BIOSPECTRA
100 Majestic Way, Bangor, PA 18013 / www.biospectra.us

HEPES 2023 LONG-TERM STABILITY REPORT: HEPE-0123-00003

TABLE OF CONTENTS

1. OVERVIEW:

The purpose of this report is to analyze and conclude on the data obtained from the long-term stability study of HEPES Bio Excipient Grade material manufactured in 2023 at the Majestic, PA facility. Testing intervals are designated by T_n, 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 long-term stability analysis will assess the stability of HEPES Bio Excipient Grade, lot HEPE-0123-00003, that completed thirty-six (36) months of long-term stability in January 2026. This stability study included the analyses listed in Table 1 below.

TABLE 1: HEPES STABILITY SPECIFICATIONS

Analysis		Specification
Absorbance (0.1M)	280 nm	0.080 a.u. max.
	260 nm	0.050 a.u. max.
	250 nm	0.050 a.u. max.
Appearance and Color		White/Crystals
Assay (Dried)		99.0% minimum
Loss on Drying		0.5% max.
pH (5%) Solution		5.0-6.5

Results from all analyses are summarized in Tables 4 and 5. 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 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. The following product codes are commercially available.

- HEPE-3220
- HEPE-3221
- HEPE-3250
- HEPE-3251
- HEPE-3354
- HEPE-4220
- HEPE-4250

2. REFERENCES:

2.1. BSI-SOP-0136, Stability Testing Program
2.2. BSI-SOP-0146, Stability Inventory
2.3. Current USP
2.4. ICH Q1E

3. SAMPLE DESIGNATION:

3.1. The samples placed on the Stability Testing Program consisted of one lot of HEPES Bio Excipient grade material. Stability samples from this lot were put into P/P and Labline packaging configurations. The samples were packaged in accordance with the Stability Inventory SOP, BSI-SOP-0146. Reference, Table 2, below for packaging configurations and descriptions. The type of packaging utilized in this stability study was based on BioSpectra's packaging configurations offered to customers.

TABLE 2: PACKAGING CONFIGURATIONS

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

4. STORAGE:

4.1. The packaging and storage requirements for HEPES Bio Excipient grade material are to be in a tightly closed container in a dry and well-ventilated place. For this study, samples were stored in the Long-Term Stability Chamber, H03SC01, at the Majestic, PA facility. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature, mean kinetic temperature and relative humidity. For the time period of January 2023 to January 2026 the samples were located in the long-term stability chamber, and all future time point samples remain at this condition.

TABLE 3: STORAGE CONDITIONS

Condition	Specification	Value
Minimum Temperature	25°C ±2°C	20.58°C
Maximum Temperature		26.20°C
Average Temperature		25.37°C
Mean Kinetic Temperature	Monitor	25.37°C
Minimum Humidity	60% RH±5%RH	43.6%RH
Maximum Humidity		80.5%RH
Average Humidity		61.3%RH

Maximum and minimum values that were outside the limits for temperature and humidity due to opening the door of the chamber as explained in the Temperature and Humidity Monitoring Assessments for the chambers did not require an investigation. 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. 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 temperature and humidity on 8/15/24 at 2222 in H03SC01 with a humidity reading of 54.4% due to a blown fuse. The fuse was replaced, and the chamber was back into specification on 8/16/24 at 0842. The minimum temperature during this time was 21.81°C and minimum humidity was 50.3%. There was no impact to the material located in the chamber.

