MES, MONOHYDRATE
LONG TERM STABILITY REPORT 2017

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1. OVERVIEW

The purpose of this Report is to analyze the data obtained from the Long Term Stability of MES, Monohydrate manufactured in Excipient Cell 1, E02 of BioSpectra's Bangor, PA facility. This Report will also pertain to the MES, Monohydrate manufactured in Excipient Cell 2, E03 of BioSpectra's Bangor, PA facility. Samples were placed on the Stability Testing Program in 2013 consisting of seven Process Validation batches. The long term Real-Time Stability Program consists of testing every three months for the first year, every six months for the second year and annually for each subsequent year, notated as T_0, T_3, T_6, T_9, T_{12}, T_{18}, T_{24}, and T_{36}. Analysis has been conducted for a total of thirty six months in order to assure that the manufactured product remains stable while stored in 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.

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 data can be found in the MES, Monohydrate Long Term Stability Program binders.

2. REFERENCES

2.1. Current USP
2.2. ICH Q1
2.3. Stability Testing Program

3. DEFINITIONS

3.1. <u>CL:</u> Control Limit, the average
3.2. <u>UCL:</u> Upper control limit, 3 sigma above the CL
3.3. <u>LCL:</u> Lower control limit, 3 sigma below the CL
3.4. <u>OOL</u>: Point(s) that fall outside the UCL or LCL
3.5. <u>OOT</u>: Out Of Trend, this means that the material still meets control limits but was not in trend with the rest of the material.
3.6. <u>OOS:</u> Out of Specification.
3.7. <u>T:</u> Time in months.

4. SAMPLE DESIGNATION

Samples placed on the Stability Testing Program consisted of seven MES, Monohydrate Bio Excipient Grade Process Validation batches. Stability samples from each of the batches were put into a round poly drum lined with a poly liner (P/P), with the liner being goose-neck tied closed. These batches were placed on stability in the Zone M Warehouse located in the BioSpectra Bangor, PA facility. The type of packaging utilized in the stability study was based on BioSpectra packaging.

