0.0079 a.u.	0.0078 a.u.	0.0088 a.u.	0.0130 a.u.
Assay (As Is)	99.0% min.	100.1%	99.8%	99.7%	100.3%	100.2%	99.8%	99.6%	100.4%
Appearance and Color	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying (105°C)	7.0 – 10.0%	8.8%	8.6%	8.5%	8.5%	8.4%	8.4%	8.5%	8.5%

TABLE 2C: REAL TIME STABILITY RESULTS FOR ME3200-104-0318 2P/F

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0032 a.u.	0.0068 a.u.	0.0062 a.u.	0.0092 a.u.	0.0070 a.u.	0.0075 a.u.	0.0070 a.u.	0.0107 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0042 a.u.	0.0077 a.u.	0.0074 a.u.	0.0107 a.u.	0.0085 a.u.	0.0086 a.u.	0.0082 a.u.	0.0126 a.u.
Assay (As Is)	99.0% min.	100.1%	100.0%	100.3%	100.4%	100.0%	99.7%	99.7%	100.6%
Appearance and Color	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying (105°C)	7.0 – 10.0%	8.8%	8.6%	8.5%	8.5%	8.5%	8.5%	8.4%	8.5%

TABLE 2D: REAL TIME STABILITY RESULTS FOR ME3200-104-0318 LABLINE

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0032 a.u.	0.0042 a.u.	0.0033 a.u.	0.0037 a.u.	0.0043 a.u.	0.0100 a.u.	0.0041 a.u.	0.0087 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0042 a.u.	0.0050 a.u.	0.0042 a.u.	0.0047 a.u.	0.0053 a.u.	0.0092 a.u.	0.0049 a.u.	0.0098 a.u.
Assay (As Is)	99.0% min.	100.1%	99.6%	99.9%	99.8%	100.0%	99.6%	99.8%	100.9%
Appearance and Color	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying (105°C)	7.0 – 10.0%	8.8%	8.7%	8.7%	8.6%	8.5%	8.5%	8.5%	8.5%

TABLE 2E: REAL TIME STABILITY RESULTS FOR ME3200-134-0319 P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0026 a.u.	0.0070 a.u.	0.0058 a.u.	0.0154 a.u.	0.0085 a.u.	0.0079 a.u.	0.0068 a.u.	0.0082 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0032 a.u.	0.0082 a.u.	0.0066 a.u.	0.0146 a.u.	0.0096 a.u.	0.0092 a.u.	0.0072 a.u.	0.0097 a.u.
Assay (As Is)	99.0% min.	99.5%	99.6%	99.6%	99.5%	99.6%	100.3%	100.2%	100.1%
Appearance and Color	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying (105°C)	7.0 – 10.0%	9.0%	8.8%	8.7%	8.7%	8.6%	8.6%	8.5%	8.5%

TABLE 2F: REAL TIME STABILITY RESULTS FOR ME3200-134-0319 2P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0026 a.u.	0.0062 a.u.	0.0047 a.u.	0.0073 a.u.	0.0077 a.u.	0.0078 a.u.	0.0066 a.u.	0.0085 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0032 a.u.	0.0073 a.u.	0.0054 a.u.	0.0079 a.u.	0.0088 a.u.	0.0092 a.u.	0.0074 a.u.	0.0099 a.u.
Assay (As Is)	99.0% min.	99.5%	99.6%	99.5%	99.3%	99.4%	100.2%	100.2%	100.2%
Appearance and Color	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying (105°C)	7.0 – 10.0%	9.0%	8.8%	8.7%	8.6%	8.6%	8.6%	8.6%	8.5%

