MOPS BIO EXCIPIENT GRADE 2016 - 2018
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 MOPS. 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.

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 Testing Program. All quantitative data was analyzed using these methods. The data can be found in the MOPS Real Time Stability Program binders.

This Long Term Stability analysis will assess the stability of 7 lots of MOPS that have concluded stability studies.

2. DEFINITIONS:

CL: Control Limit, the average

UCL: Upper control limit, 3 sigma above the CL

LCL: Lower control limit, 3 sigma below the CL

OOT: Out Of Trend, this means that the material still meets control limits but was not in trend with the rest of the material.

OOS: Out of Specification, for the purpose of this stability analysis, OOS will mean that there is a point(s) that fall outside of the UCL or LCL.

3. SAMPLE DESIGNATION:

Samples initially placed on the Stability Testing Program consisted of all process validation batches and one lot per year. Stability samples from each of these batches were packaged as Poly/Poly (P/P) in accordance with the Sampling Matrix SOP.

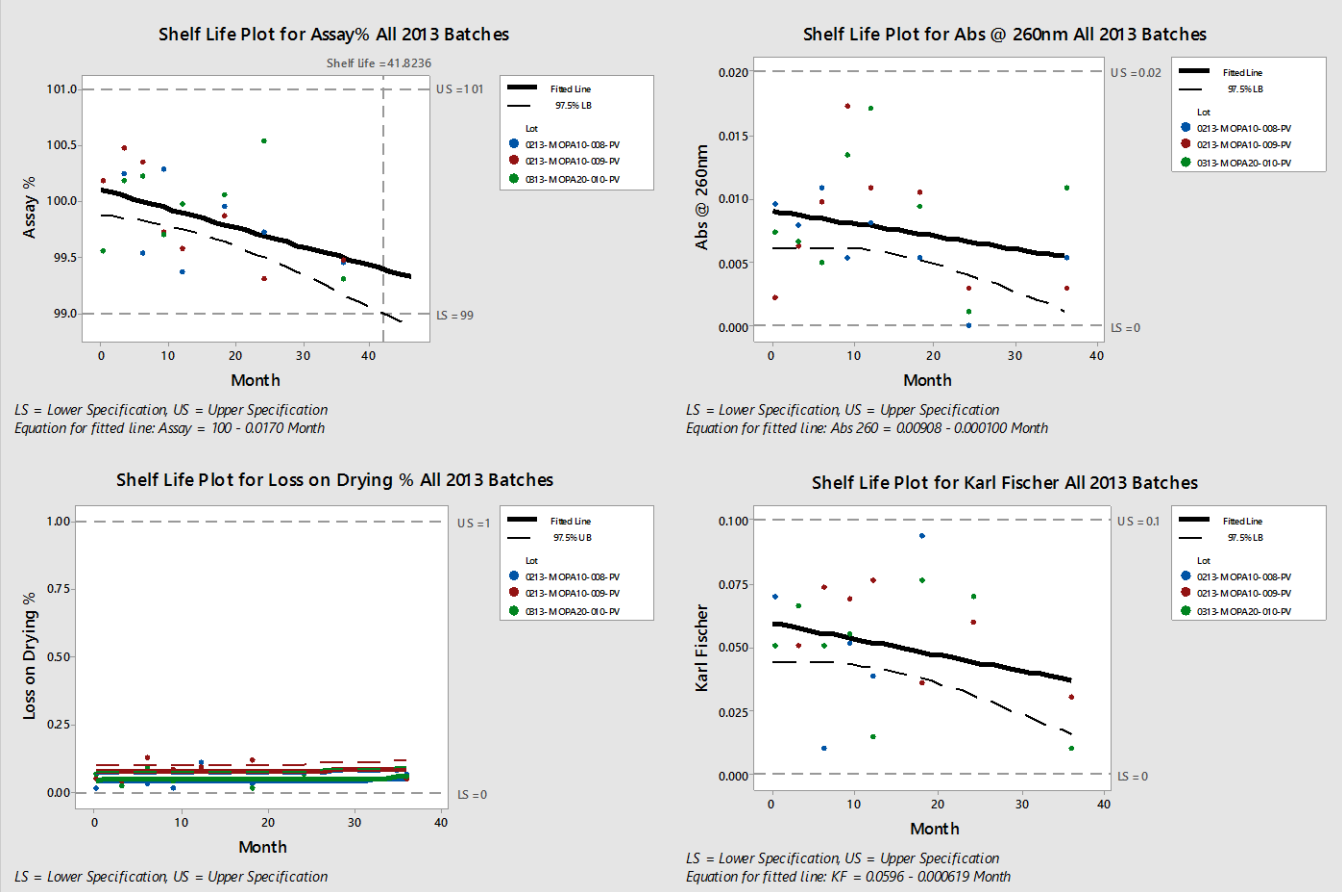
4. STORAGE:

Although there are currently no storage conditions for MOPS, storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (15-30°C) and humidity (monitor).

