BIOSPECTRA
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HEPES REAL-TIME STABILITY REPORT: HE3200-019-0420

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 HEPES Bio Excipient material lot manufactured in 2020 at BioSpectra's Bangor, PA facility. Testing intervals are designated by Tn, where n equals 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 stability analysis will assess the stability of HEPES Bio Excipient material lot HE3200-019-0420 that completed thirty-six (36) months of real-time stability in April 2023. This study includes the following analyses: Absorbance (0.1M), Appearance and Color, Assay (Dried), Loss on Drying, and pH (5%). Results from all analyses are summarized in Tables 2 and 3. This study will be used to establish shelf life for all product codes for HEPES. The following product codes are commercially available.

- HEPES-3220
- HEPES-3221
- HEPES-3250
- HEPES-3251
- HEPES-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 Q1E

3. SAMPLE DESIGNATION:

The samples placed on the Stability Testing Program consisted of lot HE3200-019-0420. The lot was packaged into two different packaging configurations, as dictated by the BioSpectra Stability Checklist. The type of packaging utilized in this stability study was based on BioSpectra packaging offered to the customer. Refer to Table 1 below for packaging configurations and descriptions.

TABLE 1: PACKAGING CONFIGURATIONS

Packaging Configurations	Description of Packaging Configurations
Poly/Poly (P/P)	Samples are individually placed into small poly bags and are sealed with a zip tie. All individual bags are then placed into a poly pail and sealed.
Lab Screw-Top Bottle (Labline)	Samples are individually placed into small lab screw-top bottles and sealed with a tamper-evident lid.

4. STORAGE:

4.1. The packaging and storage requirements for HEPES are to be in a tightly closed container in a dry and well-ventilated place. For this study, samples were stored in the real time stability chamber 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), relative humidity (60% ± 5) and mean kinetic temperature (monitor). For the time period of April 2020 to April 2023 the samples were located in the real time stability chamber, H03SC01, and all remaining testing interval samples remain at this condition. The maximum temperature recorded was 27.80°C, the minimum temperature was 22.63°C, the average temperature was 25.46°C, and the average mean kinetic temperature was 25.46°C. The maximum relative humidity recorded was 72.4%, the minimum relative humidity was 31.1%, and the average relative humidity was 61.4%. Maximum and minimum values that are outside limits for temperature and humidity are due to opening the door of the chamber as explained in the temperature and humidity monitoring assessments for the chamber. Section 5 will include any excursions from these conditions that resulted in an investigation.

5. INVESTIGATIONS:

5.1. BDI22-61: This discrepancy documents missing data points from the download of the MadgeTech temperature loggers between 1/28/22 and 2/09/22. The logger was reset and started to work. No known reason could be identified as to why the logger stopped recording. There was no impact to the stability samples being stored in the chamber as the analog chart recorders showed no temperature deviations.

5.2. BDI22-138: This discrepancy documents an out of specification humidity reading. The out of specification humidity result was 50.8% and lasted for over 4 hours. This was due to a valve that regulates the humidity being turned off. There is no impact to the stability samples because the excursion was brief and lasted less than 5 hours.

5.3. BDI22-143: This discrepancy investigation documents the observed deviation in the real time stability chamber in November 2021 for missing data points. The root cause was identified as expired batteries in the MadgeTech temperature loggers. There is no impact to the stability samples being stored in the chamber as the analog chart recorders showed no temperature deviations.

