# HEPES
# REAL-TIME STABILITY REPORT:
# HE3201-015-1015

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## 1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the Real-Time Stability of HEPES Bio Excipient material manufactured at BioSpectra's Bangor, PA facility. Samples of HE3201-015-1015 were placed on the Stability Testing Program in June 2017 to fulfil the requirements of adding one GMP manufactured batch per year. 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. The lot of HEPES Bio Excipient material that was analyzed for this stability study was manufactured in October 2015, but was not entered into the Stability Program until June 2017. For consistency and clarity, the timepoints in the report will stand to be referenced as the number of months the material has been on the stability program, rather than the number of months since manufacturing.

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. The data was analyzed utilizing a Shelf-Life Plot for each quantitative analysis, 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 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.

This Real-Time Stability analysis assesses the stability of HE3201-015-1015 that completed three years of long-term stability in June 2020. The study included the following analyses: Absorbance (0.1M), Appearance and Color, Assay (Dried), Loss on Drying, and pH (5%). Results from all analyses are summarized in Table 2.

## 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 HEPES. Stability samples from HE3201-015-1015 were separated into three 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 ziptie. All individual bags are then placed into a poly pail and sealed. |
| 2 Poly/Fiber (2P/F) | Samples are individually placed into small poly bags and are sealed with a ziptie. All individual bags are then placed into a larger poly bag and sealed with a ziptie. The larger poly bag is then |

| | |
|---|---|
| | placed into a fiber drum 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:

At the start of this stability study, all 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 30, 2017 to September 25, 2019, the samples were stored in the Zone M Warehouse. The temperature was monitored continuously using Madge Tech data loggers; the specification for temperature was 10 – 40°C. The maximum temperature of the warehouse during the stability study was 33.67°C and the minimum temperature was 12.17°C.

From September 25, 2019 to June 28, 2020, the samples were stored in the long-term stability chamber. The temperature was monitored continuously using Madge Tech data loggers; the specification for temperature was 23 – 27°C. The maximum temperature of the chamber during the stability study was 27.72°C and the minimum temperature of the chamber was 23.97°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 alarm 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. There is no storage temperature specification for HEPES Bio Excipient material; $T_6$ and $T_9$ samples were pulled and tested during this timeframe, and all results met specification.

5.2. BDI18-92: On various days between 8/24/18 and 11/8/18, data was not able to be downloaded from the data loggers located in the Zone M Warehouse. Timepoint $T_{18}$ was pulled and tested after this occurrence, and all results met specification.

5.3. BDI18-97: Madge Tech data loggers located in the Zone J and Zone M warehouses were not replaced before the calibration due dates. There were no temperature excursions from 10/4/18 to 11/15/18 when the loggers were replaced. Timepoint $T_{18}$ was pulled and tested after this occurrence, and all results met specification.

5.4. BDI19-01: Temperature and Humidity Monitoring assessments were not completed on a quarterly basis for multiple locations that are monitored with Madge Tech data loggers for 2018. All stability testing in 2018 for timepoints $T_6$, $T_9$, and $T_{12}$ met requirements.

5.5. BDI19-24: Madge Tech data logger was not replaced prior to the calibration due date on 3/23/19. There is no impact to product quality as this logger was one of fourteen loggers recording data in the Zone M Warehouse. Timepoint $T_{24}$ was tested and met requirements.

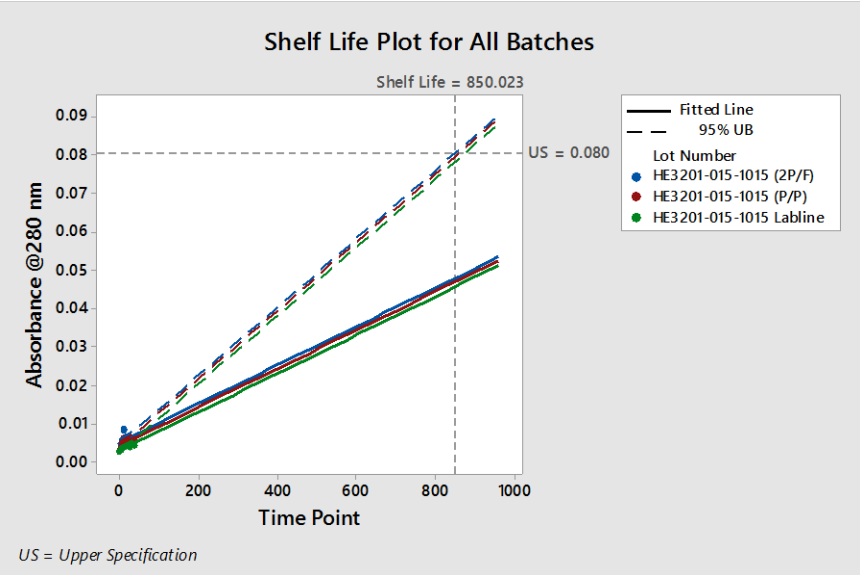
## 6. LOT EVALUATION:

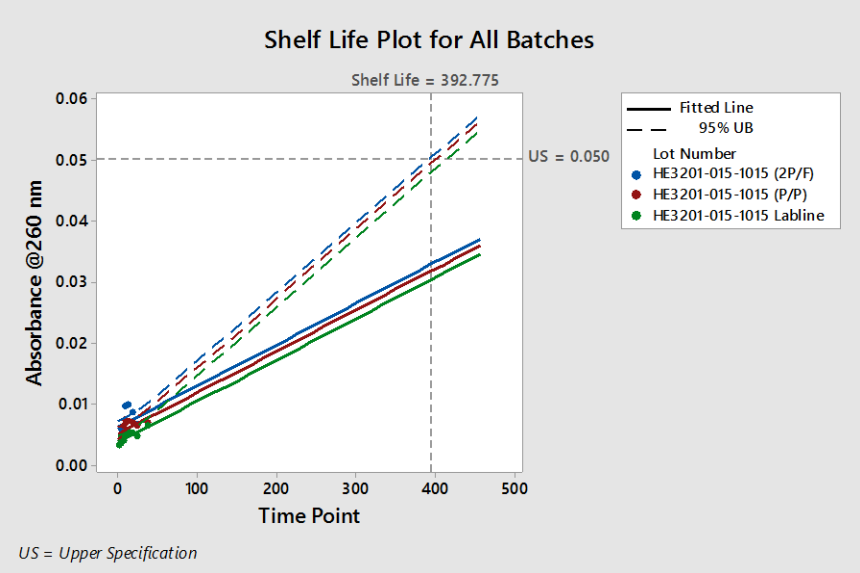
### TABLE 2: RESULTS OF LONG-TERM STABILITY ANALYSES

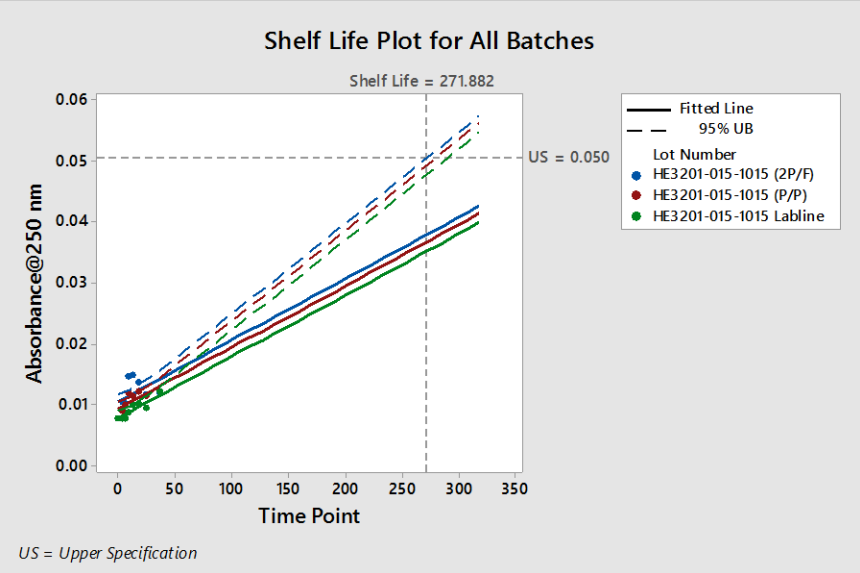
| All-Inclusive Data Table for HE3201-015-1015 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Lot Number** | **Analysis** | **Specification** | **$T_0$** | **$T_3$** | **$T_6$** | **$T_9$** | **$T_{12}$** | **$T_{18}$** | **$T_{24}$** | **$T_{36}$** |
| HE3201-015-1015-P/P | Absorbance (0.1M) | 0.080 @ 280 nm | 0.0027 | 0.0036 | 0.0048 | 0.0062 | 0.0058 | 0.0058 | 0.0055 | 0.0056 |
| | | 0.050 @ 260 nm | 0.0034 | 0.0044 | 0.0064 | 0.0075 | 0.0072 | 0.0071 | 0.0065 | 0.0069 |
| | | 0.050 @ 250 nm | 0.0078 | 0.0090 | 0.0099 | 0.0120 | 0.0116 | 0.0123 | 0.0116 | 0.0122 |
| | 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 | 100.08% | 99.95% | 100.75% | 100.34% | 100.82% | 100.35% | 100.51% | 100.45% |
| | Loss on Drying | 0.5% max | < 0.0256% | 0.1169% | 0.0283% | < 0.0150% | < 0.0150% | < 0.0245% | 0.0337% | 0.0394% |
| | pH (5%) | 5.0-6.5 | 5.267@ 22.61°C | 5.27@ 22.7°C | 5.28@ 18.7°C | 5.25@ 20.7°C | 5.30@ 20.6°C | 5.30@ 23.5°C | 5.27@ 23.1°C | 5.27@ 23.7°C |
| HE3201-015-1015-2P/F | Absorbance (0.1M) | 0.080 @ 280 nm | 0.0027 | 0.0047 | 0.0052 | 0.0083 | 0.0084 | 0.0066 | 0.0056 | 0.0059 |
| | | 0.050 @ 260 nm | 0.0034 | 0.0060 | 0.0064 | 0.0098 | 0.0100 | 0.0087 | 0.0068 | 0.0071 |
| | | 0.050 @ 250 nm | 0.0078 | 0.0106 | 0.0103 | 0.0146 | 0.0149 | 0.0138 | 0.0118 | 0.0121 |
| | 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 | 100.08% | 100.31% | 100.75% | 101.34% | 100.61% | 100.38% | 100.65% | 100.54% |
| | Loss on Drying | 0.5% max | < 0.0256% | < 0.0150% | < 0.0150% | < 0.0150% | < 0.0150% | 0.0261% | 0.0333% | 0.0354% |
| | pH (5%) | 5.0-6.5 | 5.267@ 22.61°C | 5.28@ 22.7°C | 5.19@ 18.8°C | 5.23@ 20.8°C | 5.29@ 20.3°C | 5.24@ 23.2°C | 5.27@ 23.1°C | 5.26@ 24.4°C |
| HE3201-015-1015-Labline | Absorbance (0.1M) | 0.080 @ 280 nm | 0.0027 | 0.0029 | 0.0033 | 0.0039 | 0.0043 | 0.0042 | 0.0038 | 0.0044 |
| | | 0.050 @ 260 nm | 0.0034 | 0.0035 | 0.0041 | 0.0047 | 0.0055 | 0.0054 | 0.0047 | 0.0066 |
| | | 0.050 @ 250 nm | 0.0078 | 0.0079 | 0.0077 | 0.0089 | 0.0099 | 0.0103 | 0.0096 | 0.0122 |
| | 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 | 100.08% | 100.01% | 100.75% | 100.47% | 100.49% | 100.80% | 100.42% | 100.48% |
| | Loss on Drying | 0.5% max | < 0.0256% | < 0.0150% | < 0.0150% | 0.0487% | < 0.0150% | 0.0242% | 0.0175% | < 0.0191% |
| | pH (5%) | 5.0-6.5 | 5.267@ 22.61°C | 5.28@ 22.9°C | 5.19@ 18.6°C | 5.35@ 20.6°C | 5.29@ 20.4°C | 5.25@ 23.2°C | 5.27@ 23.4°C | 5.27@ 24.4°C |