5. LOT ANALYSIS 2013 BATCHES:

The following graphs will evaluate the three batches of MOPS placed on stability in 2013: 0213-MOPA10-008-PV, 0213-MOPA10-009-PV, 0213-MOPA10-010-PV. All batches were analyzed for Assay, Appearance and Color, Absorbance @ 260nm, Loss on Drying and Karl Fischer at each of the nine time points. Only quantitative data will be analyzed by the Shelf Life Plot. All batches passed analysis for Appearance and Color at all nine time points.

GRAPH 1. ASSAY (%), ABS @ 260NM, LOSS ON DRYING (%) AND KARL FISCHER (%)



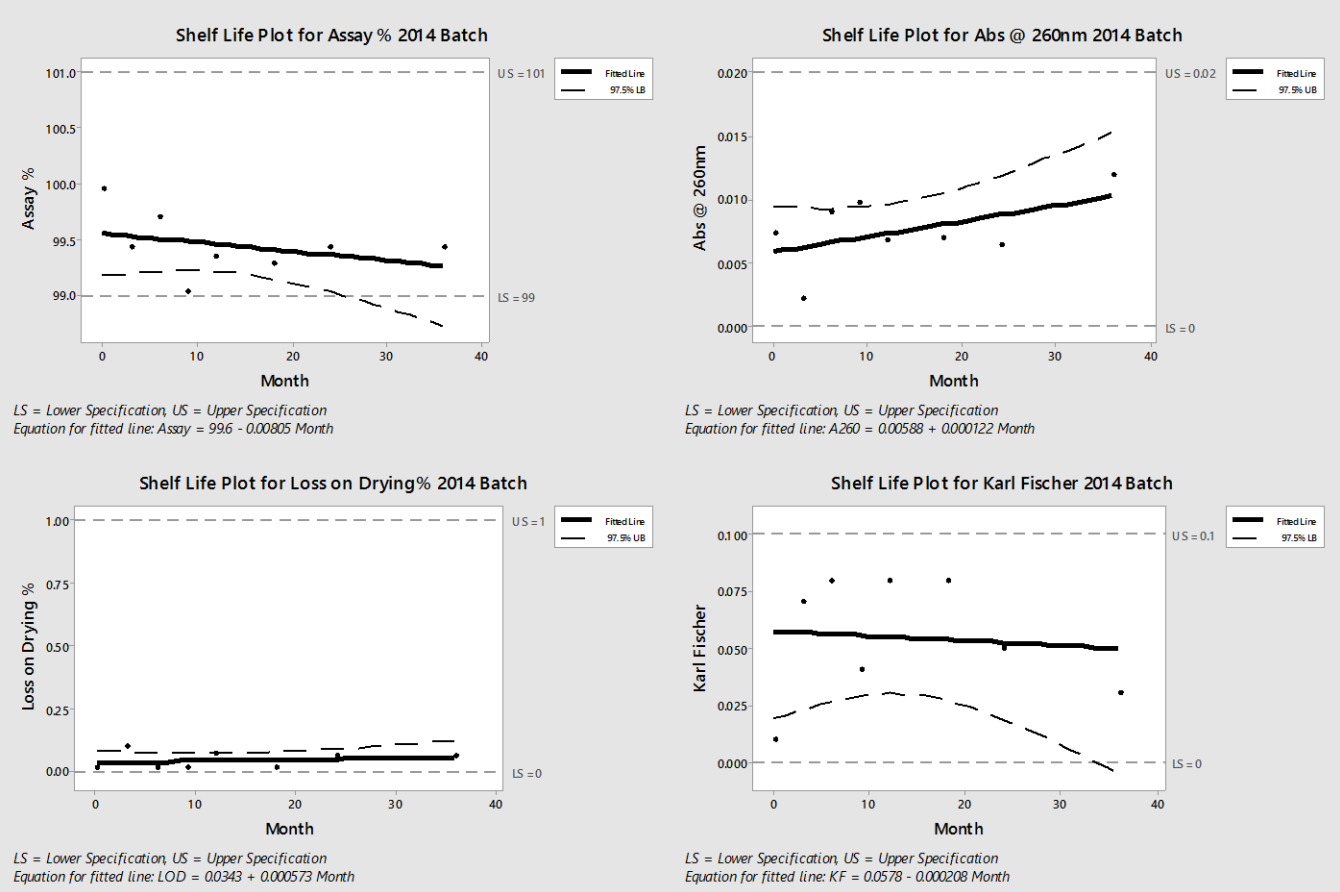
Results for absorbance at 260nm, loss on drying, and karl fischer showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is little