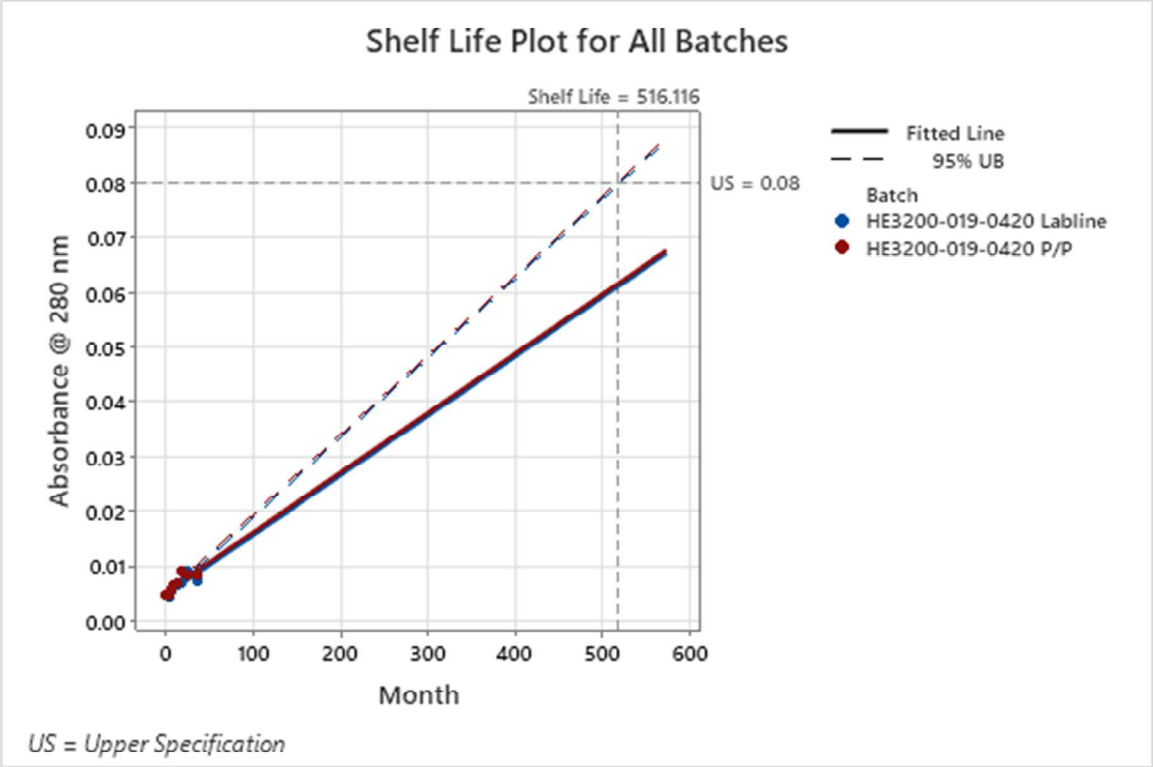
6. LOT EVALUATION:

TABLE 2: HE3200-019-0420 P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (0.1M)	0.080 a.u. max @ 280 nm	0.0047 a.u.	0.0048 a.u.	0.0059 a.u.	0.0065 a.u.	0.0070 a.u.	0.0090 a.u.	0.0084 a.u.	0.0085 a.u.
	0.050 a.u. max @ 260 nm	0.0055 a.u.	0.0052 a.u.	0.0065 a.u.	0.0070 a.u.	0.0077 a.u.	0.0104 a.u.	0.0111 a.u.	0.0094 a.u.
	0.050 a.u. max @ 250 nm	0.0103 a.u.	0.0096 a.u.	0.0110 a.u.	0.0119 a.u.	0.0124 a.u.	0.0154 a.u.	0.0161 a.u.	0.0140 a.u.
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	100.10%	100.31%	100.52%	100.46%	100.75%	100.21%	100.32%	100.24%
pH (5%)	5.0-6.5	5.18	5.26	5.26	5.25	5.20	5.22	5.19	5.20
Loss on Drying	0.5% max.	0.0619%	0.0459%	0.0275%	0.0589%	0.0603%	0.0630%	0.0701%	0.1049%

