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MES MONOHYDRATE 2022 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 MESM-0122-00153 that completed 24-months of long-term stability in September 2024. 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 Table 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:

3.1. Samples initially placed on the stability program for long-term testing consisted of one lot of MES. Stability samples from this lot were 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 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/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 long-term study, the samples were stored in the Long-Term Stability Chamber, H03SC01 at the Bangor, PA facility. 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 September 2022 to September 2024 the samples were located in the long-term stability chamber. For this time period, the maximum temperature recorded was 26.20°C, the minimum temperature recorded was 21.81°C, the average temperature recorded was 25.43°C, and the average kinetic temperature recorded was 25.43°C. The maximum relative humidity recorded was 80.5%, the minimum relative humidity recorded was 43.6%, 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. **BDI24-13** Out of range humidity for the Long-Term Stability Chamber H03SC01 caused by improper work order completion to prevent water leaking from the stability chamber. On 1/15/24 while conducting a maintenance walkthrough of the Bangor facility water was observed on the floor of room H03RM01. The issue was found to be a faulty pump and later repaired. There was no impact to the current list of materials in the stability chamber.

5.2. **BDI24-126** Out of specification humidity and temperature for H03SC01 occurred on 8/15/24 with a humidity reading of 54.4% and a temperature of 21.81°C. It was discovered that a 20-amp fuse had blown. The fuse was replaced and the chamber went back into specification on 8/16/24 with a humidity reading of 62.3%. There is no impact on the stability samples as this excursion lasted less than 24 hours.

6. LOT EVALUATION:

TABLE 2: LONG-TERM STABILITY RESULTS FOR MESM-0122-00153 P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0029 a.u.	0.0036 a.u.	0.0052 a.u.	0.0036 a.u.	0.0052 a.u.	0.0044 a.u.	0.0057 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0038 a.u.	0.0037 a.u.	0.0056 a.u.	0.0039 a.u.	0.0059 a.u.	0.0045 a.u.	0.0076 a.u.
Assay (As Is)	99.0% min.	100.08%	100.13%	99.99%	100.08%	100.32%	100.66%	100.18%
Appearance and Color	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
Loss on Drying (105°C)	7.0 – 10.0%	8.5012%	8.5039%	8.5520%	8.5310%	8.4366%	8.4419%	8.4381%

- **Remaining Interval Pull Dates**
  - T = 36: Scheduled for September 9, 2025
  - T = 48: Scheduled for September 9, 2026
  - T = 60: Scheduled for September 9, 2027

TABLE 3: LONG-TERM STABILITY RESULTS FOR MESM-0122-00153 2P/F

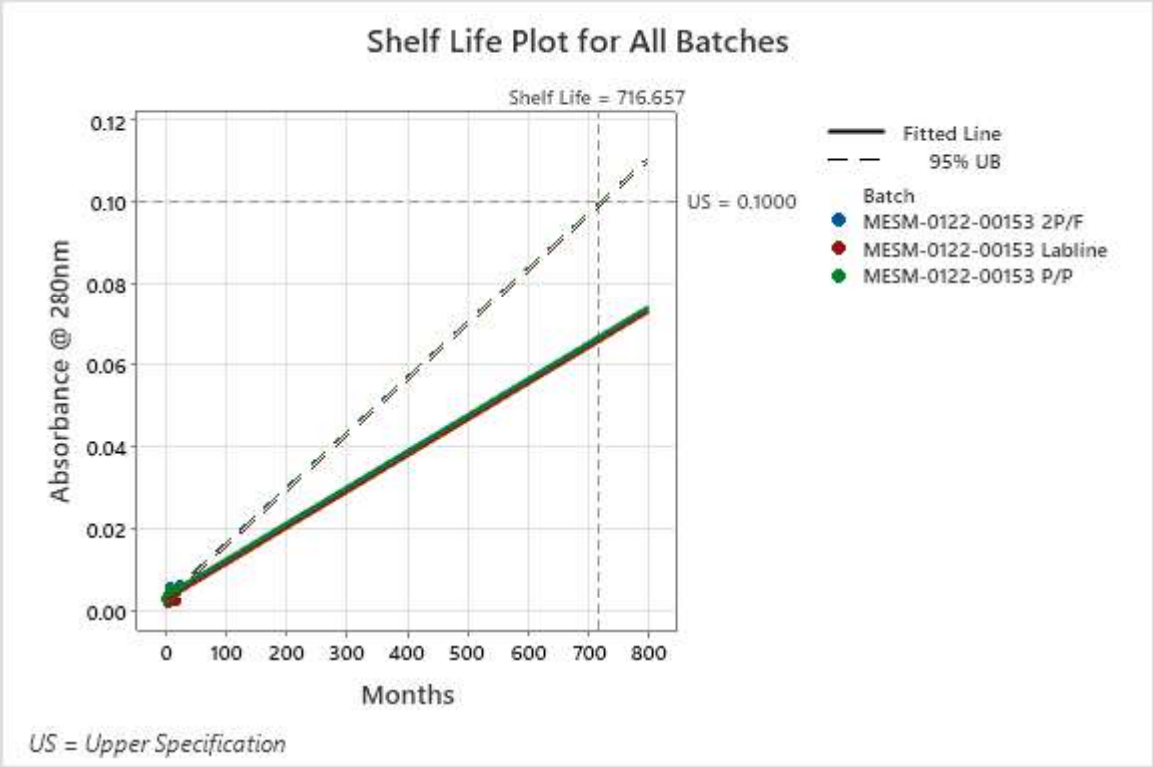
Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0029 a.u.	0.0036 a.u.	0.0059 a.u.	0.0040 a.u.	0.0049 a.u.	0.0047 a.u.	0.0060 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0038 a.u.	0.0035 a.u.	0.0066 a.u.	0.0043 a.u.	0.0057 a.u.	0.0052 a.u.	0.0073 a.u.
Assay (As Is)	99.0% min.	100.08%	99.91%	99.95%	100.11%	100.33%	100.17%	100.24%
Appearance and Color	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
Loss on Drying (105°C)	7.0 – 10.0%	8.5012%	8.4920%	8.5330%	8.4414%	8.4275%	8.4085%	8.4088%