degradation of the product shown from these analyses. A Shelf life of 41.8 months was predicted based on data for assay. The predicted shelf life exceeds the current 24 month retest date as well as the 36 month maximum expiration date assigned to this material.

6. LOT ANALYSIS 2014 BATCH:

The following graphs will evaluate the batch of MOPS placed on stability in 2014: MP3200-031-1114. This batch was analyzed for Assay, Appearance and Color, Absorbance @ 260nm, Loss on Drying and Karl Fischer at each of the nine time points. Only quantitative data will be analyzed by the Shelf Life Plot. This batch passed analysis for Appearance and Color at all nine time points.

GRAPH 2. ASSAY (%), ABS @ 260NM, LOSS ON DRYING (%) AND KARL FISCHER (%) FOR MP3200-031-1114

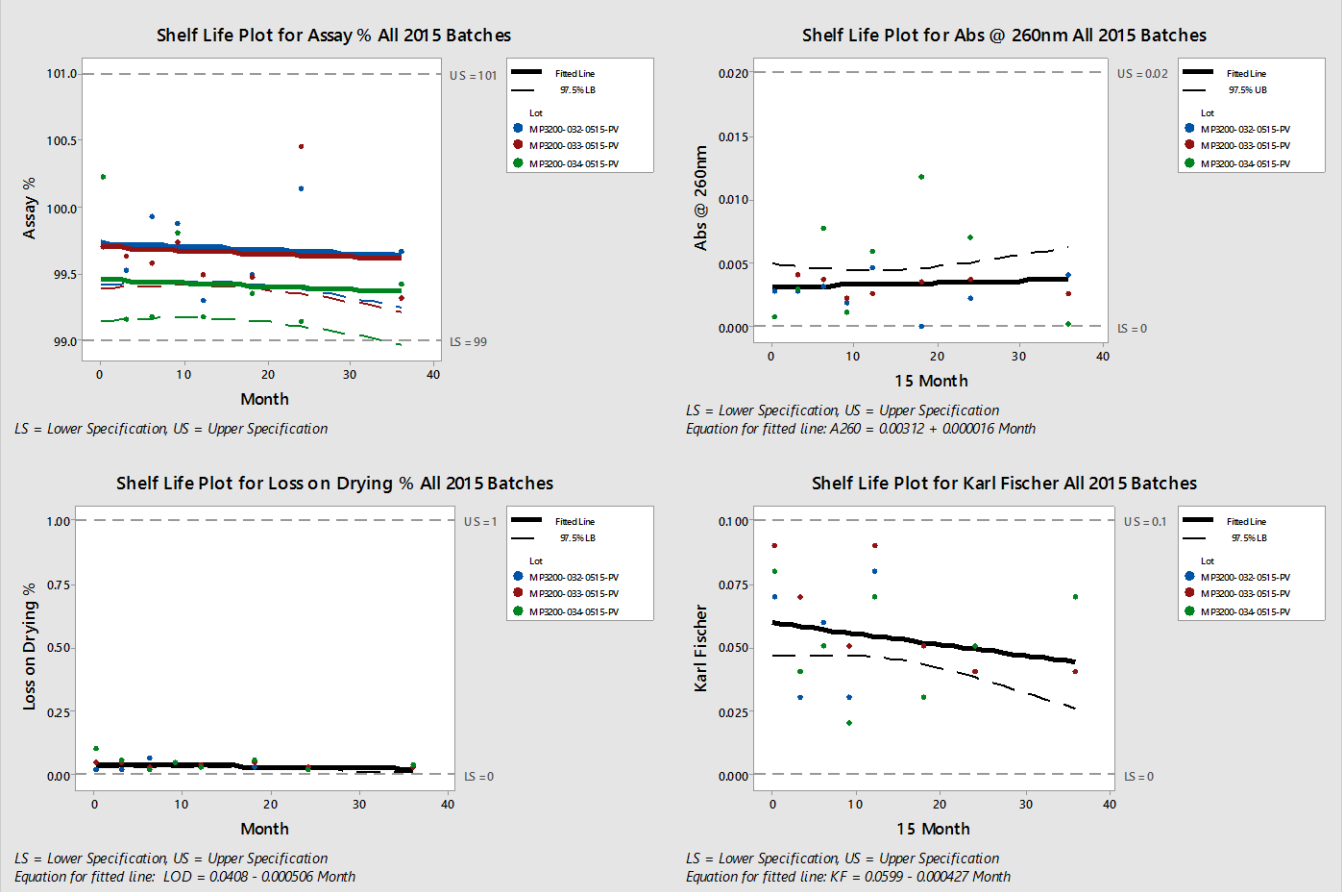


Results for assay, absorbance at 260nm, loss on drying, and karl fischer showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from these analyses in the 36 month analysis time frame.

7. LOT ANALYSIS 2015 BATCHES:

The following graphs will evaluate the batch of MOPS placed on stability in 2015: MP3200-032-0515-PV, MP3200-033-0515-PV, and MP3200-034-0515-PV. All batches were analyzed for Assay, Appearance and Color, Absorbance @ 260nm, Loss on Drying and Karl Fischer at each of the nine time points. Only quantitative data will be analyzed by the Shelf Life Plot. All batches passed analysis for Appearance and Color at all nine time points.

GRAPH 3. ASSAY (%), ABS @ 260NM, LOSS ON DRYING (%) AND KARL FISCHER (%)



Results for assay, absorbance at 260nm, loss on drying, and karl fischer showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from these analyses in the 36 month analysis time frame.

8. CONCLUSION:

Long Term Stability Data obtained for lots manufactured from 2013-2015 indicate that the material is stable for a minimum of 36 months. A 2 year retest date remains for this material since all lots that have reached the 24 month data point have met specifications. Additional time after the two years may be given based on historical and current data up to one year after a retest has been conducted.

9. STATEMENT OF COMMITMENT:

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

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

MOPS BIO EXCIPIENT GRADE
REAL-TIME STABILITY REPORT: MP3200-048-0116