Shelf Life Plots have been created for all quantitative results. For analyses with a specification of maximum value only, no Lower Specification value was included in the Shelf Life Plots. This includes Absorbance and Loss on Drying. For analyses with a specification of minimum value only, no Upper Specification value was included in the Shelf Life Plots. This includes Assay.

## GRAPH 1: SHELF LIFE PLOTS – ABSORBANCE @ 280NM, 260NM, AND 250NM

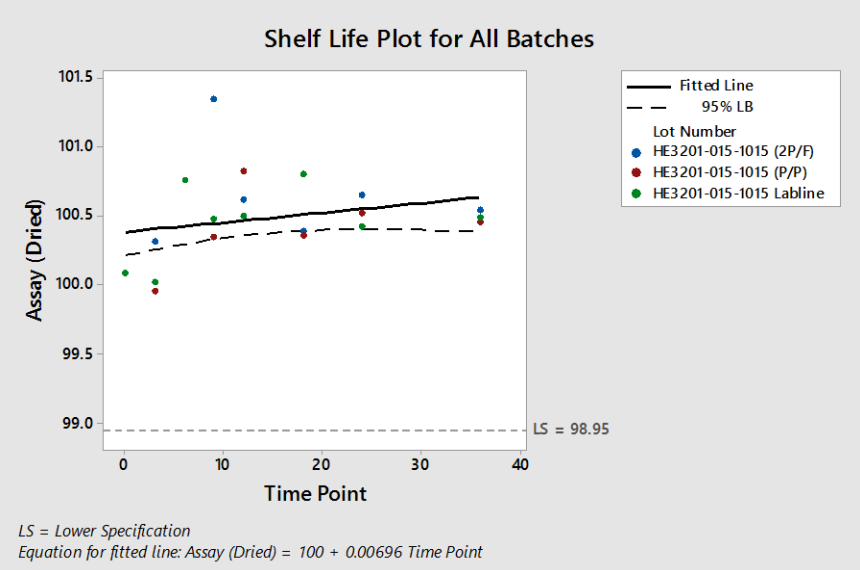




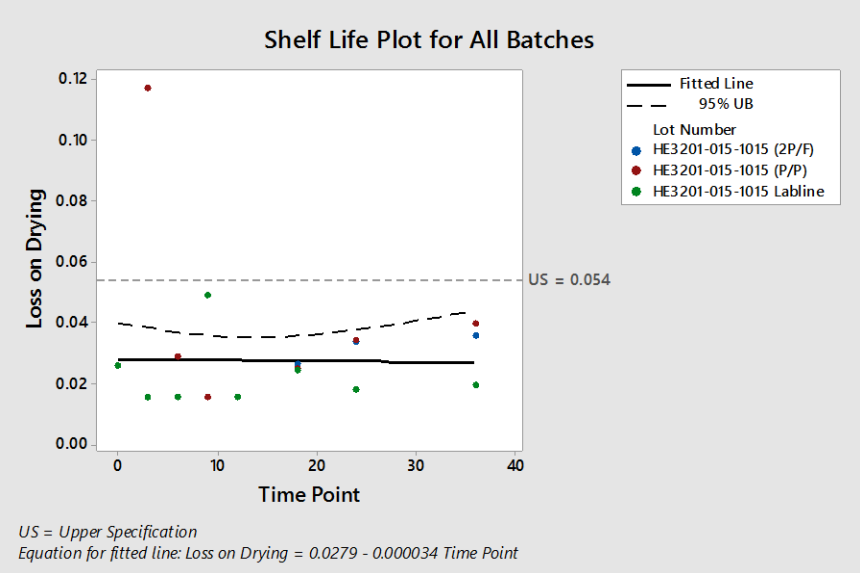

The predicted shelf life for Absorbance is 271.882 months, based on the shelf life plot for Absorbance @ 250nm. The predicted shelf life extends well beyond the current expiration date for HEPES Bio Excipient material.