TABLE 2G: REAL TIME STABILITY RESULTS FOR ME3200-134-0319 2P/F

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0026 a.u.	0.0070 a.u.	0.0050 a.u.	0.0073 a.u.	0.0081 a.u.	0.0075 a.u.	0.0089 a.u.	0.0083 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0032 a.u.	0.0081 a.u.	0.0058 a.u.	0.0080 a.u.	0.0093 a.u.	0.0088 a.u.	0.0100 a.u.	0.0097 a.u.
Assay (As Is)	99.0% min.	99.5%	99.8%	99.5%	99.3%	99.5%	100.0%	100.3%	100.3%
Appearance and Color	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying (105°C)	7.0 – 10.0%	9.0%	8.7%	8.6%	8.5%	8.6%	8.5%	8.5%	8.5%

TABLE 2H: REAL TIME STABILITY RESULTS FOR ME3200-134-0319 LABLINE

| Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0026 a.u.	0.0059 a.u.	0.0033 a.u.	0.0131 a.u.	0.0060 a.u.	0.0060 a.u.	0.0042 a.u.	0.0057 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0032 a.u.	0.0070 a.u.	0.0040 a.u.	0.0128 a.u.	0.0070 a.u.	0.0073 a.u.	0.0050 a.u.	0.0067 a.u.
Assay (As Is)	99.0% min.	99.5%	99.5%	99.3%	99.3%	99.3%	100.3%	100.0%	100.0%
Appearance and Color	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying (105°C)	7.0 – 10.0%	9.0%	8.9%	8.8%	8.9%	8.8%	8.6%	8.7%	8.6%

