BIOSPECTRA

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MES MONOHYDRATE 2020 LOT 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 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 long-term analysis will assess the stability of MES lot ME3200-189-0220 that completed 36-months of long-term stability in March 2023. This study includes the following analyses: Absorbance (1M) @ 280 nm, Absorbance (1M) @ 260 nm, Assay (As Is), Appearance and Color, Identification (IR), and Loss on Drying (LOD). Results from all analyses are summarized in Tables 2 through 4. 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
- MESM-3251
- MESM-4220

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:

Samples initially placed on the stability program for long term testing consisted of one lot of MES Monohydrate. Stability samples from this lot was put into multiple packaging configurations. The samples were packaged in accordance with the Stability Inventory SOP, BSI-SOP-0146. Reference Table 1, below, for packaging configuration and description. The type of packaging utilized in this stability study were 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.
Poly/Fiber (P/F)	Samples are individually placed into small polyethylene bags and are 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 monohydrate are to be in a tightly closed container and stored in a dry, well-ventilated area. The storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25°C ±2) and relative humidity (60% ±5). For the time period of March 2020 to March 2023 the samples were located in the long-term stability chamber, H03SC01, in the Bangor facility of BioSpectra. For this time period, the maximum temperature recorded was 27.80°C, the minimum temperature recorded was 22.63°C, the average temperature recorded was 25.46°C, and the average kinetic temperature recorded was 25.47°C. The maximum relative humidity recorded was 72.4%, the minimum relative humidity recorded was 31.1%, 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. **BDI22-61**: This discrepancy investigation covers missing data points for the MadgeTech data loggers located in the Long-Term 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.

5.2. **BDI22-138**: This discrepancy investigation covers out of specification humidity readings on 4/26/2022 due to a valve that regulates humidity was closed. There is no impact on stability samples in the chamber because this excursion was brief, lasting less than five hours.

5.3. **BDI22-143**: This discrepancy investigation covers missing data points for the MadgeTech data loggers located in the Long-Term 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.

6. LOT EVALUATION:

Table 2: Long-Term Stability Results for ME3200-189-0220 P/P

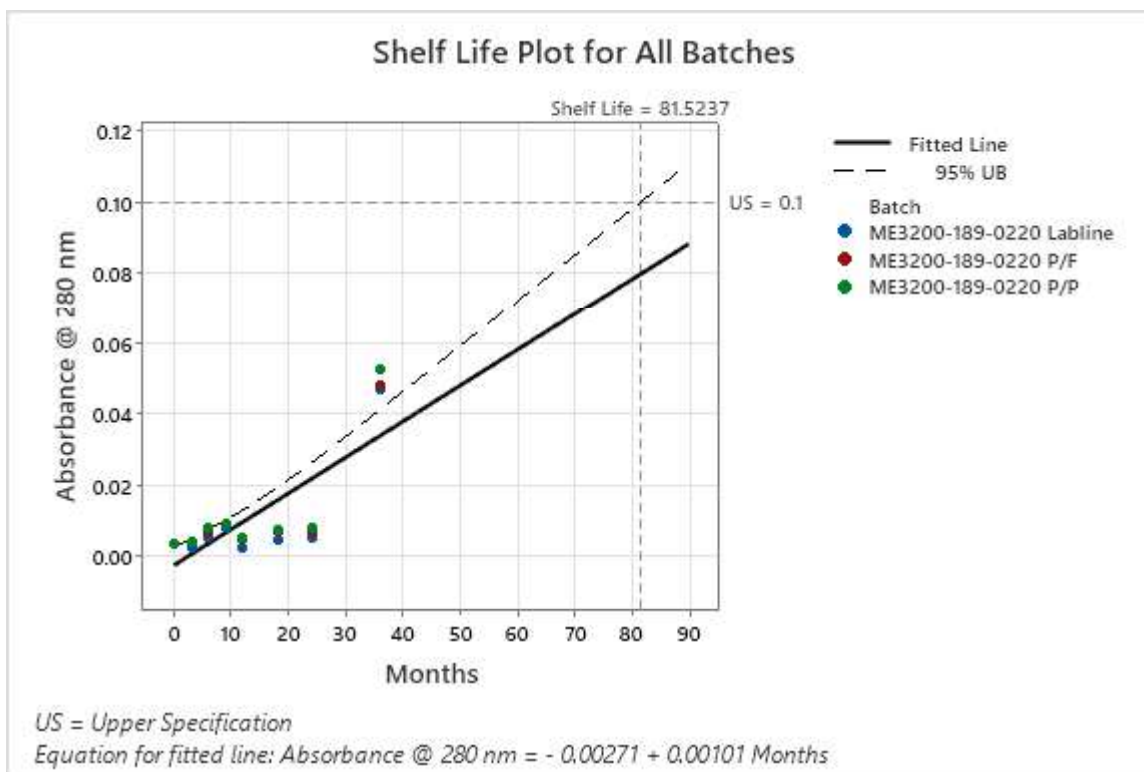| Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0034 a.u.	0.0041 a.u.	0.0077 a.u.	0.0092 a.u.	0.0052 a.u.	0.0074 a.u.	0.0076 a.u.	0.0525 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0041 a.u.	0.0041 a.u.	0.0076 a.u.	0.0099 a.u.	0.0049 a.u.	0.0083 a.u.	0.0086 a.u.	0.0441 a.u.
Assay (As Is)	99.0% min.	99.46%	100.00%	99.89%	99.85%	100.20%	99.55%	99.68%	99.51%
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%	8.8498%	8.7176%	8.6029%	8.6081%	8.5692%	8.6076%	8.5334%	8.5103%