**GRAPH 2: SHELF LIFE PLOT – ASSAY (DRIED)**



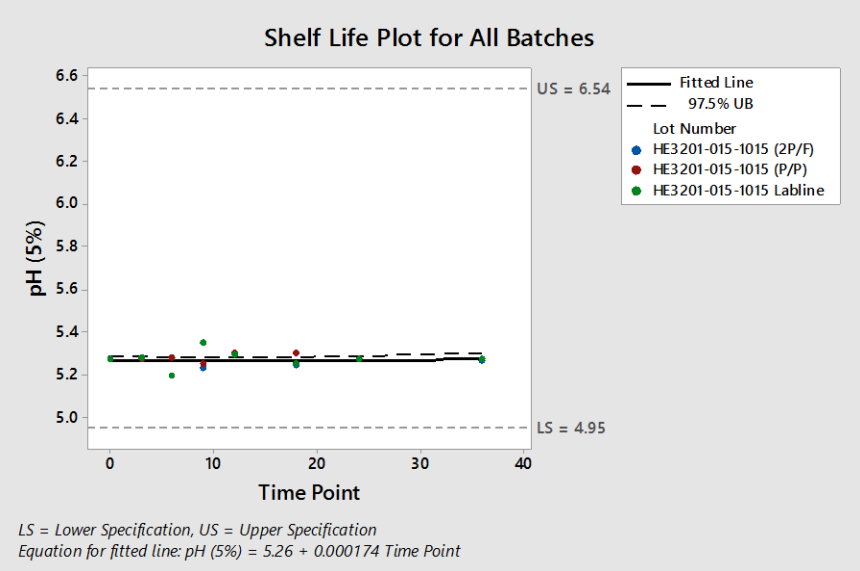

Results for Assay (Dried) showed no predictable shelf life, as the mean response slope is not significantly different than zero. This is observed as there is negligible degradation of the product shown from this analysis throughout the 36-month stability study.

**GRAPH 3: SHELF LIFE PLOT – LOSS ON DRYING**




Results for Loss on Drying showed no predictable shelf life, as the mean response slope is not significantly different than zero. This is observed as there is negligible degradation of the product shown from this analysis throughout the 36-month stability study.

**GRAPH 4: SHELF LIFE PLOT – PH (5%)**




Results for pH (5%) showed no predictable shelf life, as the mean response slope is not significantly different than zero. This is observed as there is negligible degradation of the product shown from this analysis throughout the 36-month stability study.

## 7. CONCLUSION:

All data for the HE3201-015-1015 long-term stability study met the specifications 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 HEPES Bio Excipient material packaged in Poly/Poly, 2Poly/Fiber, and Labline packagings are stable for a minimum of 36-months. A re-test date of 36-months may be assigned to all HEPES lots manufactured at BioSpectra in the Bangor, PA facility.

## 8. STATEMENT OF COMMINTMENT:

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.

# HEPES BIO EXCIPIENT GRADE 2014

# LONG TERM REAL TIME STABILITY REPORT

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## 1. OVERVIEW:

The purpose of this Report is to analyze the data obtained from the Long Term Real Time stability of HEPES Bio Excipient Grade manufactured in Excipient Cell 2, Room E03 of BioSpectra's Bangor, PA facility. Samples were initially placed on the Stability Testing Program in 2014 consisting of four Process Validation batches with each lot contained in one poly drum.

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 Real-Time Stability Program binder, including the individual Stability Summary Sheets for analysis of the product.

This Long Term Stability analysis assesses the stability of the four validation lots of HEPES Bio Excipient Grade that came off of Long Term Real-Time stability in January-March of 2017. The study included the following analysis: Absorbance @ 250, 260, and 280 nm, Assay, pH (5%), and Loss on Drying. All Appearance and Color results met requirements. These results will not be analyzed as they are qualitative.

## 2. REFERENCES:

2.1. HEPES Stability Analysis Sheet, DCN: 16-000730

2.2. ICH Q1E§; 2.4.1 No significant change at Long Term condition

2.3. Stability Testing Program, DCN:16-000505

## 3. 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.

## 4. SAMPLE DESIGNATION:

Samples initially placed on the stability program consisted of four Process Validation batches. The type of packaging utilized in the Long Term stability samples was based on BioSpectra packaging. Stability samples from each of the batches were put into a poly drum lined with two poly liners (P/P), with the outer liner being goose-neck tied closed. These batches were placed on stability in the Warehouse located in the BioSpectra Stroudsburg, PA facility.

## 5. STORAGE:

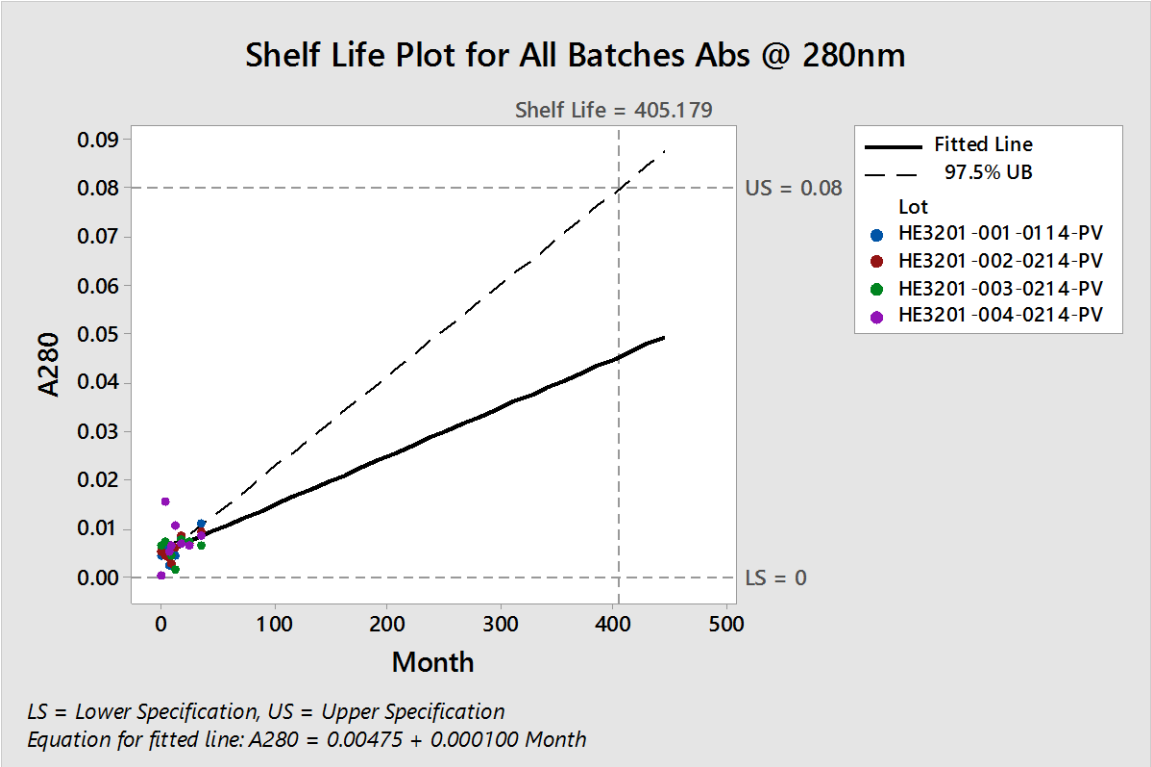
Although there are currently no storage conditions for HEPES, storage conditions have been continuously measured and recorded. The temperature and humidity was monitored continuously utilizing MadgeTech data loggers located in the Stroudsburg, PA Warehouse. The temperature is expected to be within 15-30°C and the humidity is monitored.