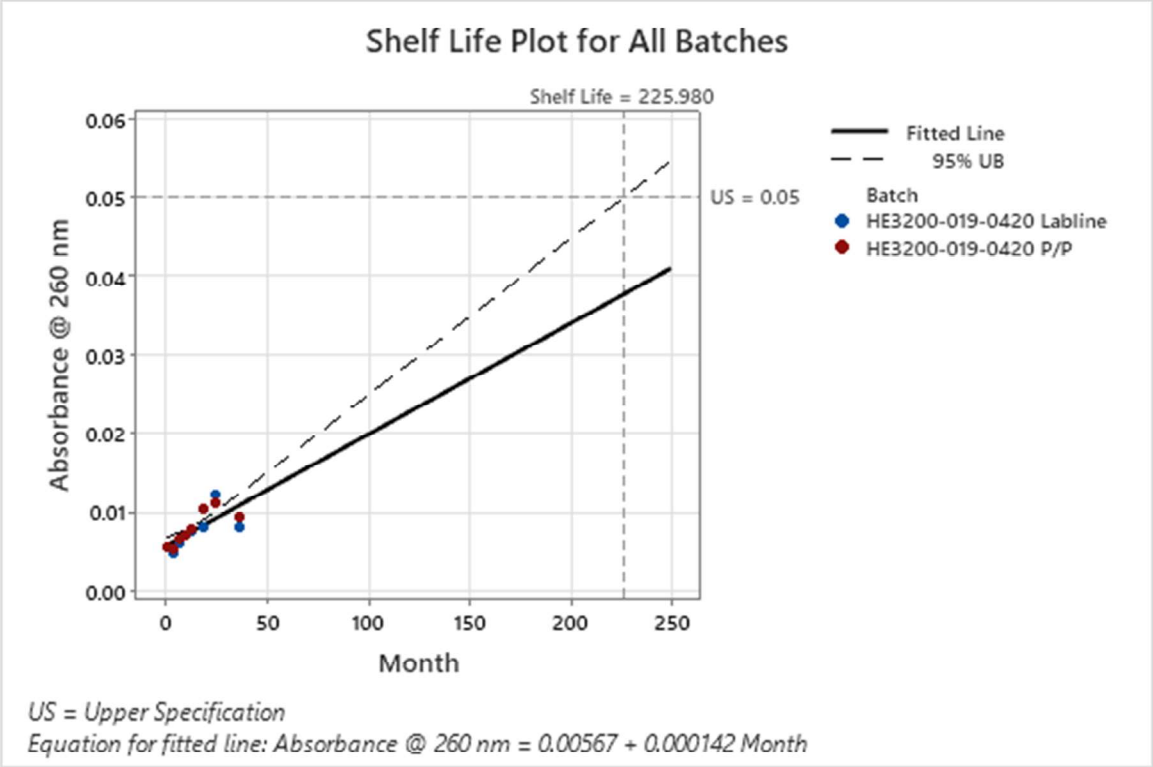
TABLE 3: HE3200-019-0420 Labline

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (0.1M)	0.080 a.u. max @ 280 nm	0.0047 a.u.	0.0042 a.u.	0.0055 a.u.	0.0063 a.u.	0.0067 a.u.	0.0069 a.u.	0.0089 a.u.	0.0071 a.u.
	0.050 a.u. max @ 260 nm	0.0055 a.u.	0.0046 a.u.	0.0061 a.u.	0.0069 a.u.	0.0075 a.u.	0.0080 a.u.	0.0120 a.u.	0.0080 a.u.
	0.050 a.u. max @ 250 nm	0.0103 a.u.	0.0091 a.u.	0.0106 a.u.	0.0117 a.u.	0.0124 a.u.	0.0129 a.u.	0.0173 a.u.	0.0125 a.u.
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	100.10%	100.27%	100.64%	100.45%	101.07 %	100.17%	100.32%	100.36%
pH (5%)	5.0-6.5	5.18	5.25	5.27	5.26	5.19	5.22	5.24	5.23
Loss on Drying	0.5% max.	0.0619%	0.0443%	0.0352%	0.0496%	<0.0170%	0.1312%	0.0266%	0.1099%