6. LOT EVALUATION:

TABLE 4: HEPE-0123-00003 P/P

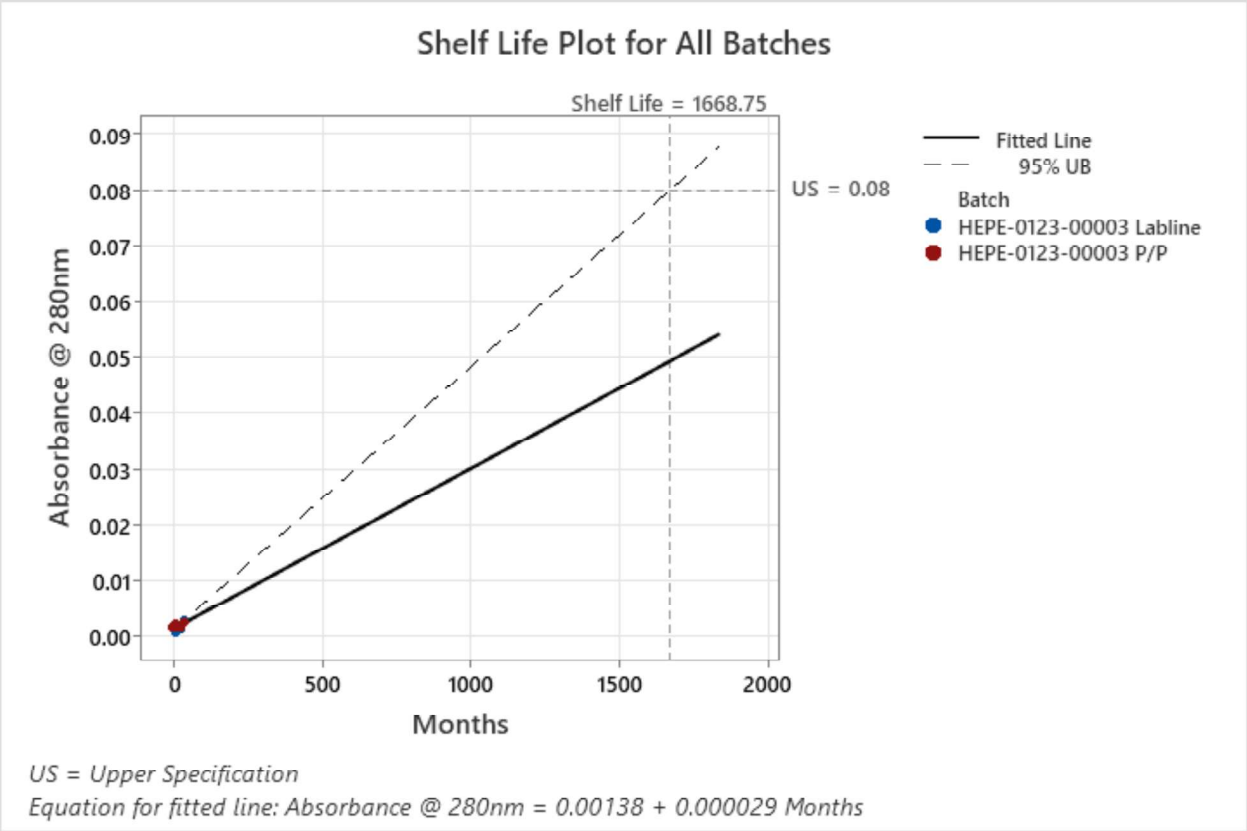
Time Point	Absorbance (0.1M)			Appearance and Color	Assay	pH (5%)	Loss on Drying
	0.080 a.u. max @ 280 nm	0.050 a.u. max @ 260 nm	0.050 a.u. max @ 250 nm	White/Crystals	99.0% min	5.0 – 6.5	0.5% max
T_0	0.0016 a.u.	0.0024 a.u.	0.0067 a.u.	White/Crystals	100.26%	5.27	0.0334%
T_3	0.0016 a.u.	0.0026 a.u.	0.0065 a.u.	White/Crystals	100.44%	5.27	0.0205%
T_6	0.0016 a.u.	0.0028 a.u.	0.0067 a.u.	White/Crystals	100.25%	5.31	0.0125%
T_9	0.0018 a.u.	0.0025 a.u.	0.0066 a.u.	White/Crystals	100.48%	5.29	<0.0073%
T_{12}	0.0024 a.u.	0.0031 a.u.	0.0072 a.u.	White/Crystals	100.35%	5.25	<0.0080%
T_{18}	0.0016 a.u.	0.0025 a.u.	0.0067 a.u.	White/Crystals	99.88%	5.30	0.0390%
T_{24}	0.0017 a.u.	0.0021 a.u.	0.0059 a.u.	White/Crystals	100.11%	5.31	0.0456%
T_{36}	0.0027 a.u.	0.0035 a.u.	0.0074 a.u.	White/Crystals	100.27%	5.31	0.0103%