There were two excursions that took place during the time period that the HEPES, placed on stability in 2014, was on stability. Reference DI14-13 for excursions that occurred in 2014. Reference SDI16-57 for excursions that occurred in 2016. Both discrepancies were issued for the temperature of the warehouse dropping below 15°C. There was no impact to the HEPES lots on stability as there are no specified storage conditions for HEPES.

## 6. LOT EVALUATION:

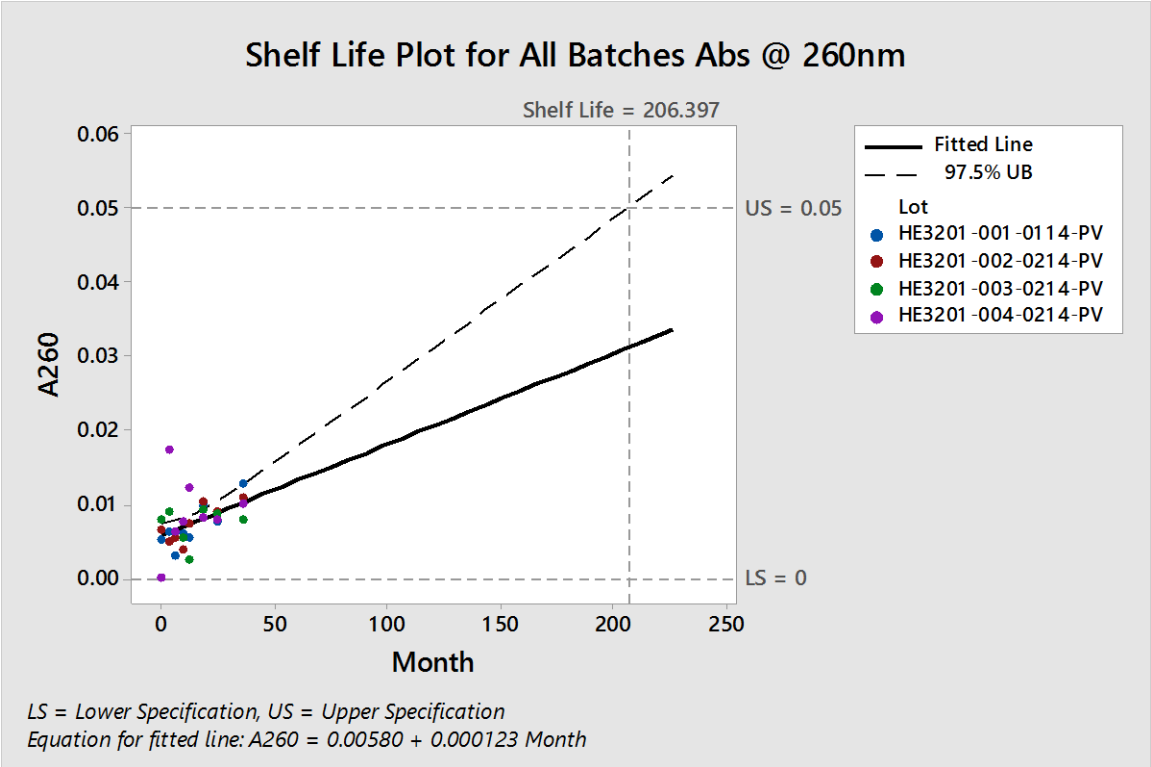
The following graphs evaluate HEPES validation lots HE3201-001-0114-PV, HE3201-002-0214-PV, HE3201-003-0214-PV, and HE3201-004-0214-PV.