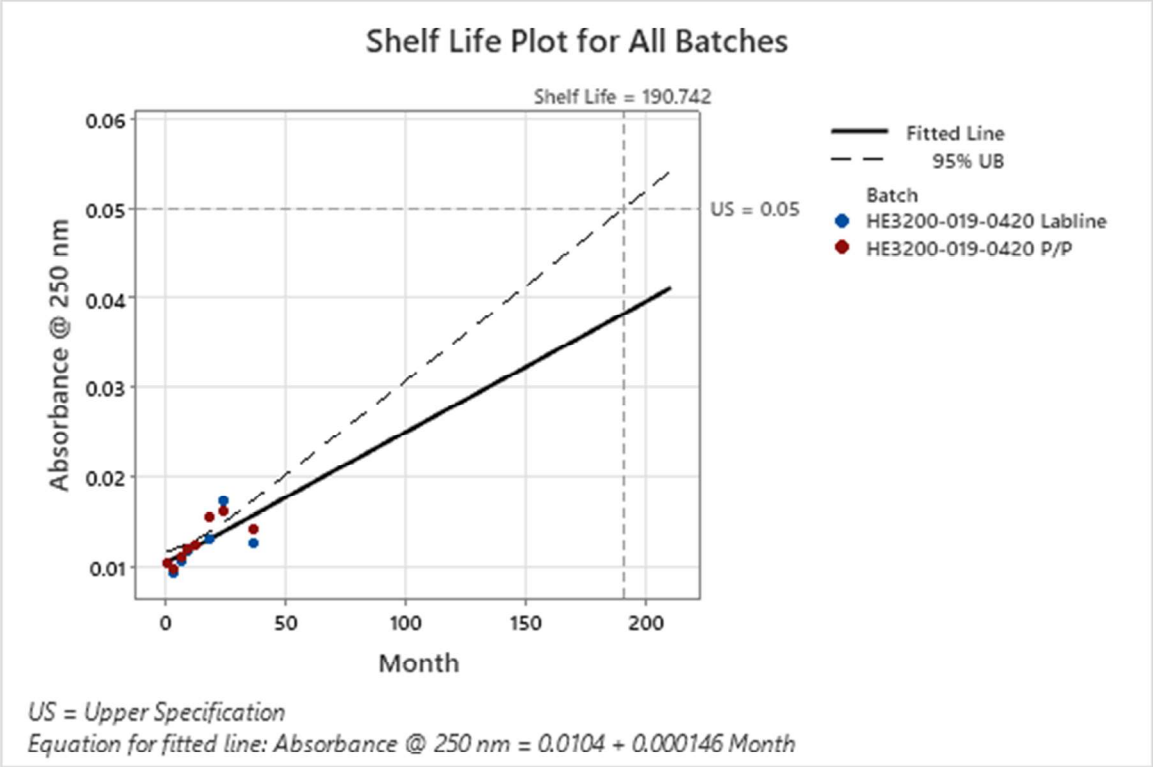
Graph 1: Absorbance @ 280 NM

The predicted Shelf-Life for Absorbance @ 280 nm was determined to be 516.116 months as of the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material.