- **Remaining testing interval pull dates**
  - T = 48: Scheduled for January 27, 2027
  - T = 60: Scheduled for January 27, 2028

TABLE 5: HEPE-0123-00003 LABLINE

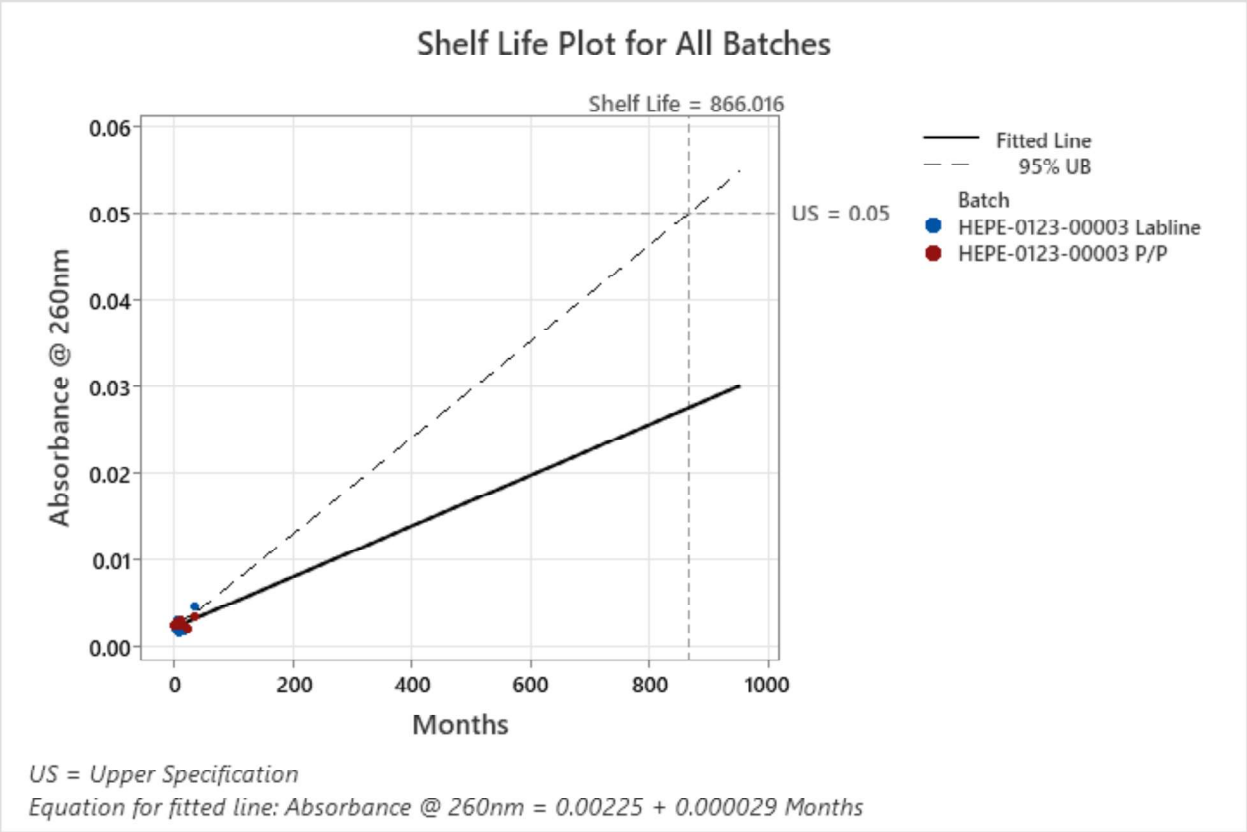
Time Point	Absorbance (0.1M)			Appearance and Color	Assay	pH (5%)	Loss on Drying
	0.080 a.u. max @ 280 nm	0.050 a.u. max @ 260 nm	0.050 a.u. max @ 250 nm	White/Crystals	99.0% min	5.0 – 6.5	0.5% max
T_0	0.0016 a.u.	0.0024 a.u.	0.0067 a.u.	White/Crystals	100.26%	5.27	0.0334%
T_3	0.0014 a.u.	0.0021 a.u.	0.0058 a.u.	White/Crystals	100.56%	5.26	0.0530%
T_6	0.0015 a.u.	0.0031 a.u.	0.0067 a.u.	White/Crystals	100.22%	5.32	0.0364%
T_9	0.0009 a.u.	0.0016 a.u.	0.0051 a.u.	White/Crystals	100.63%	5.28	0.0202%
T_{12}	0.0022 a.u.	0.0031 a.u.	0.0070 a.u.	White/Crystals	100.27%	5.30	0.0416%
T_{18}	0.0013 a.u.	0.0019 a.u.	0.0060 a.u.	White/Crystals	100.11%	5.31	0.0597%
T_{24}	0.0013 a.u.	0.0020 a.u.	0.0058 a.u.	White/Crystals	100.13%	5.29	0.0203%
T_{36}	0.0031 a.u.	0.0046 a.u.	0.0083 a.u.	White/Crystals	100.12%	5.31	0.0101%