Table 3: Long-Term Stability Results for ME3200-189-0220 P/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.	0.0034 a.u.	0.0040 a.u.	0.0066 a.u.	0.0091 a.u.	0.0047 a.u.	0.0065 a.u.	0.0069 a.u.	0.0477 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0041 a.u.	0.0045 a.u.	0.0069 a.u.	0.0106 a.u.	0.0057 a.u.	0.0089 a.u.	0.0092 a.u.	0.0424 a.u.
Assay (As Is)	99.0% min.	99.46%	100.12%	99.95%	99.90%	100.08%	99.58%	100.00%	99.78%
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%	8.8498%	8.7170%	8.5870%	8.5487%	8.6291%	8.4885%	8.5531%	8.5179%

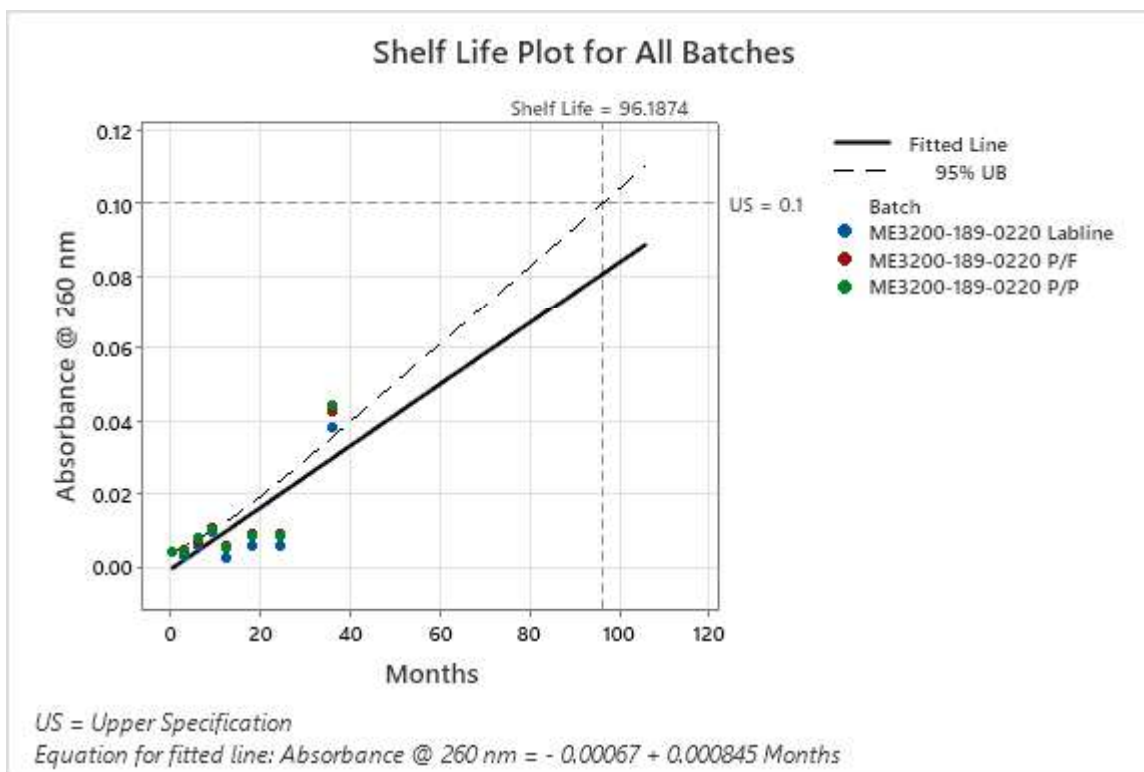### Table 4: Long-Term Stability Results for ME3200-189-0220 LABLINE