5. STORAGE

Although there are currently no storage conditions for MES, Monohydrate, storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (10-40°C) and humidity (monitor).
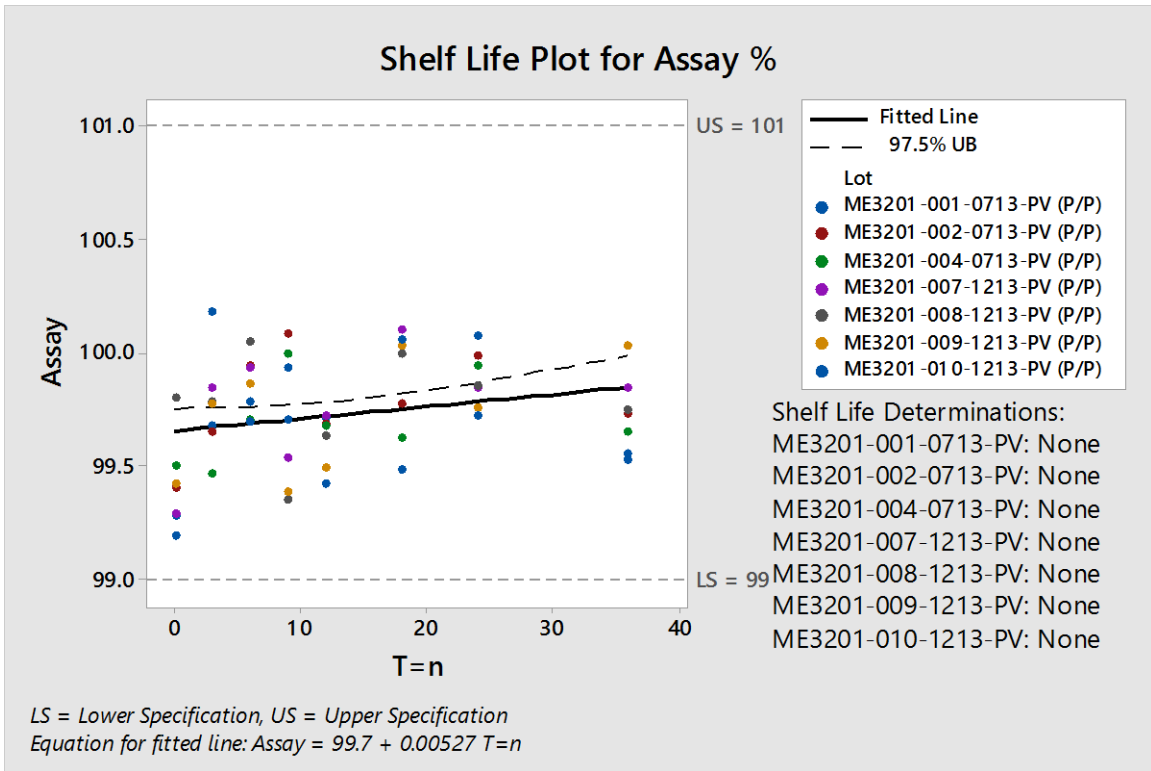
6. LOT EVALUATION
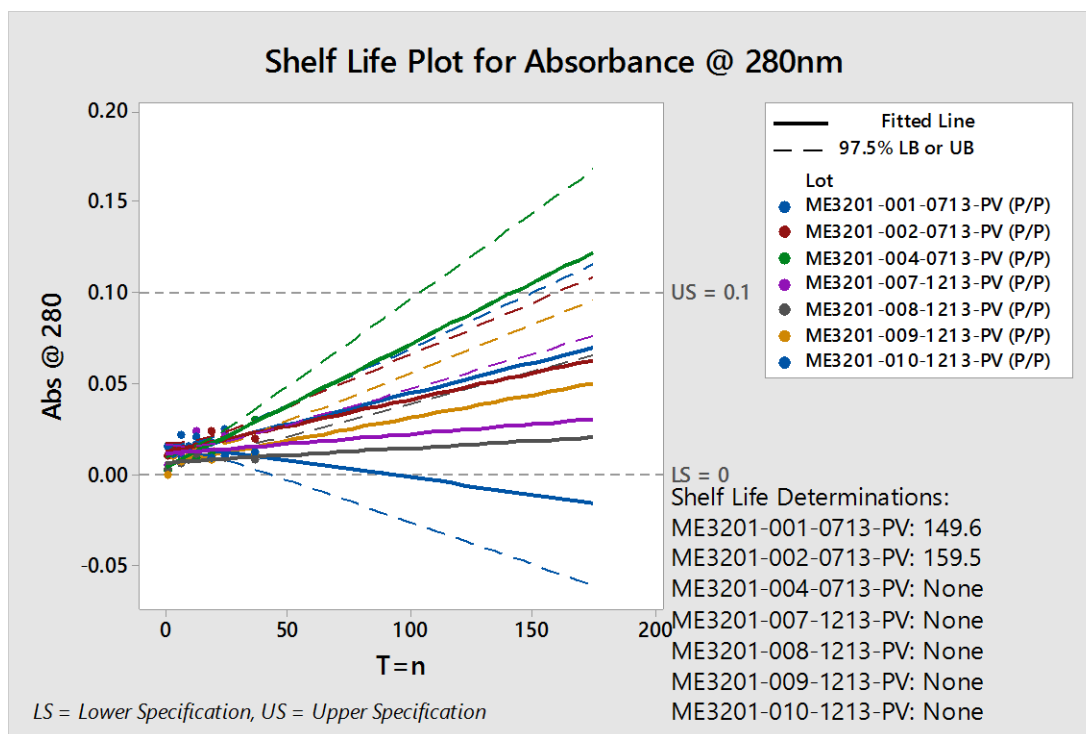
GRAPH 1: ABSORBANCE @ 280NM