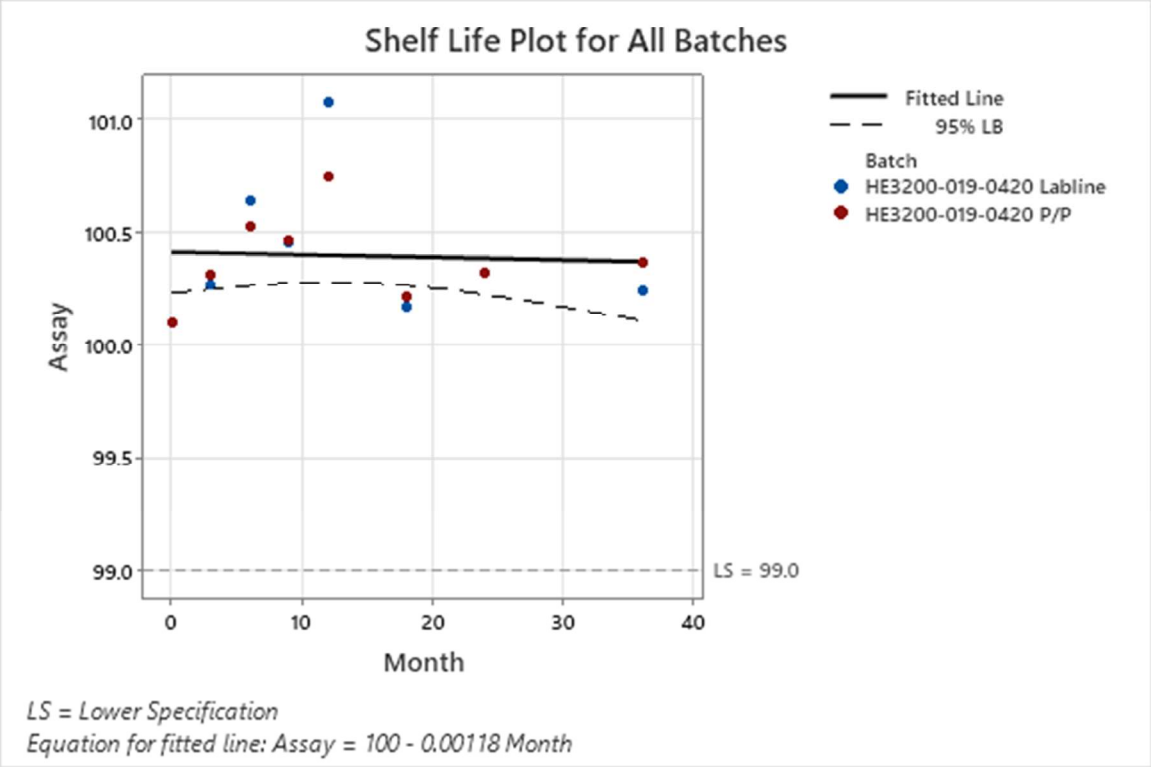
Graph 2: Absorbance @ 260 NM

The predicted Shelf-Life for Absorbance @ 260 nm was determined to be 225.980 months as of the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material.



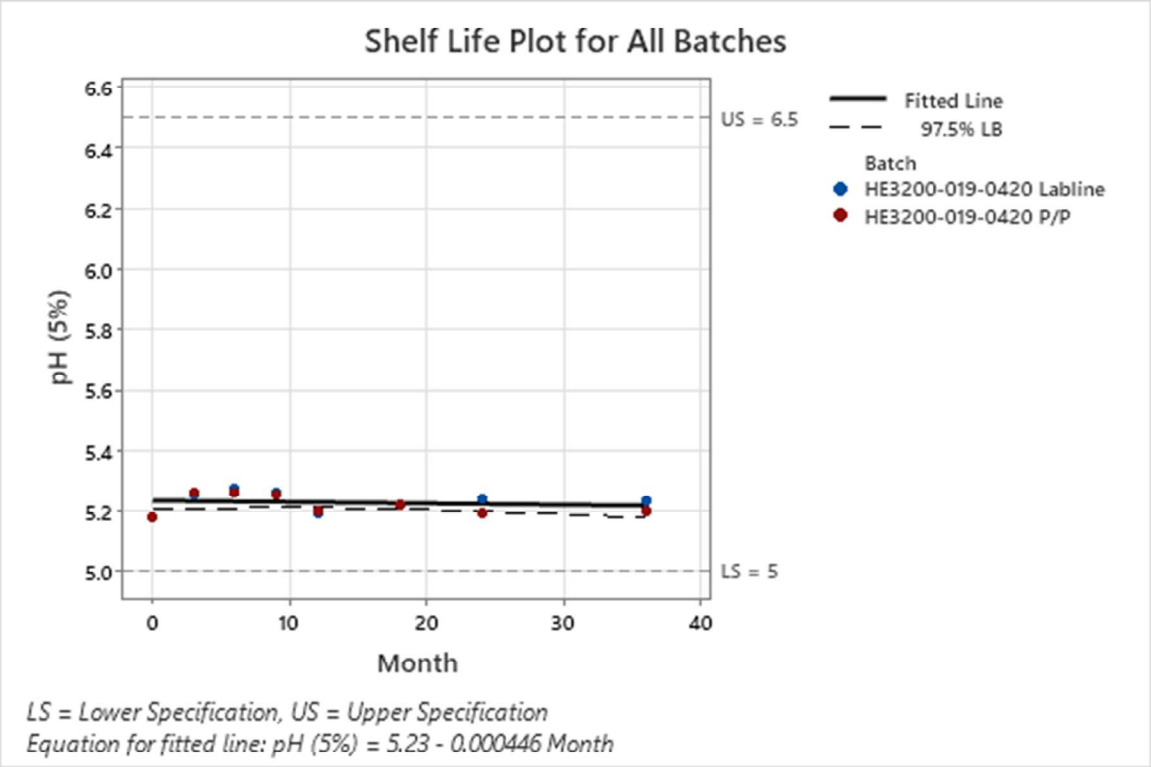
Graph 3: Absorbance @ 250 NM

The predicted Shelf-Life for Absorbance @ 250 nm was determined to be 190.742 months as of the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material.