- **Remaining testing interval pull dates**
  - T = 48: Scheduled for January 27, 2027
  - T = 60: Scheduled for January 27, 2028



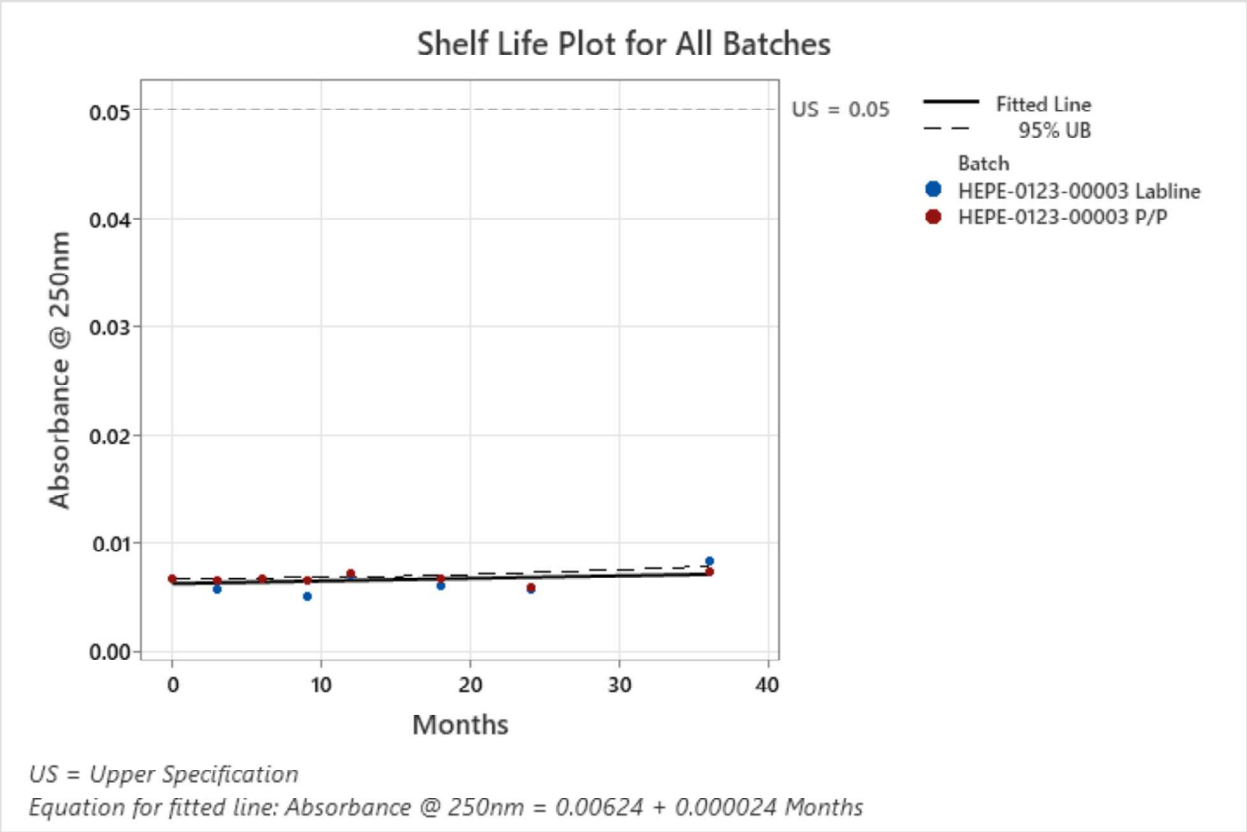
GRAPH 1: ABSORBANCE @ 280 NM

A predicted shelf-life for Absorbance @ 280 nm was determined to be 1668.75 months for the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material, as this is beyond the completion of the study.