- **Remaining Interval Pull Dates**
  - T = 36: Scheduled for September 9, 2025
  - T = 48: Scheduled for September 9, 2026
  - T = 60: Scheduled for September 9, 2027

TABLE 4: LONG-TERM STABILITY RESULTS FOR MESM-0122-00153 LABLINE

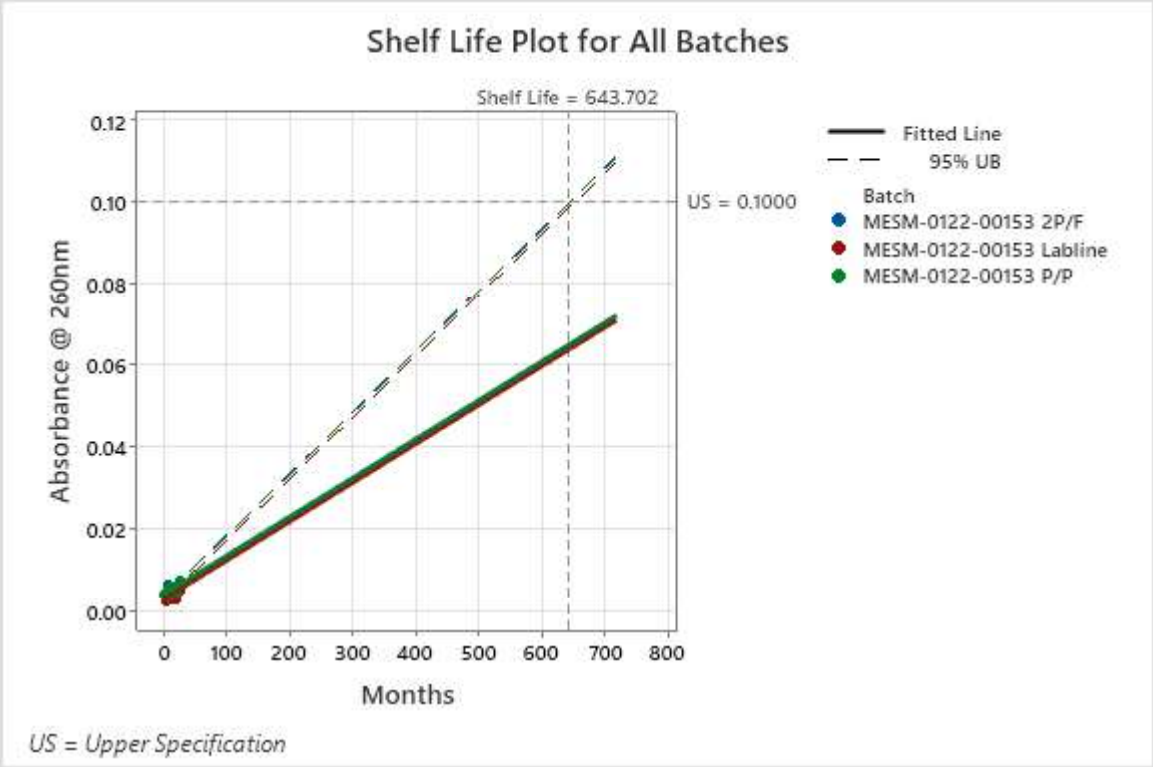
Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
Absorbance (1M) @ 280 nm	0.1000 a.u. max.	0.0029 a.u.	0.0019 a.u.	0.0049 a.u.	0.0028 a.u.	0.0038 a.u.	0.0024 a.u.	0.0057 a.u.
Absorbance (1M) @ 260 nm	0.1000 a.u. max.	0.0038 a.u.	0.0023 a.u.	0.0056 a.u.	0.0032 a.u.	0.0045 a.u.	0.0029 a.u.	0.0051 a.u.
Assay (As Is)	99.0% min.	100.08%	100.10%	99.86%	100.22%	100.32%	100.12%	100.34%
Appearance and Color	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
Loss on Drying (105°C)	7.0 – 10.0%	8.5012%	8.5206%	8.5827%	8.4993%	8.5417%	8.4311%	8.4276%