Results for absorbance @ 280nm showed no predictable shelf life on the combine graph for all lots, as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from this analysis in the 36 month analysis time frame. The shelf lives predicted for lots ME3201-001-0713-PV and ME3201-002-0713-PV exceed the current 24 month retest date as well as the 36 month expiration date assigned to this material.
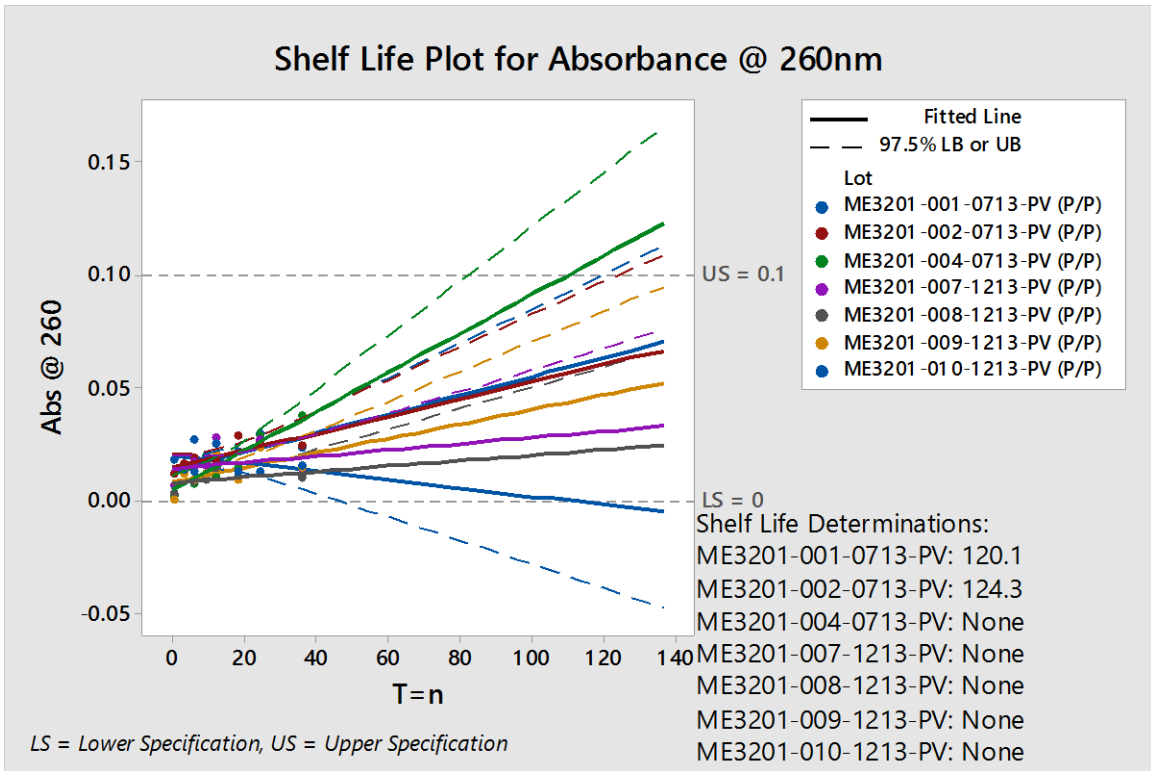
GRAPH 2: ABSORBANCE @ 260NM

Results for absorbance @ 260nm showed no predictable shelf life on the combine graph for all lots, as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from this analysis in the 36 month analysis time frame. The shelf lives predicted for lots ME3201-001-0713-PV and ME3201-002-0713-PV exceed the current 24 month retest date as well as the 36 month expiration date assigned to this material.

Shelf Life Plot for Assay %

LS = Lower Specification, US = Upper Specification
Equation for fitted line: Assay = 99.7 + 0.00527 T=n

GRAPH 3: ASSAY %

Results for assay % showed no predictable shelf life on the combined graph for all lots, as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from this analysis in the 36 month analysis time frame.

7. CONCLUSION

All data met the specifications set forth in the Stability Testing Program. Long Term Stability Data obtained for lots manufactured in 2013 indicate that the material is stable for a minimum of 36 months as all data met the specifications and there were no significant changes observed. Based on the data obtained, a 36-month shelf life can be assigned to all MES, Monohydrate lots. Data will continue to be assessed with future lots within the Stability Testing Program.

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.

        8.1.1.1. 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.

    8.1.2. If a stability analysis is found to be out of specification, the batch will be withdrawn from the market through communication with the Applicant and any additional customer. Additionally, an investigation will be conducted to determine the possible withdrawal of the batches produced before and after the batch in question.