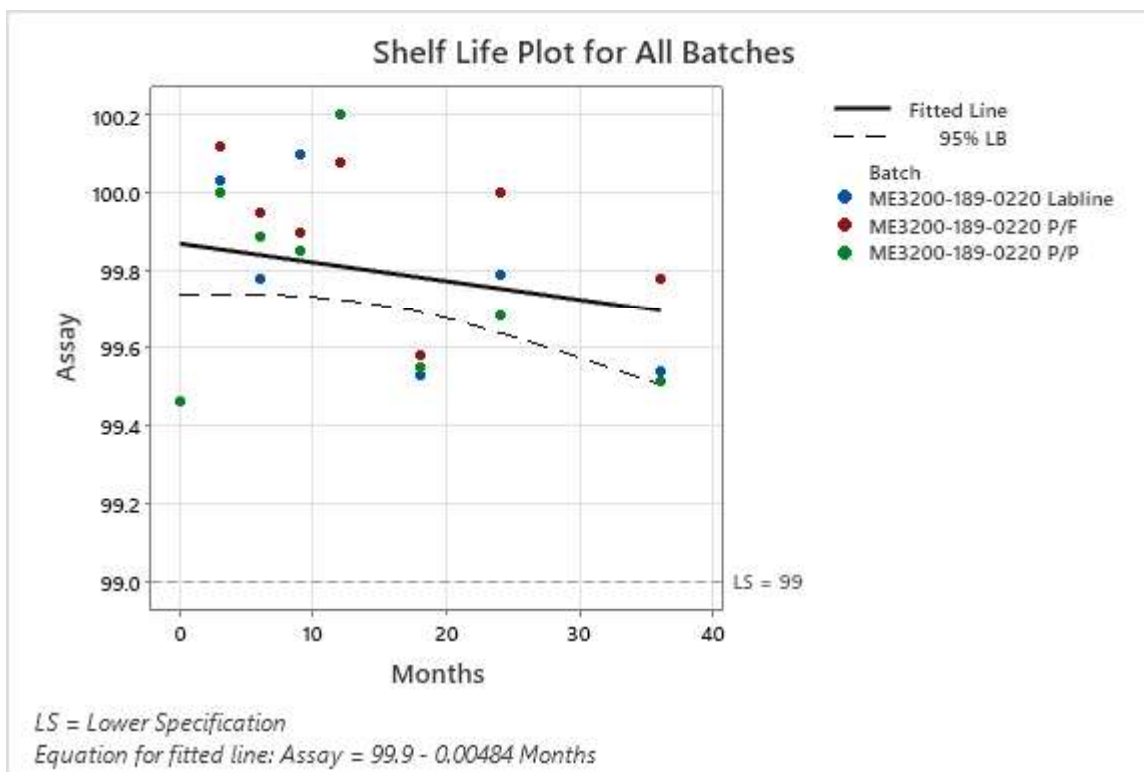| Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0034 a.u.	0.0023 a.u.	0.0048 a.u.	0.0080 a.u.	0.0022 a.u.	0.0046 a.u.	0.0048 a.u.	0.0464 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0041 a.u.	0.0029 a.u.	0.0057 a.u.	0.0095 a.u.	0.0025 a.u.	0.0054 a.u.	0.0057 a.u.	0.0379 a.u.
Assay (As Is)	99.0% min.	99.46%	100.03%	99.78%	100.10%	100.08%	99.53%	99.79%	99.54%
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%	8.8498%	8.7262%	8.6243%	8.6665%	8.6477%	8.6014%	8.5142%	8.5172%

Figure 1: Graph ME3200-189-0220 Absorbance @ 280nm

The predicted Shelf-Life for ME3200-189-0220 Absorbance @ 280nm was determined to be 81.5237 months at the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material.