GRAPH 1: ME3200-104-0318 ABSORBANCE @ 280NM
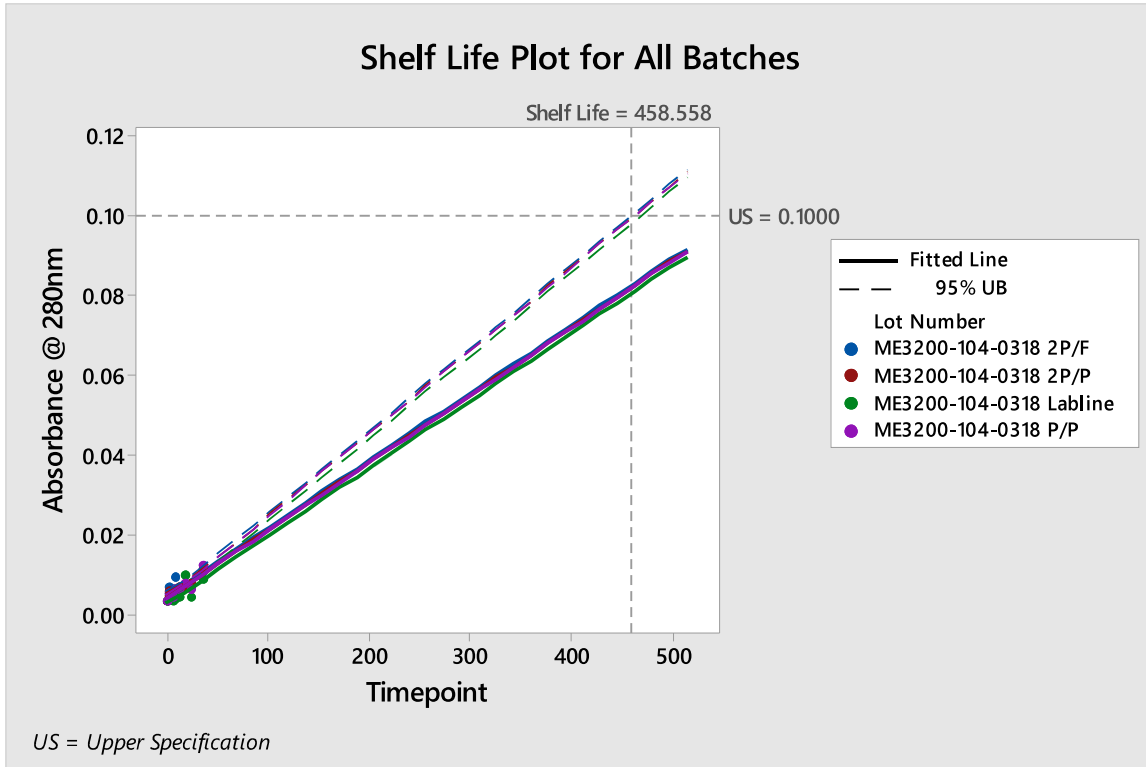
The predicted Shelf-Life for ME3200-104-0318 Absorbance @ 280nm was determined to be 458.558 months at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.
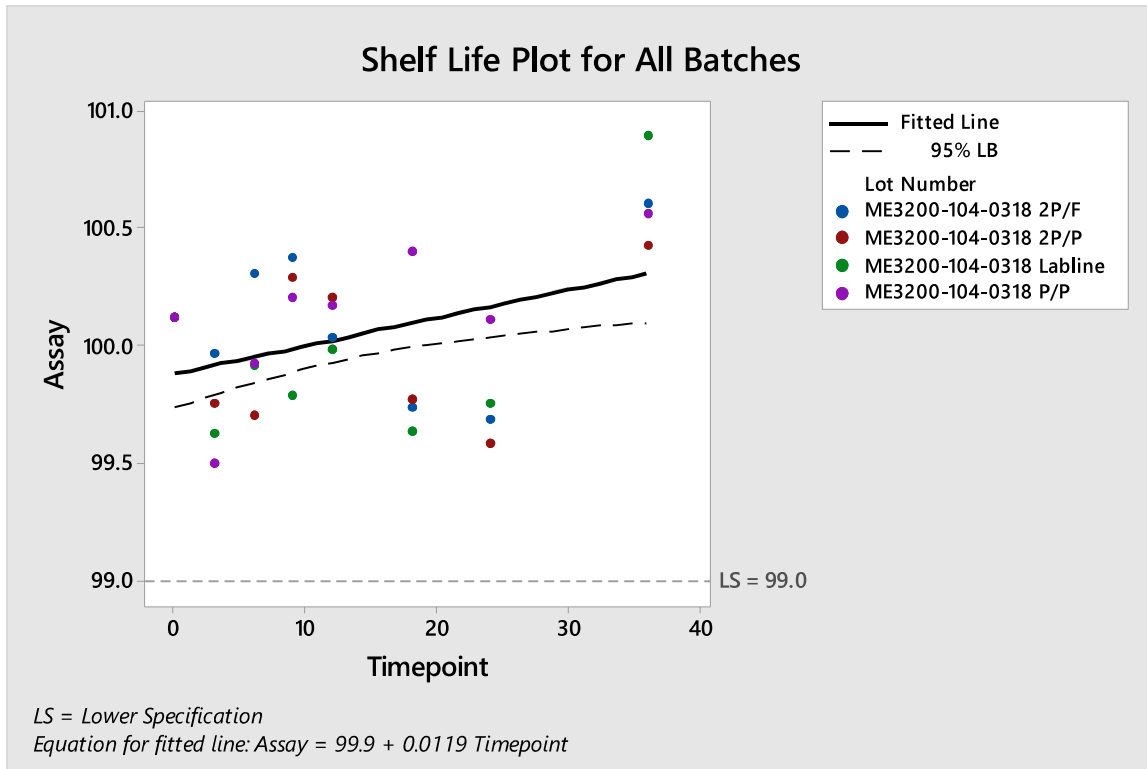