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

MES, MONOHYDRATE
REAL-TIME STABILITY REPORT:
ME3200-054-0517-PV

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1   OVERVIEW:

The purpose of this report is to analyze the data obtained from the Real-Time Stability of MES, Monohydrate manufactured at BioSpectra's Bangor, PA facility. Samples were placed on the Stability Testing Program in June 2017, to fulfil the requirements of adding all process validation batches. The long-term Real-Time Stability Program consists of testing every three months for the first year, every six months for the second year and annually for each subsequent year, notated as T_n, where n represents the number of months on stability. Analysis has been conducted for a total of thirty-six months in order to assure that the manufactured material remains stable under the specified conditions and for the specified interval of time. The analysis of the compiled data may be used to re-evaluate the retest period for future lots of manufactured material.

This Real-Time Stability analysis assesses the stability of one lot of MES, Monohydrate that completed three years of long-term stability in June 2020. The study included the following analyses: Absorbance (1M at 280 and 260nm), Appearance and Color, Assay (As-is), Identification (IR), and Loss on Drying. Results from all analyses are summarized in Table 1 and Shelf-Life Plot determinations have been created for quantitative analyses. Shelf-Life Plots determine 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 Predicted Shelf Life. This allows BioSpectra to ensure that the product will be stable over the time period in which it is part of the Stability Testing Program.

2   REFERENCES:

2.1   Current USP
2.2   ICH Q1
2.3   Stability Testing Program
2.4   Stability Inventory

3   SAMPLE DESIGNATION:

Samples placed on the Stability Testing Program consisted of one lot of MES, Monohydrate. Stability samples were individually placed into small poly bags and were sealed with a ziptie. All small poly bags were then placed into one larger poly bag and sealed with a ziptie. The large poly bag containing all samples was then placed into a poly pail and sealed. This packaging configuration is denoted as 2Poly/Poly (2P/P). The type of packaging utilized in this stability study was based on BioSpectra packaging offered to the customer.

4   STORAGE:

At the start of this stability study, MES, Monohydrate stability samples were being stored in the Zone M Warehouse. Due to the inability to control the temperature of the warehouse during the summer months, the stability samples were relocated to the long-term stability chamber.

From June 2, 2017 through September 25, 2019, the samples were stored in the Zone M Warehouse. The temperature was monitored continuously using MadgeTech data loggers. The maximum temperature of the warehouse during the stability study was 33.67°C and the minimum temperature of the warehouse was 12.17°C.

On September 25, 2019, all stability samples were moved from the Zone M Warehouse to the long-term stability chamber. The samples were stored in this location until the end of the 36-month stability study on May 29, 2020. The temperature was monitored continuously using MadgeTech data loggers, with an allowable temperature range of 23°C – 27°C. The minimum temperature reached during this time was 23.97°C and the maximum temperature reached was 27.72°C. The maximum temperature was out of specification for less than one hour and the humidity remained within specification during this time. No discrepancy was issued for this excursion.
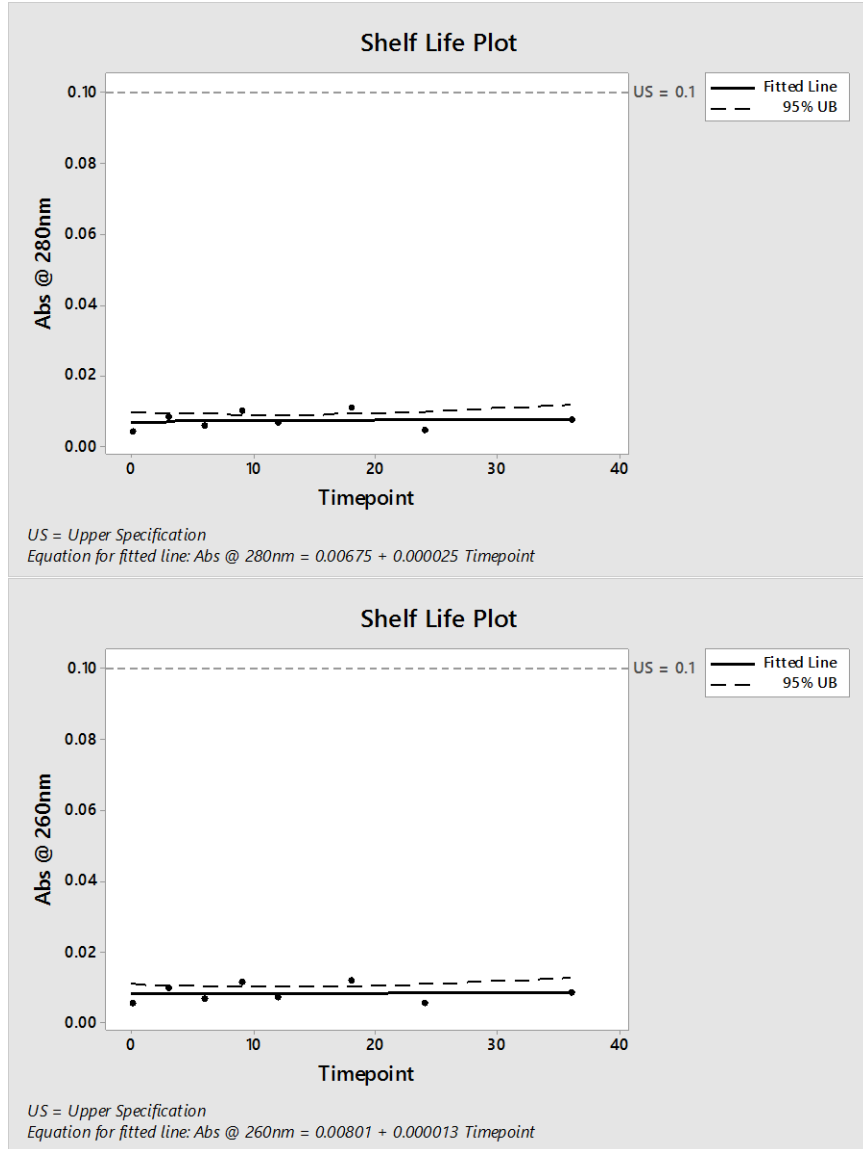
5 INVESTIGATIONS:

5.1 BDI18-20: The temperature Alarm Notifications were not received by BioSpectra due to the way the alarms rules were established. The temperature in the Zone M Warehouse was reported as less than 15°C on multiple dates ranging from 12/28/17 to 3/4/18. The average temperature was reported as 18.87°C and the minimum temperature was reported as 12.20°C. T_9 samples were pulled and tested immediately after this timeframe, and all results met specification.

6 LOT EVALUATION:

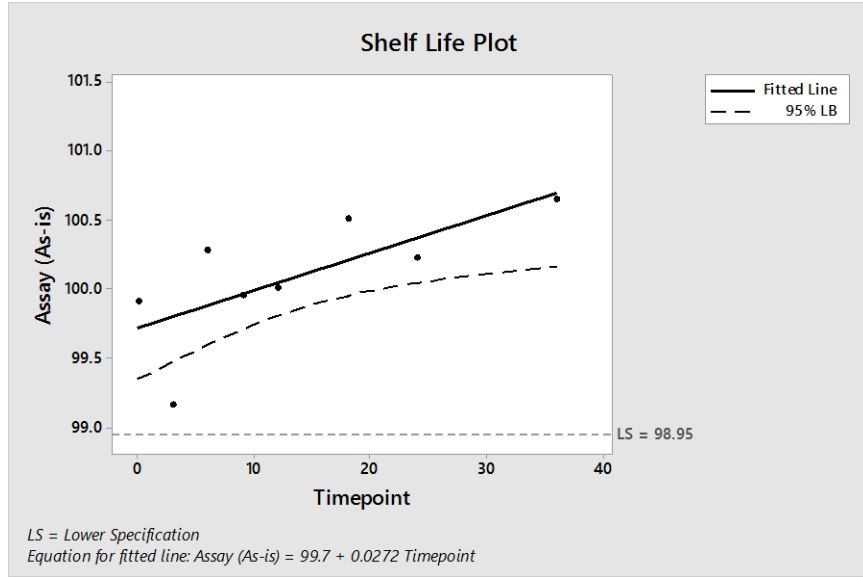### TABLE 1: RESULTS OF LONG-TERM STABILITY ANALYSES