**GRAPH 1. ABSORBANCE (0.1M) AT 280NM FOR ALL BATCHES**



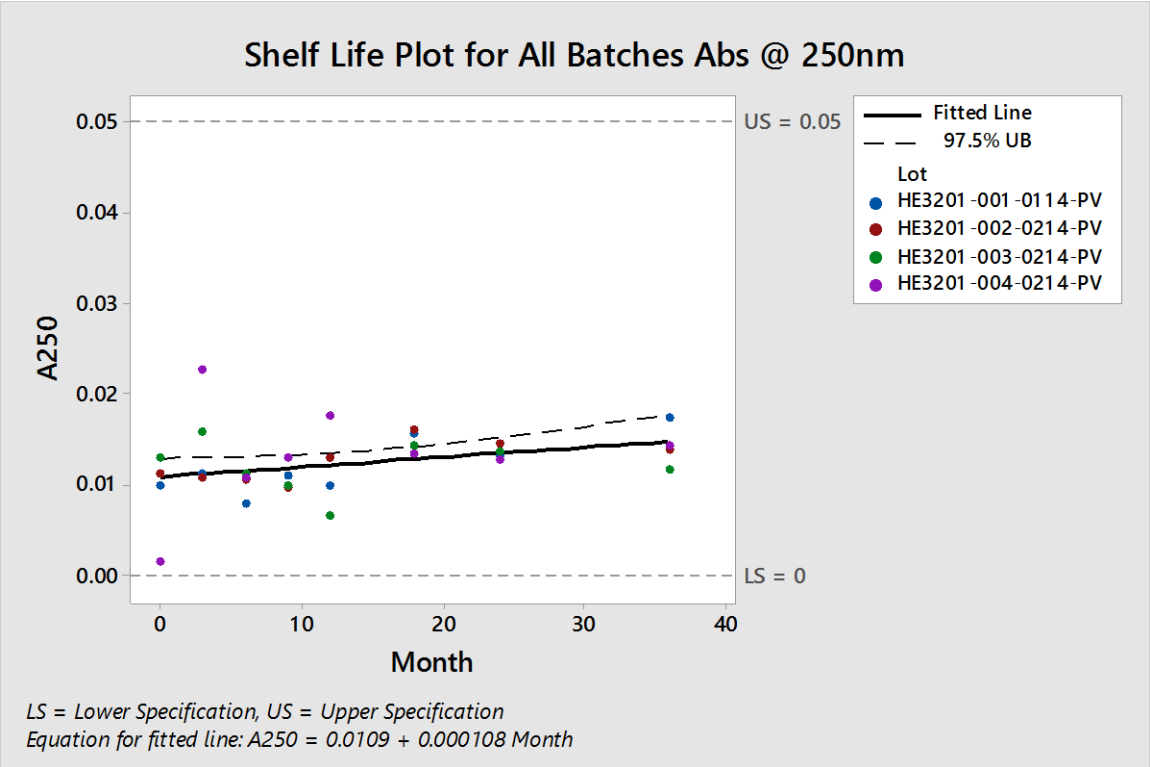

A Shelf life of 405.179 months was predicted based on data for absorbance at 280 nm. The predicted shelf life exceeds the current 24 month retest date. There is supporting Long Term data for the 36 month stability testing program. Extrapolating this data by utilizing the shelf life plot above shows that the material remains stable throughout and exceeding 36 months.

**GRAPH 2. ABSORBANCE (0.1M) AT 260NM FOR ALL BATCHES**



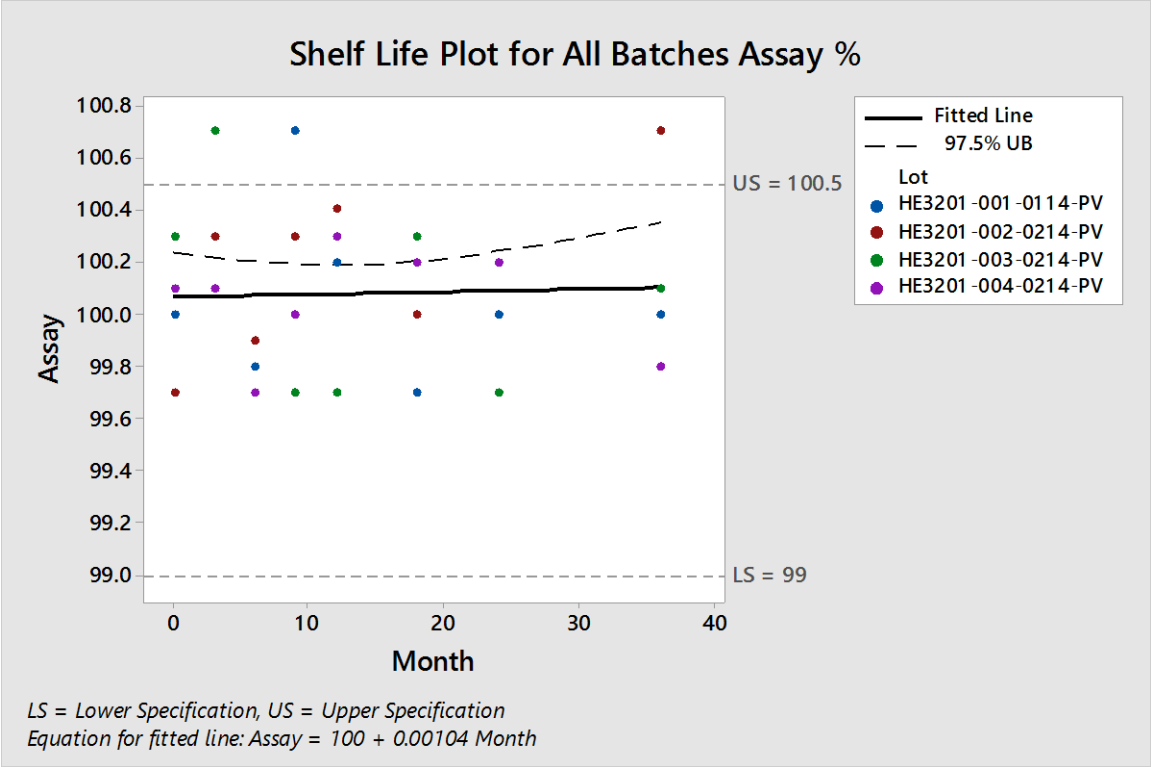

A Shelf life of 206.397 months was predicted based on data for absorbance at 260 nm. The predicted shelf life exceeds the current 24 month retest date. There is supporting Long Term data for the 36 month stability testing program. Extrapolating this data by utilizing the shelf life plot above shows that the material remains stable throughout and exceeding 36 months.