GRAPH 2: ME3200-104-0318 ABSORBANCE @ 260NM
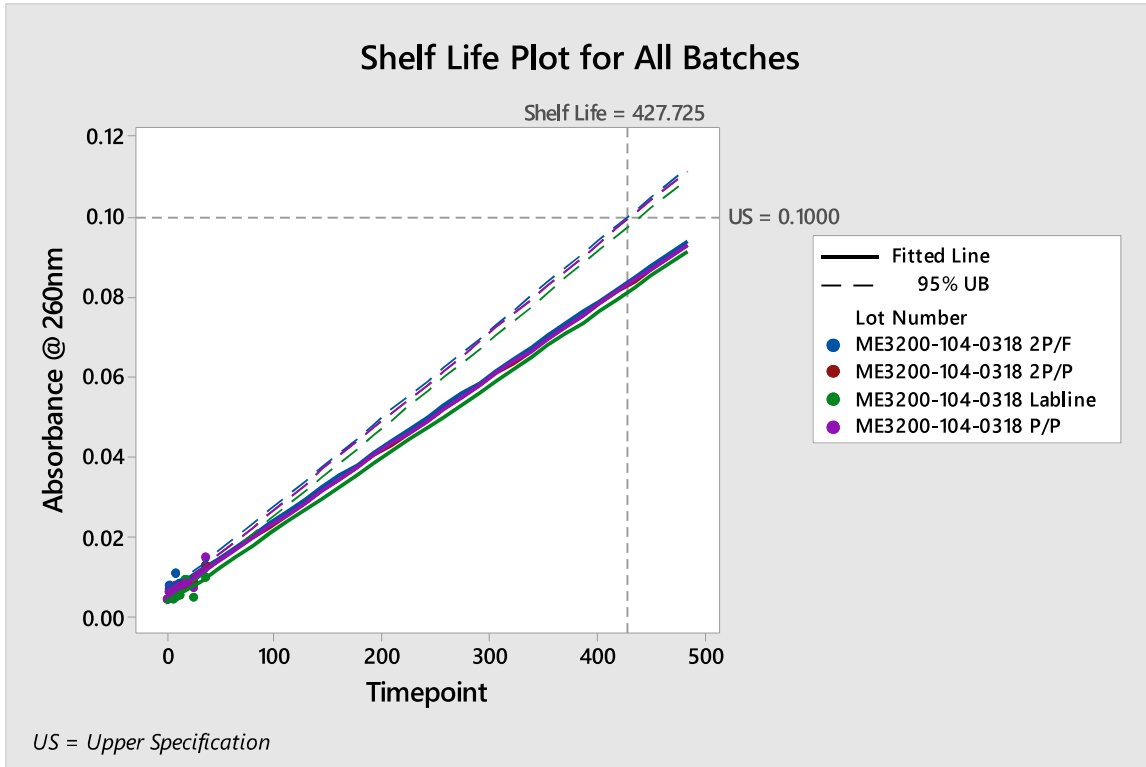
The predicted Shelf-Life for ME3200-104-0318 Absorbance @ 260nm was determined to be 427.725 months at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.
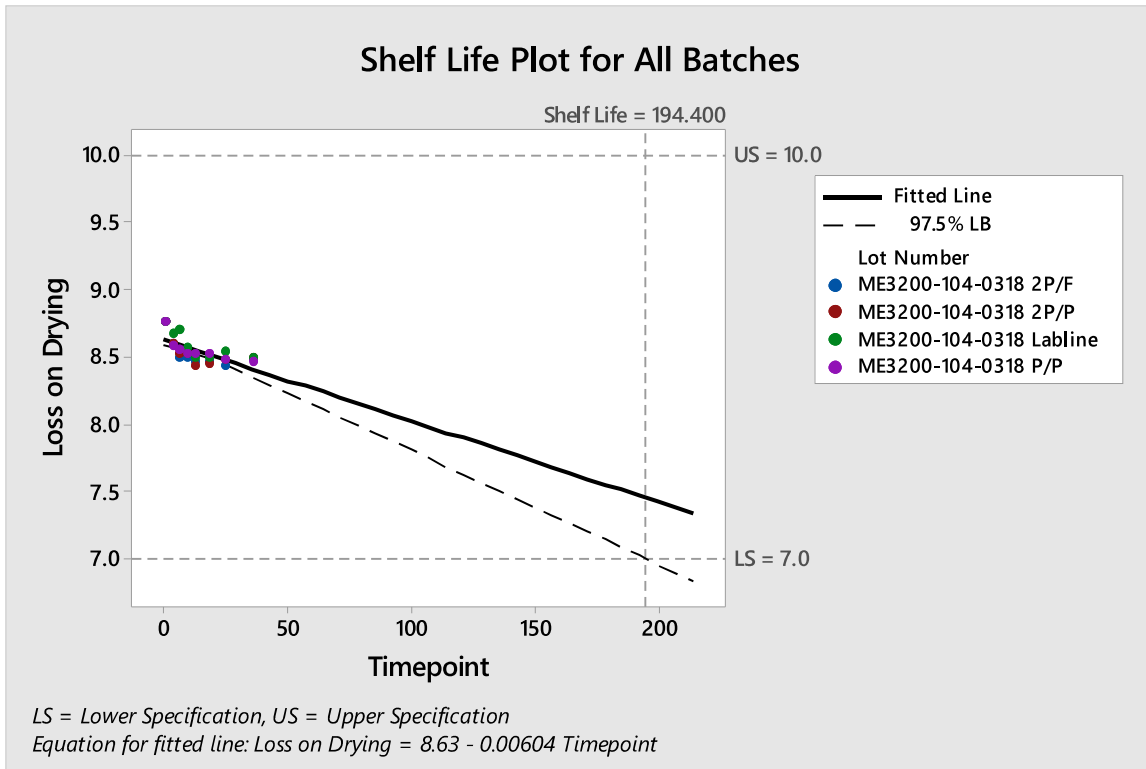
GRAPH 3: ME3200-104-0318 ASSAY (AS IS)