- **Remaining Interval Pull Dates**
  - T = 36: Scheduled for September 9, 2025
  - T = 48: Scheduled for September 9, 2026
  - T = 60: Scheduled for September 9, 2027



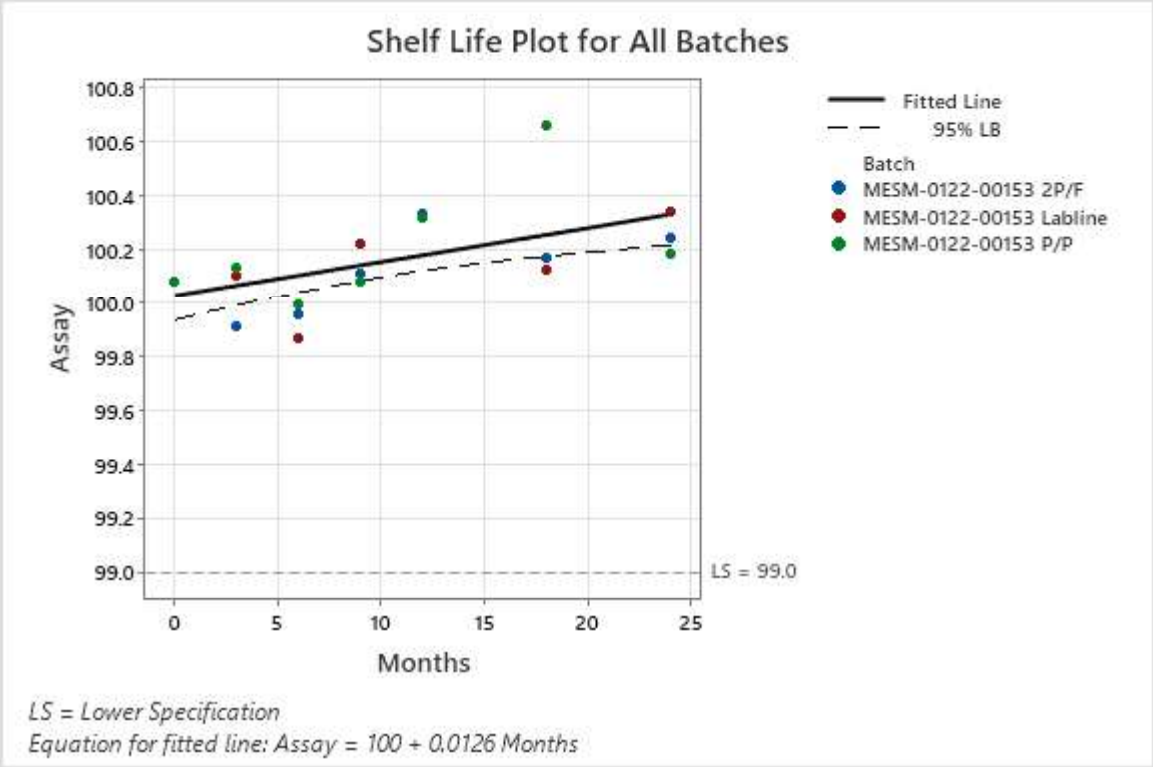
GRAPH 1: MESM-0122-00153 ABSORBANCE @ 280NM

The predicted Shelf-Life for MESM-0122-00153 Absorbance at 280 nm was determined to be 716.657 months at the T=24-month time interval. There is no impact to the product or currently assigned retest period of this material.