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the Real-Time Stability of MOPS Bio Excipient Grade manufactured at BioSpectra's Stroudsburg, PA facility. Samples were placed on the Stability Testing Program in January of 2016 to fulfil the requirements of placing one lot of manufactured material per year on the Stability Testing Program. Testing intervals are designated by T_n, where *n* represents 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 for a total of three years. Analysis has been conducted for a total of thirty-six months in order to assure that the manufactured product 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 Report assesses the stability of one lot of MOPS Bio Excipient Grade material. The study includes the following analyses: Absorbance (0.1M), Appearance and Color, Assay (Dried), Loss on Drying, Water (by KF), and Solutions Test. Results from all analyses are summarized in Table 2, and Shelf-Life Plot determinations have been created for all 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 MOPS Bio Excipient Grade material. Stability samples from this batch were placed into one packaging configuration. These samples were packaged in accordance with the Stability Inventory SOP. Reference Table 1, below, for the packaging configuration and its description. The type of packaging utilized in this stability study was based on BioSpectra final packaging offered to the customer.

TABLE 1: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Poly/Poly (P/P)	Samples are packaged into small poly bags and sealed with a ziptie. All individual samples are then placed into a poly drum.

4. STORAGE:

Samples were placed on stability in BioSpectra's Stroudsburg, PA facility Stability Area, located in the quarantine area of the Warehouse. Although there are no storage requirements for MOPS Bio Excipient Grade material, storage conditions were continuously monitored and recorded utilizing MadgeTech data loggers for temperature (specification 15-30°C) and humidity (specifications: monitor). The samples were stored in the Stroudsburg Warehouse from January 20, 2016 through January 21, 2019. The maximum temperature of the warehouse during this time was 28.14°C and the minimum temperature of the warehouse during this time was 12.63°C. See Section 5 for the discrepancy investigations initiated for temperature excursions.

5. INVESTIGATIONS:

5.1. SDI16-57 was initiated for temperatures dropping below the minimum storage temperature of 15°C. The temperature excursion had no impact on the MOPS stability samples, as the next time point, T_{12}, was pulled and tested, and all results met specification.