Shelf Life Plot for All Batches

LS = Lower Specification
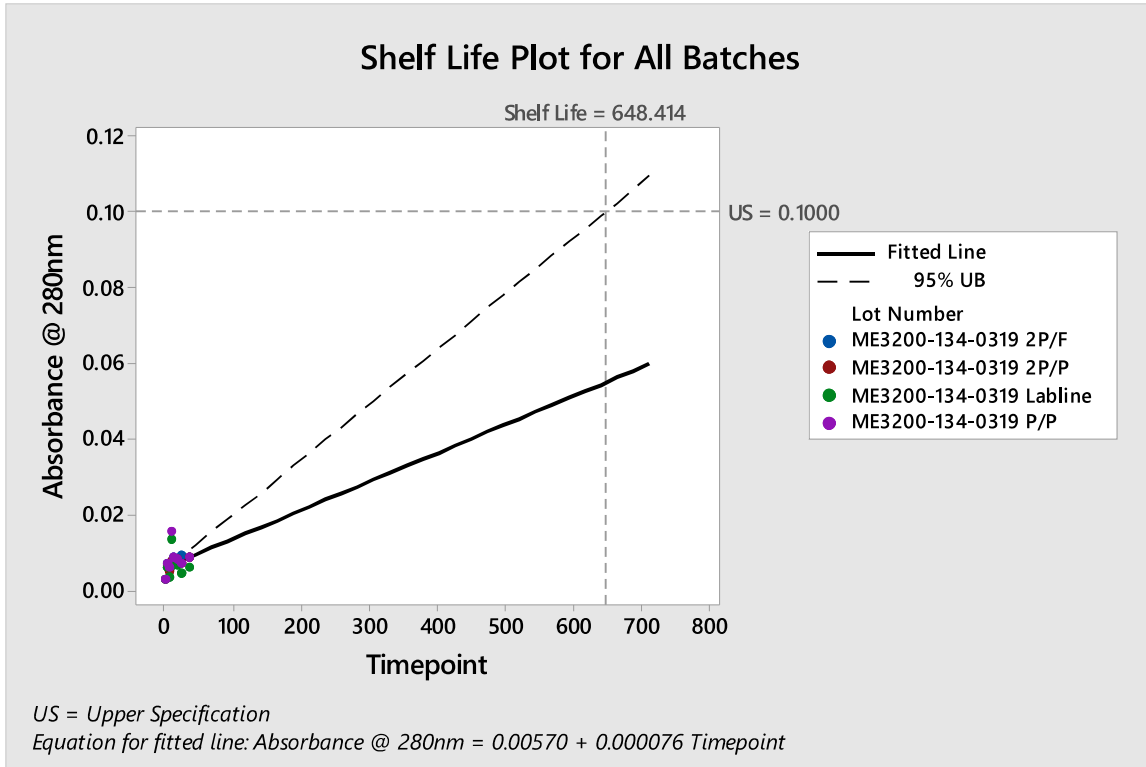Equation for fitted line: Assay = 99.9 + 0.0119 Timepoint