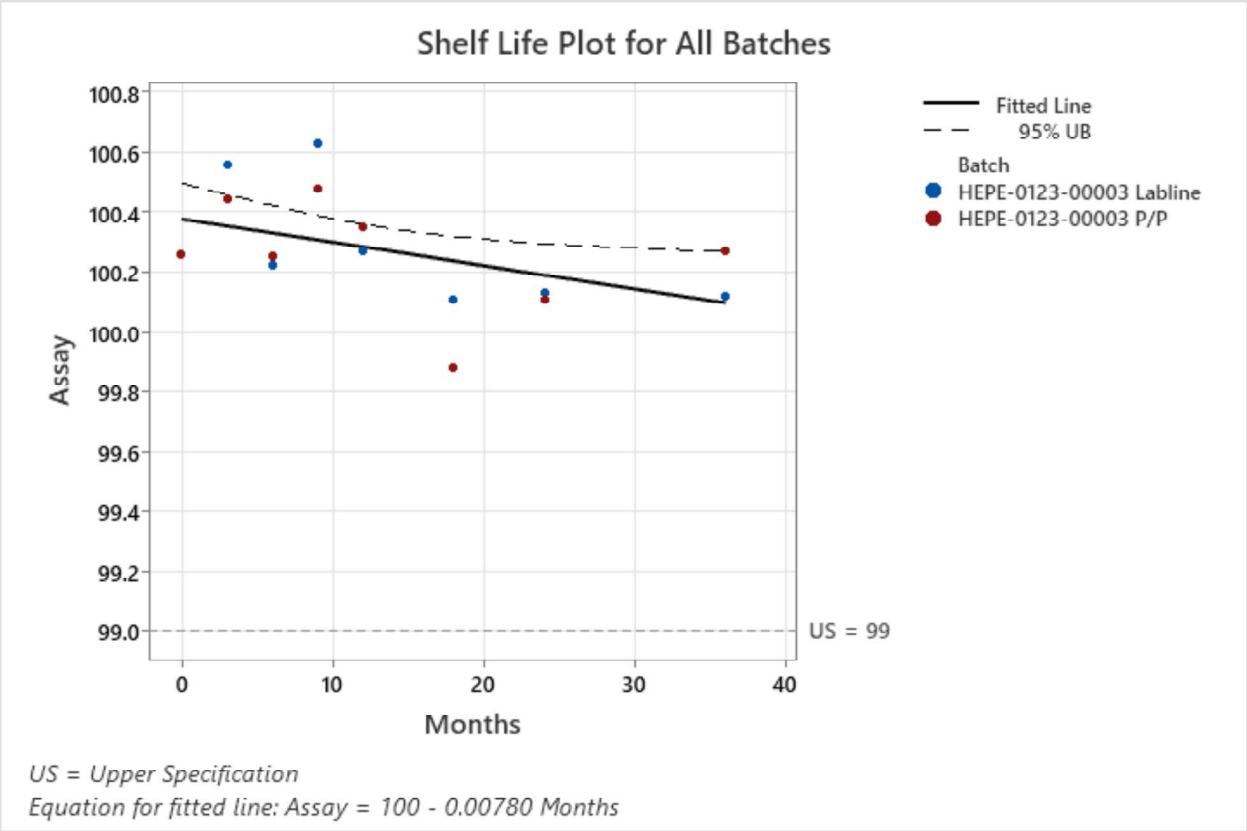
GRAPH 2: ABSORBANCE @ 260 NM

A predicted shelf-life for Absorbance @ 260 nm was determined to be 866.016 months for the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material, as this is