5.2. SDI18-01 was initiated for temperatures dropping below the minimum storage temperature of 15°C. The temperature excursion had no impact on the MOPS stability samples, as the next time point, T_{24}, was pulled and tested, and all results met specification.

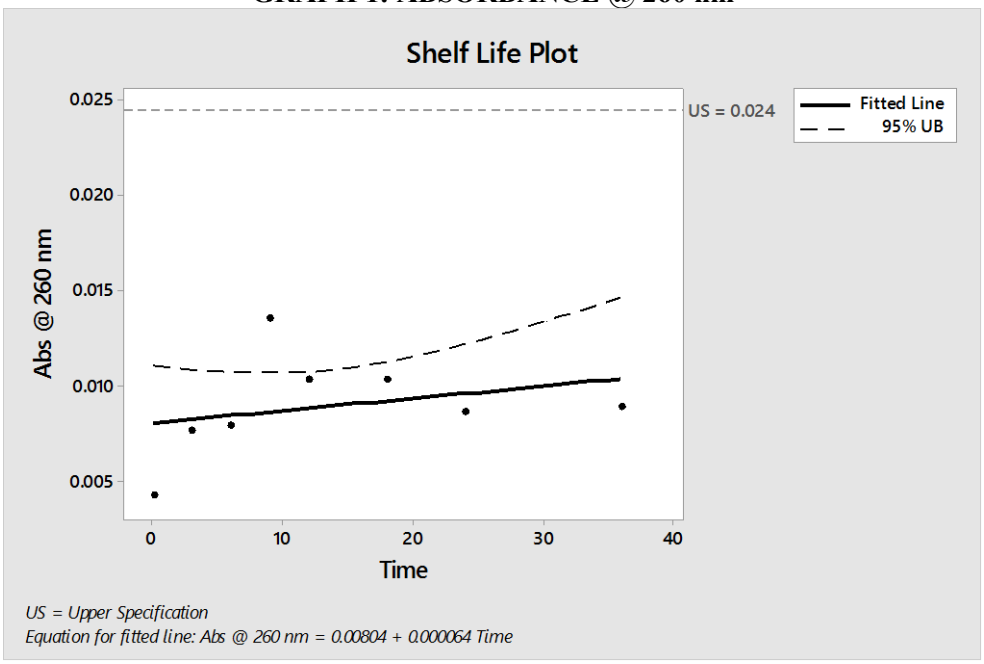
5.3. SDI18-45 was initiated for MadgeTech data loggers not being replaced before the calibration due date. This had no impact on the MOPS stability samples, as the next time point, T_{36}, was pulled and tested, and all results met specification.

6. LOT EVALUATION:

TABLE 2: ALL INCLUSIVE STABILITY DATA

MOPS Stability Data										
Lot Number	**Analysis**	**Specification**	**T_0**	**T_3**	**T_6**	**T_9**	**T_{12}**	**T_{18}**	**T_{24}**	**T_{36}**
MP3200-048-0116 (P/P)	Absorbance (0.1M)	0.02 a.u. max. @ 260 nm	0.0042	0.0076	0.0079	0.0135	0.0103	0.0103	0.0086	0.0089
	Appearance and Color	White/Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
	Assay (Dried)	99.0% min	99.03%	99.26%	99.96%	99.22%	99.12%	99.38%	99.36%	99.45%
	Loss on Drying	1.0% max.	<0.0133%	0.0330%	0.0532%	0.0533%	0.0267%	<0.0133%	0.0466%	0.0458%
	Karl Fischer	0.1% max.	0.04%	0.03%	0.04%	0.04%	0.05%	0.08%	0.04%	0.05%
	Solutions Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test