MES, Monohydrate Stability Data										
Lot Number	Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
ME3200-054-0517-PV 2P/P	Absorbance (1M) @ 280nm	0.1000 a.u. max	0.0040	0.0081	0.0057	0.0098	0.0066	0.0107	0.0044	0.0074
	Absorbance (1M) @ 260nm	0.1000 a.u. max	0.0055	0.0096	0.0064	0.0113	0.0072	0.0117	0.0053	0.0084
	Assay (As-is)	99.0% min	99.91%	99.16%	100.28%	99.95%	100.01%	100.51%	100.22%	100.65%
	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	7.0 – 10.0%	8.5599%	8.4783%	8.4837%	8.4906%	8.4515%	8.4813%	8.4728%	8.4551%

GRAPHS 1 AND 2: SHELF-LIFE PLOTS FOR ABSORBANCE

Shelf Life Plot

Abs @ 280nm vs *Timepoint*

US = 0.1 — Fitted Line, 95% UB

US = Upper Specification
Equation for fitted line: Abs @ 280nm = 0.00675 + 0.000025 Timepoint

Shelf Life Plot

Abs @ 260nm vs *Timepoint*

US = 0.1 — Fitted Line, 95% UB

US = Upper Specification
Equation for fitted line: Abs @ 260nm = 0.00801 + 0.000013 Timepoint
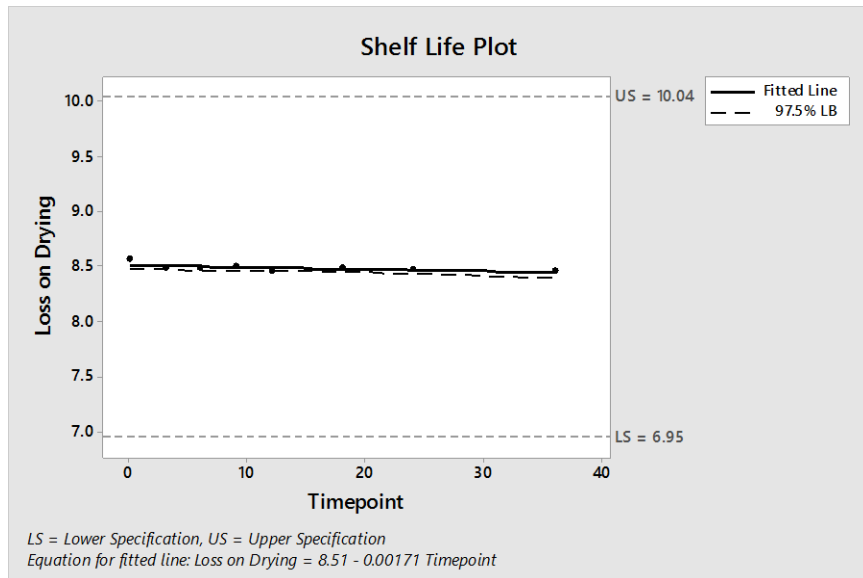
No shelf life is able to be determined for Absorbance (1M), as the mean response slopes for 260 and 280nm are not significantly different from zero. There is no impact to the product or the currently assigned twenty-four-month retest date assigned to MES, Monohydrate.

GRAPH 3: SHELF-LIFE PLOT FOR ASSAY

Shelf Life Plot

LS = Lower Specification
Equation for fitted line: Assay (As-is) = 99.7 + 0.0272 Timepoint

No shelf life is able to be determined for Assay (As-is), as the mean response slope is not significantly different from zero. There is no impact to the product or the currently assigned twenty-four-month retest date assigned to MES, Monohydrate.

GRAPH 4: SHELF LIFE PLOT FOR LOSS ON DRYING

Shelf Life Plot

LS = Lower Specification, US = Upper Specification
Equation for fitted line: Loss on Drying = 8.51 - 0.00171 Timepoint

No shelf life is able to be determined for Loss on Drying, as the mean response slope is not significantly different from zero. There is no impact to the product or the currently assigned twenty-four-month retest date assigned to MES, Monohydrate.

CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. In accordance with ICH Q1E 2.4.2.1, the re-test 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. The data obtained during this stability study indicates that the material packaged in 2P/P packaging is stable for 36 months. A re-test date of 36 months may be assigned to all MES, Monohydrate lots manufactured at BioSpectra in the Bangor, PA facility.

7   STATEMENT OF COMMITMENT:

7.1   BioSpectra is responsible for the following regarding Stability Data in this Report:

7.1.1   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.

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