**GRAPH 3. ABSORBANCE (0.1M) AT 250 NM FOR ALL BATCHES**



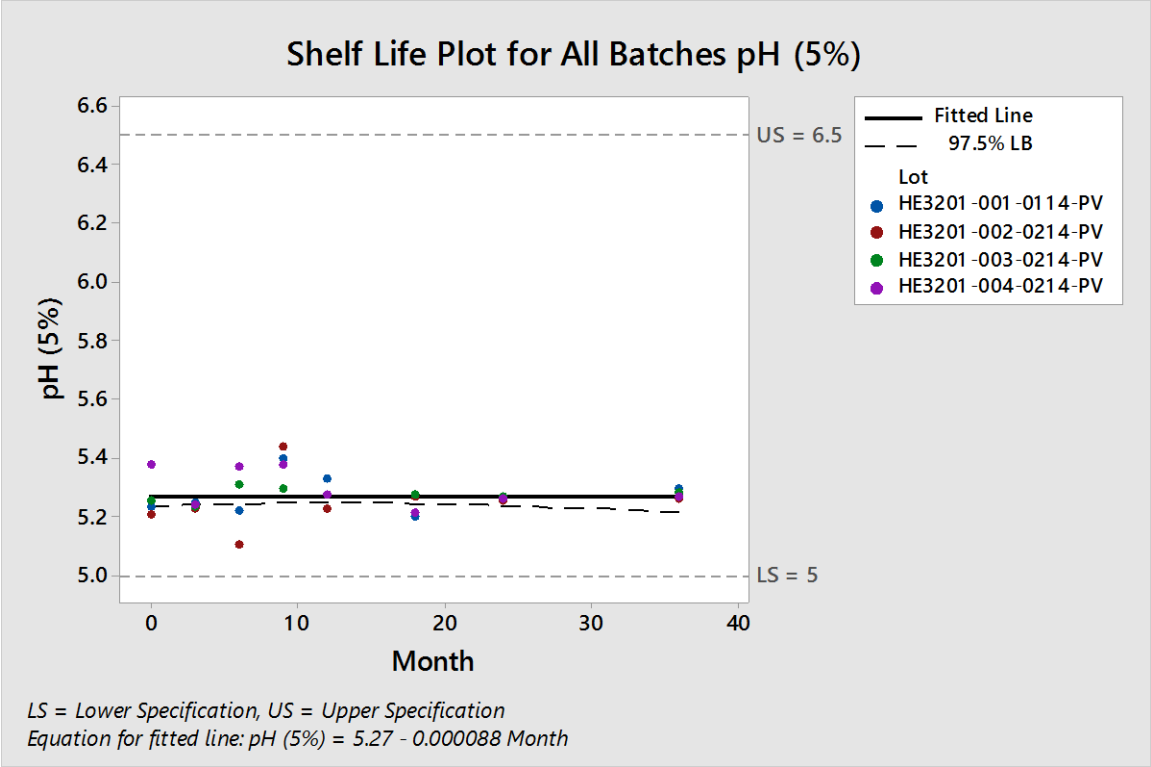

Results for absorbance at 250 nm showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is little degradation of the product shown from this analysis during the 36 month analysis timeframe.