GRAPH 1: ABSORBANCE @ 260 nm

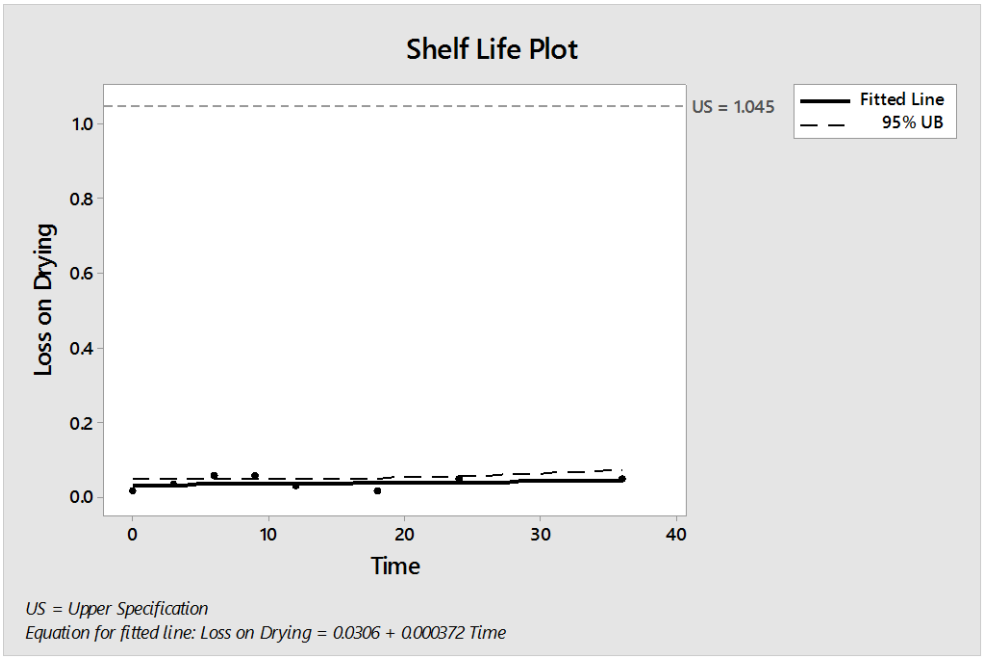


No Shelf-Life is able to be determined for Absorbance @ 260 nm, as the mean slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

GRAPH 2: ASSAY (DRIED)

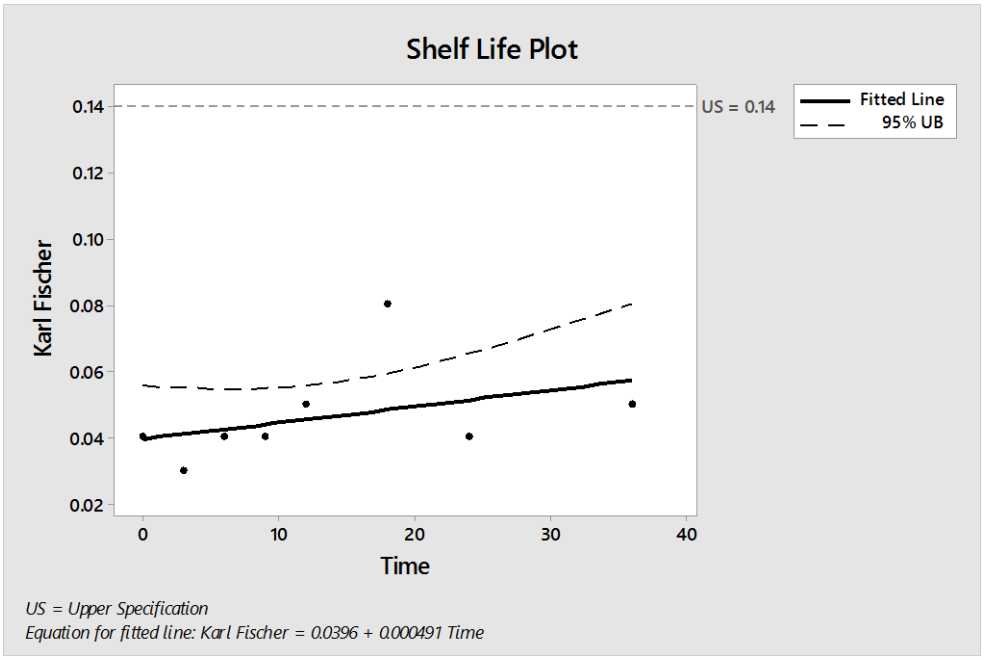
No Shelf-Life is able to be determined for Assay, as the mean response slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

GRAPH 3: LOSS ON DRYING



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 currently assigned expiration of this material.

GRAPH 4: KARL FISCHER



No Shelf-Life is able to be determined for Karl Fischer, as the mean response slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

7. CONCLUSION:

All data met the specification 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 2*x*, 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 MOPS Bio Excipient material packaged in Poly/Poly packaging is stable for 36 months. The assigned retest date will remain at 24 months unless requested on an individual lot-by-lot basis.

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.

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