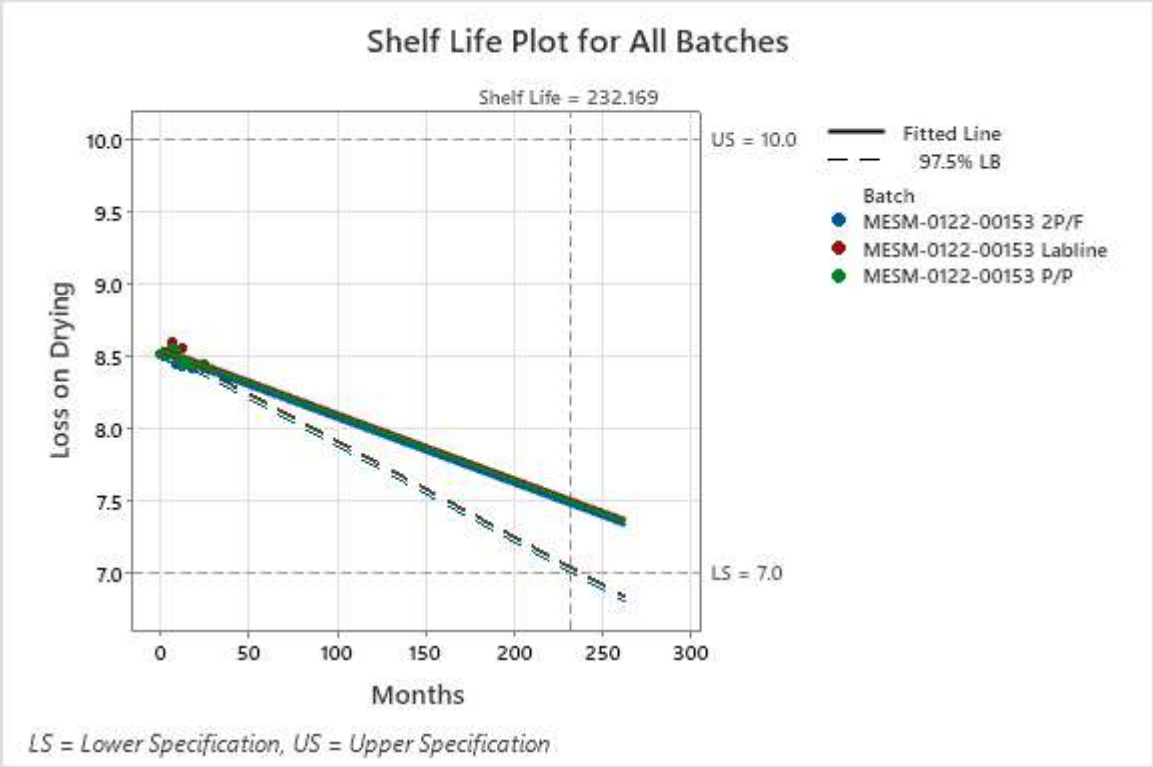
GRAPH 2: MESM-0122-00153 ABSORBANCE @ 260NM

The predicted Shelf-Life for MESM-0122-00153 Absorbance at 260 nm was determined to be 643.702 months at the T=24-month time interval. There is no impact to the product or currently assigned retest period of this material.



GRAPH 3: MESM-0122-00153 ASSAY (AS IS)

No Shelf-Life was able to be determined for MESM-0122-00153 Assay (As Is), as the mean response slope is not significantly different from zero using 95% confidence at the T=24-month time interval. There is no impact to the product or currently assigned retest period of this material.



GRAPH 4: MESM-0122-00153 LOSS ON DRYING

The predicted Shelf-Life for MESM-0122-00153 Loss on Drying was determined to be 232.169 months at the T=24-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. 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. In regards to the Long-Term Stability Study for MES, Monohydrate (MES), all data met the specifications set forth in the Stability Testing Program for the lot stored at the recommended long-term condition. The Long-Term Stability Study data, along with the predicted shelf-life plots, supports a retest date of 24 months and expiration date of 36 months for MES, Monohydrate (MES), manufactured at BioSpectra in the Bangor, PA facility.

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 long-term 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 and the product has an established shelf life, the batch will be withdrawn from the market through communication with any 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