beyond the completion of the study



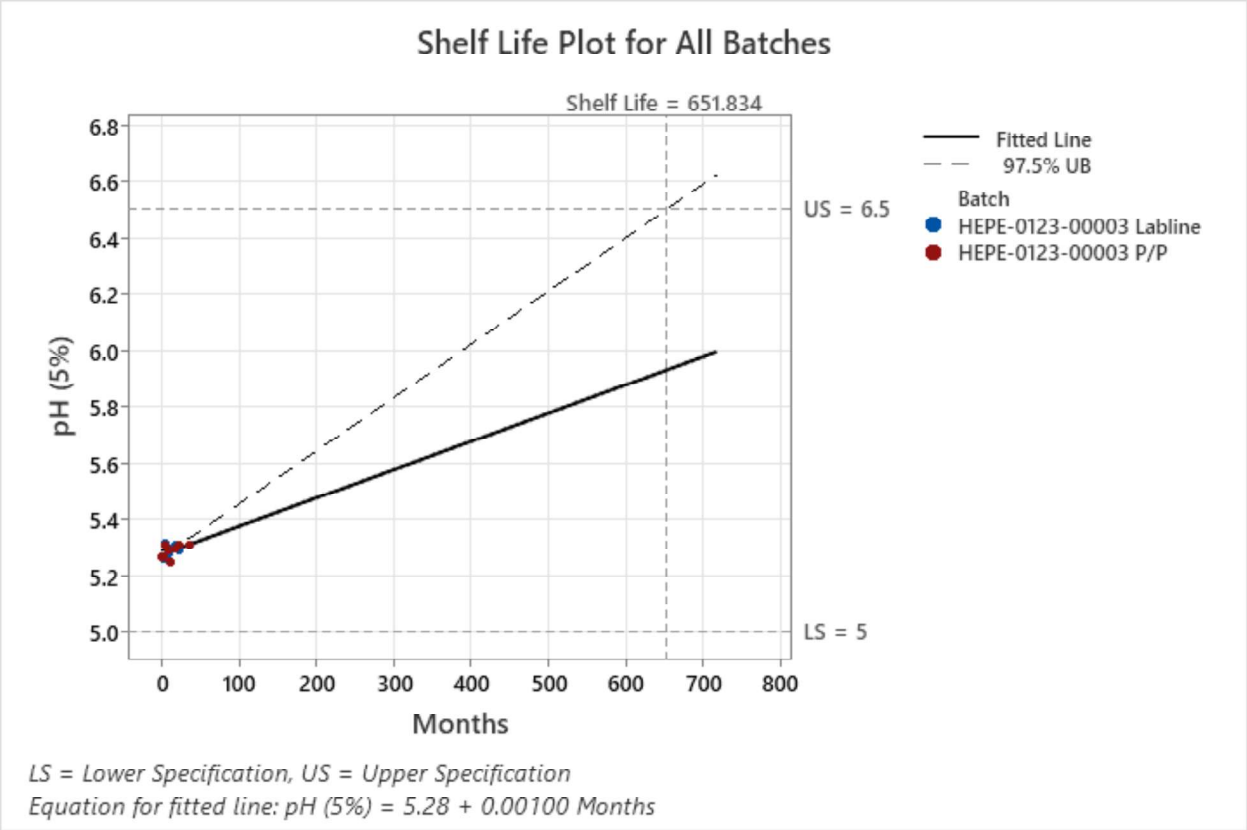
GRAPH 3: ABSORBANCE @ 250 NM

No shelf-life was able to be determined for Absorbance at 250 nm, 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.