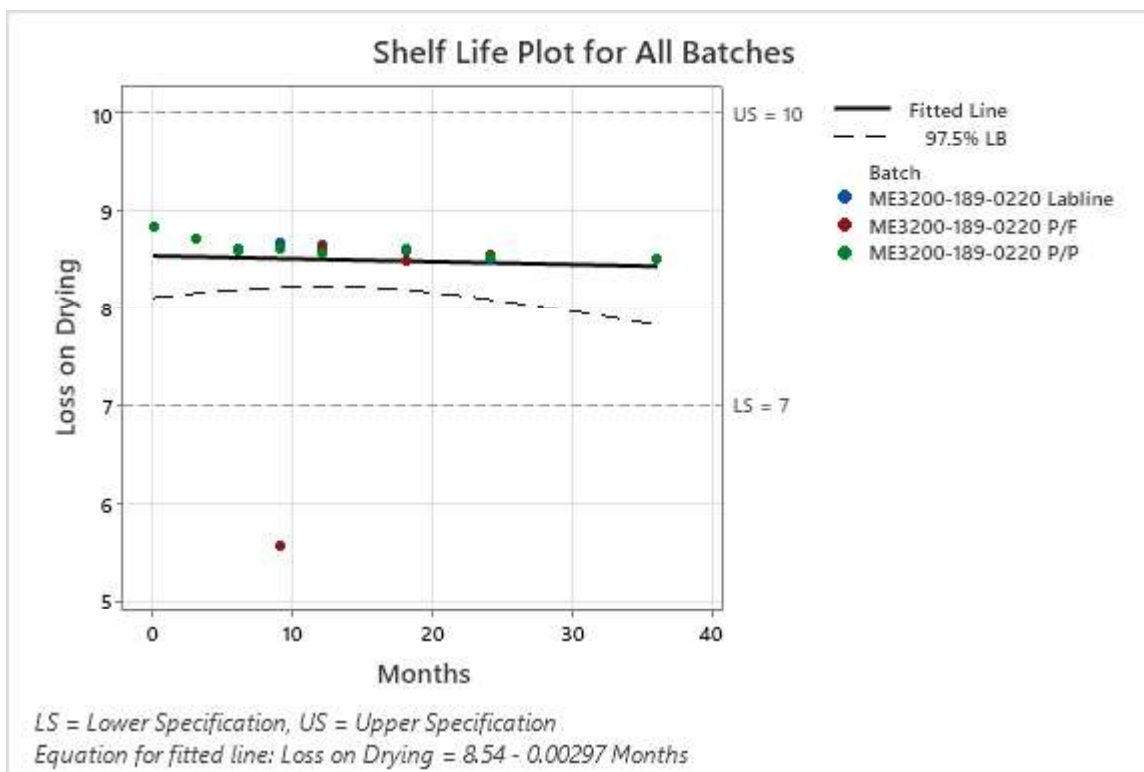**Figure 2: Graph ME3200-189-0220 Absorbance @ 260nm**

    The predicted Shelf-Life ME3200-189-0220 Absorbance @ 260nm was determined to be 96.1874 months at the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material.

Figure 3: Graph ME3200-189-0220 Assay (As Is)

No Shelf-Life was able to be determined for ME3200-189-0220 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.

Figure 4: Graph ME3200-189-0220 Loss on Drying

No Shelf-Life was able to be determined for ME3200-189-0220 Loss on Drying, 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.

7. CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. An increase in 1M Absorbance was noted from the t=24 and t=36 time point, however no further action was taken as all results were within stability specifications. In accordance with ICH Q1E, 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 long term conditions. Long-Term 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.

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.