No Shelf-Life was able to be determined for ME3200-104-0318 Assay (As Is), as the mean response slope is not significantly different from zero using 95% confidence at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.

GRAPH 4: ME3200-104-0318 LOSS ON DRYING

LS = Lower Specification, US = Upper Specification
Equation for fitted line: Loss on Drying = 8.63 - 0.00604 Timepoint
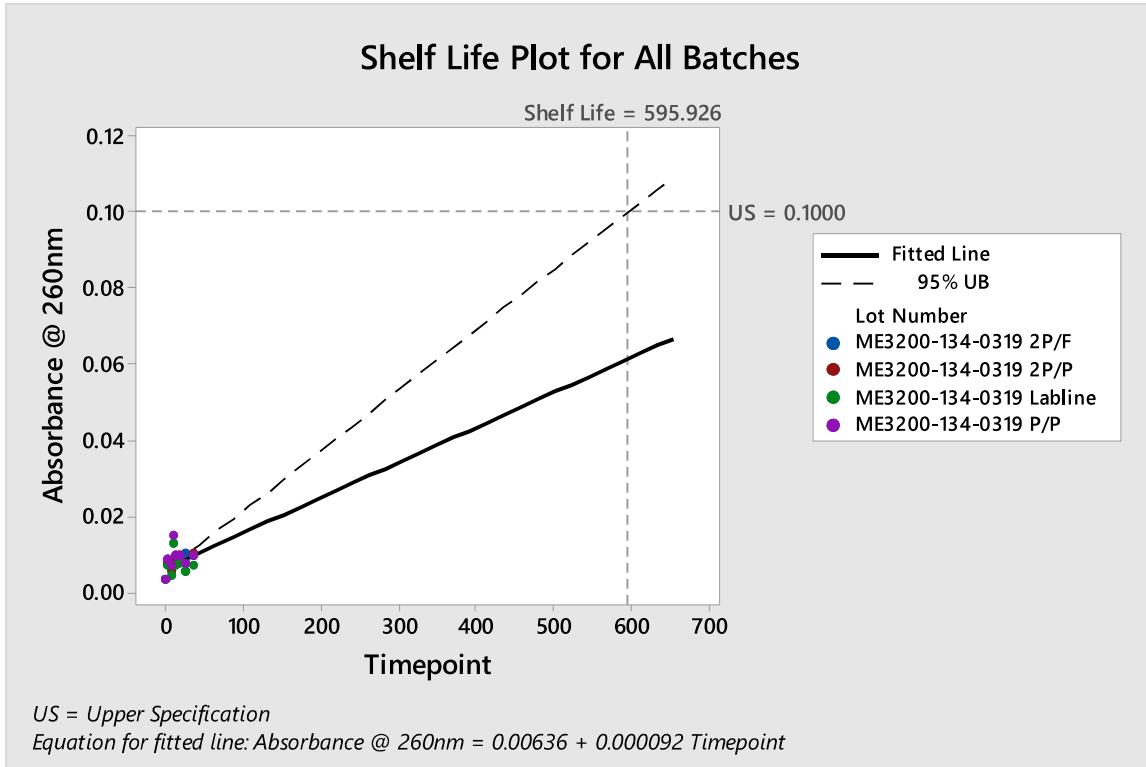
The predicted Shelf-Life for ME3200-104-0318 Loss on Drying was determined to be 194.400 months at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.