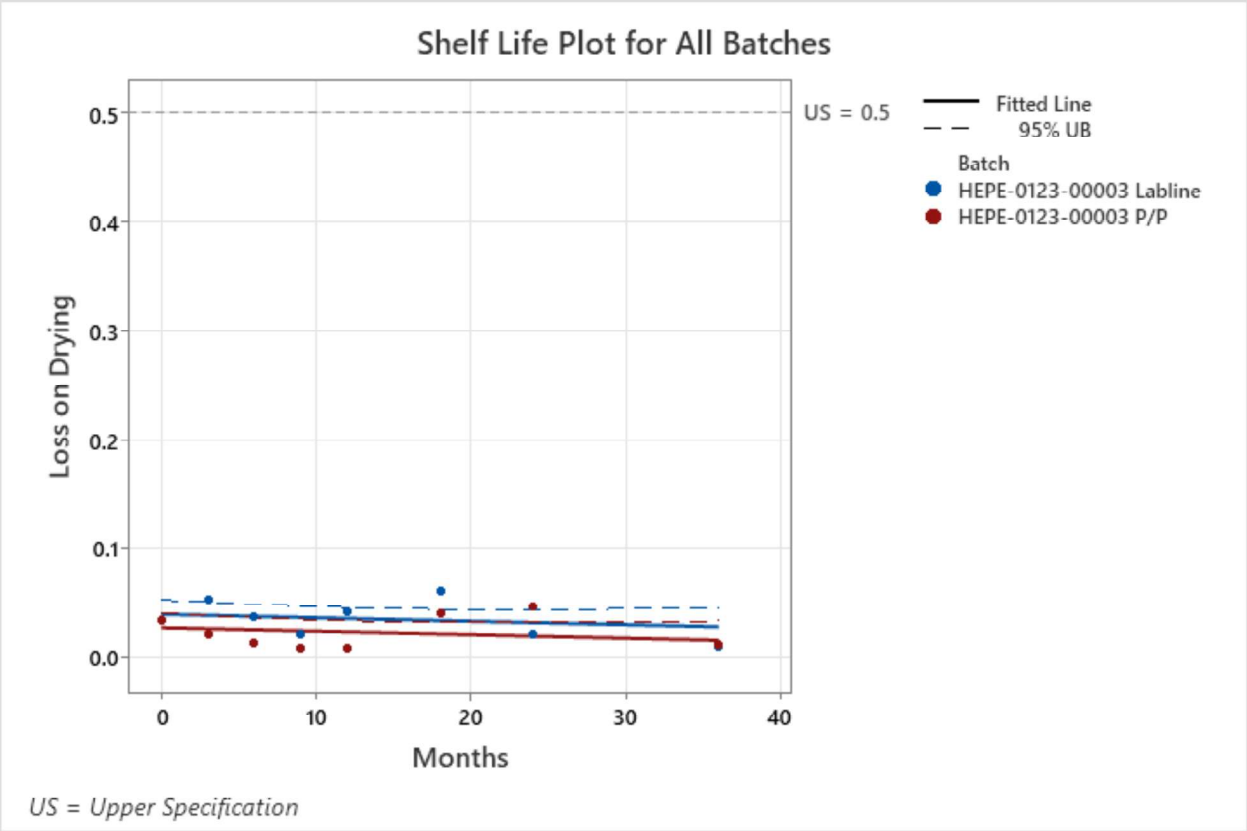
GRAPH 4: ASSAY (DRIED)

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 at the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material.



GRAPH 5: PH (5%)

A predicted shelf-life for pH (5%) was determined to be 651.834 months for the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material, as this is beyond the completion of the study



GRAPH 6: LOSS ON DRYING

No shelf-life was able to be determined for 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. 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 real time conditions. In regard to the long-term stability study for HEPES Bio Excipient material, 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 an expiration date of 36 months for HEPES Bio Excipient Grade material, manufactured at BioSpectra in the Majestic, 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.