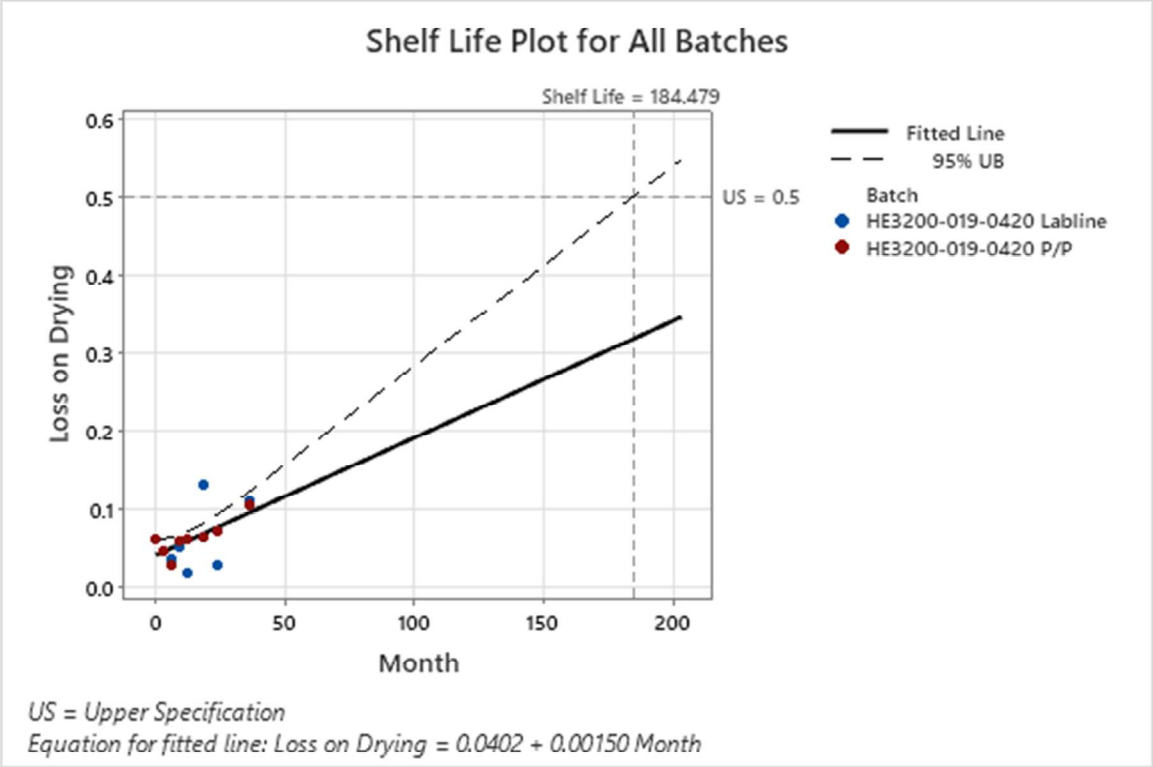
Graph 4: Assay (Dried)

No Shelf-Life was able to be determined for Assay (Dried), as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material.



Graph 5: pH (5%)

No Shelf-Life was able to be determined for pH (5%), as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material.



Graph 6: loss on drying

The predicted Shelf-Life for Loss on Drying was determined to be 184.479 months as of 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 for the HE3200-019-0420 long-term stability study 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 real time stability data, but should be no more than 12 months beyond for real time conditions. In regards to the real time stability study for HEPES Bio Excipient material packaged in poly/poly and Labline, all data met the specifications set forth in the Stability Testing Program for the lot stored at the recommended real time condition. The real time stability study data, along with the predicted shelf-life plots, supports a retest date of 24 months or expiration date of 36 months for HEPES Bio Excipient grade material, manufactured at BioSpectra's 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 real time 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.