GRAPH 5: ME3200-134-0319 ABSORBANCE @ 280NM

Shelf Life Plot for All Batches

US = Upper Specification
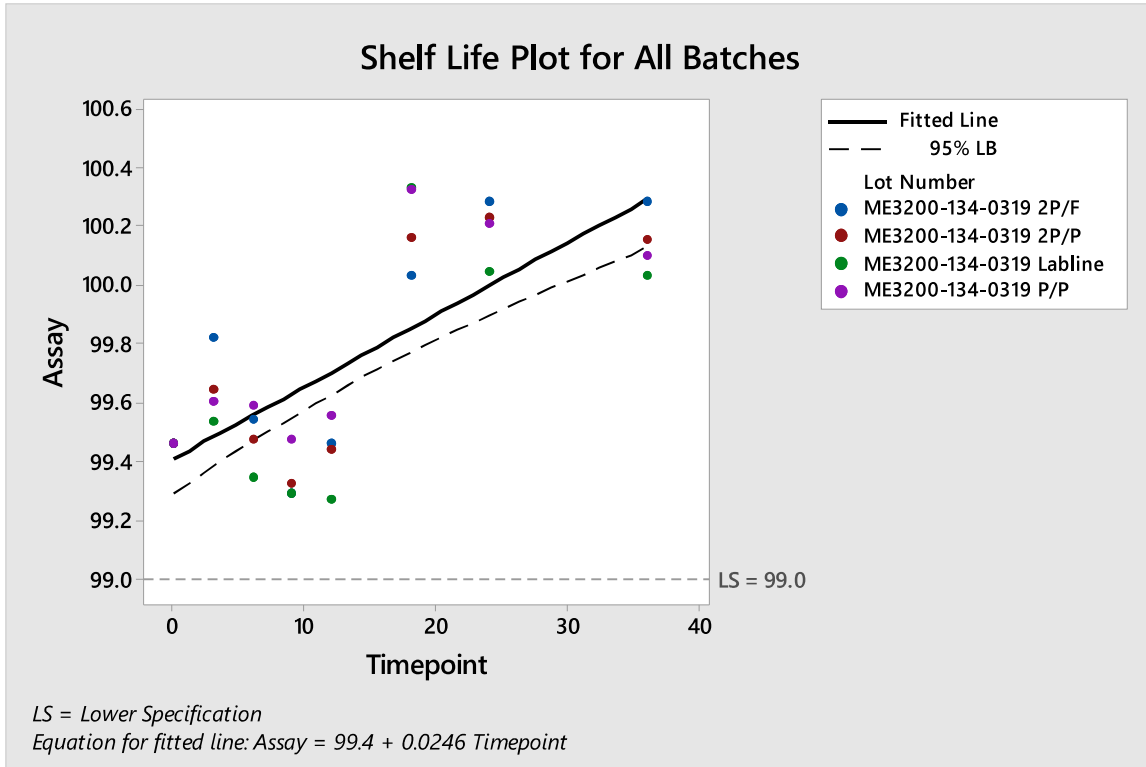*Equation for fitted line: Absorbance @ 280nm = 0.00570 + 0.000076 Timepoint*

The predicted Shelf-Life for ME3200-134-0319 Absorbance @ 280nm was determined to be 648.414 months at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.

GRAPH 6: ME3200-134-0319 ABSORBANCE @ 260NM

The predicted Shelf-Life for ME3200-134-0319 Absorbance @ 260nm was determined to be 595.926 months at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.