**GRAPH 4. ASSAY % FOR ALL BATCHES**



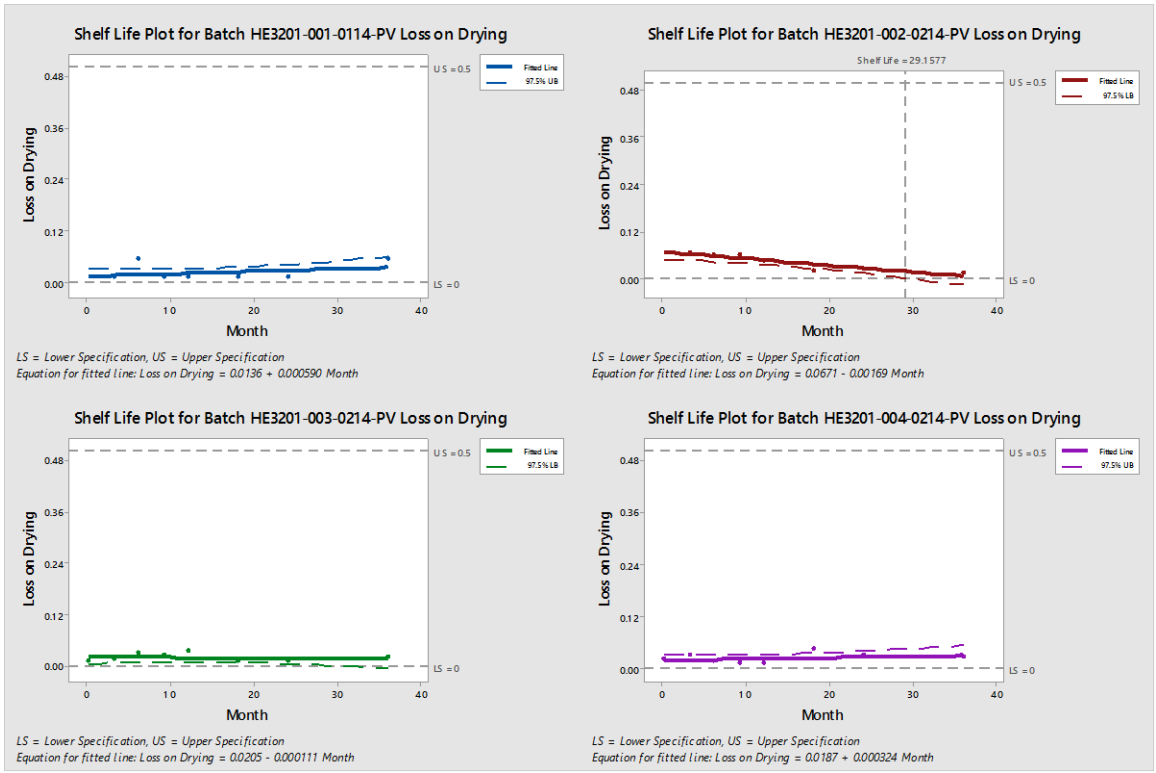

Results for assay % showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is little degradation of the product shown from this analysis during the 36 month analysis timeframe. An arbitrary maximum specification of 100.5% was set for this Shelf-life plot. The specification for HEPES stability assay is 99.0% minimum, therefore all lots met the specification and are considered acceptable.

**GRAPH 5. PH (5%) FOR ALL BATCHES**

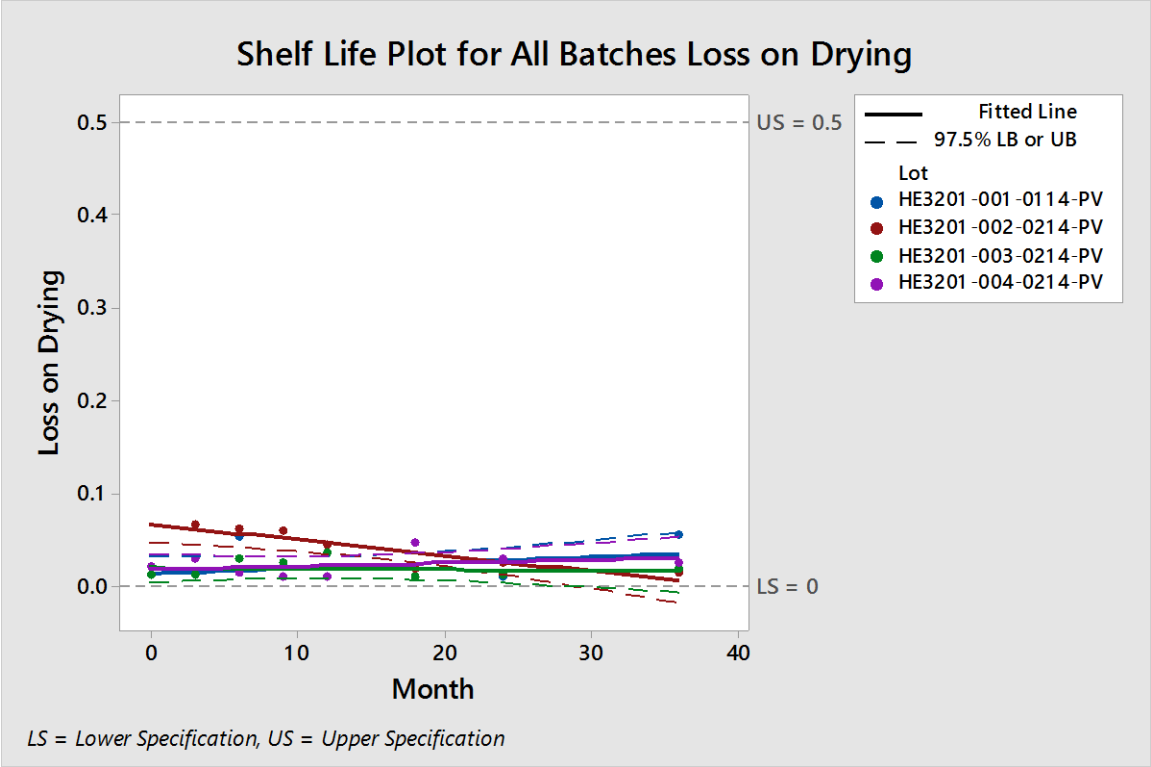



Results for pH (5%) showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is little degradation of the product shown from this analysis during the 36 month analysis timeframe.

# GRAPH 6. LOSS ON DRYING % FOR ALL BATCHES



**GRAPH 7. LOSS ON DRYING % FOR ALL BATCHES**




Results for Loss on Drying % 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 this analysis during the 36 month analysis timeframe. HE3201-002-0214-PV was the only lot that showed a predicatable shelf life, of 29.1577 months. This shelf life exceeds the current 24 month retest date and was predicted as the loss on drying % was approaching 0%, this is not a concern as loss on drying analysis has a specification of 0.5% maximum. It appears as there is a reduction in moisture, however this is most likely due to poor packaging of T3 to T12 samples as the composite sample had a Loss on Drying result of <0.0150% and T18-T36 were equivalent to the result for the intital Finished Goods sample.

## 7. CONCLUSION:

Long Term Stability Data obtained for lots manufactured in 2014 indicate that the material is stable for a minimum of 36 months. A 2 year retest date will be proposed as 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 with appropriate justification if statistical analysis from the shelf life data supports it.