GRAPH 7: ME3200-134-0319 ASSAY (AS IS)

Shelf Life Plot for All Batches

LS = Lower Specification
Equation for fitted line: Assay = 99.4 + 0.0246 Timepoint

No Shelf-Life was able to be determined for ME3200-134-0319 Assay (As Is), as the mean response slope is not significantly different from zero using 95% confidence at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.

GRAPH 8: ME3200-134-0319 LOSS ON DRYING

The predicted Shelf-Life for ME3200-134-0319 Loss on Drying was determined to be 135.265 months at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.
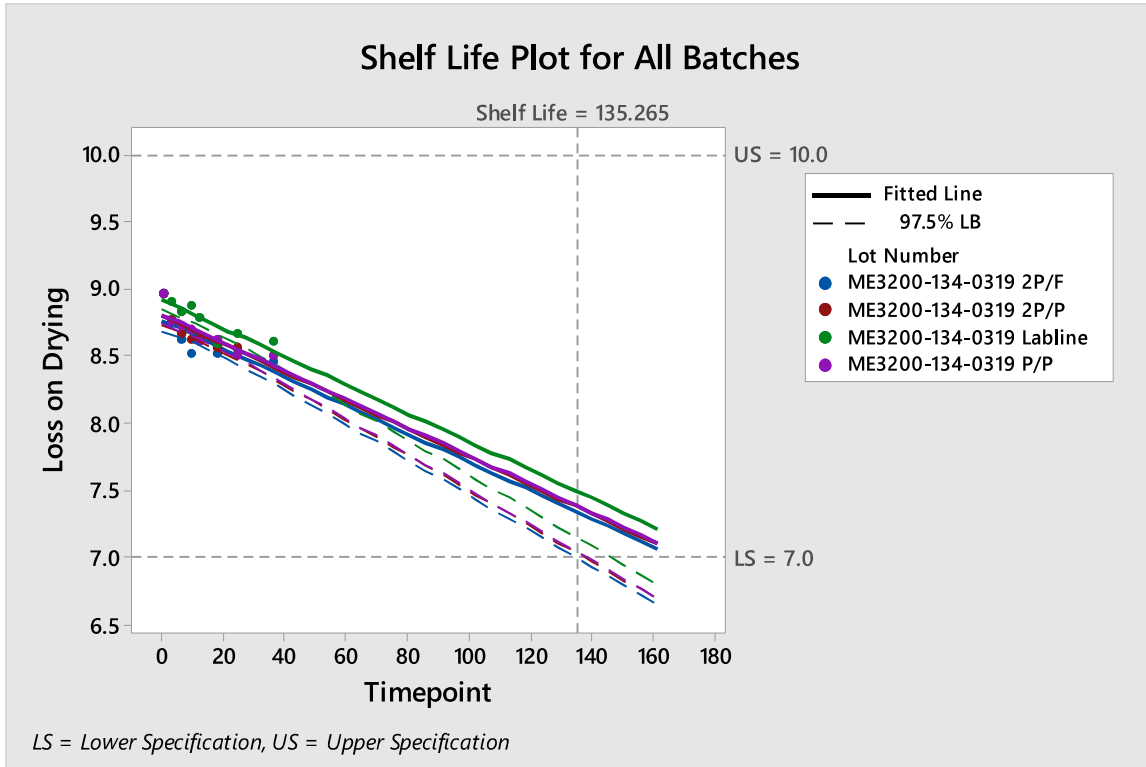
7. **CONCLUSION:**

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 2x, where x is the period covered by real time stability data, but should be no more than 12 months beyond for real time conditions. Real-Time Stability Data displayed in this report up to 36 months for MES, Monohydrate (MES) manufactured at BioSpectra in the Bangor, PA facility, along with the predicted shelf-life plots, would support a retest date of 24 months and an expiration date of 36 months. Samples have met specifications as of 36 months of empirical testing, which is the end of the studies for both lots of MES.

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.