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

BIS-TRIS
2023 VALIDATION LOTS
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 Bis-Tris manufactured at BioSpectra's Bangor, PA facility. Testing intervals are designated by T_n, where ***n*** designates 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 Bis-Tris validation lots BTRI-0123-00003-PV, BTRI-0123-00004-PV, BTRI-0123-00005-PV and BTRI-0123-00006-PV that completed twenty-four (24) months of long-term stability in April 2025 and lot BTRI-0123-00045-PV that completed eighteen (18) months of long-term stability in May 2025. This study includes analyses in Table 1 below. Results from all analyses are summarized in Table 4 through 13.

TABLE 1: STABILITY SPECIFICATIONS

Analysis	Specification
Absorbance 0.1M @ 280 nm	≤0.04 a.u.
Absorbance 0.1M @ 340 nm	≤0.02 a.u.
Appearance and Color	White Crystalline Powder
Assay (Dried Basis)	99.0 – 101.0%
Identification (IR)	Conforms to Reference Standard
Loss on Drying (LOD)	≤1.0%
Melting Point	100 – 105°C
pH (1% aqueous)	8.8 – 9.8
pKa	6.3 – 6.7

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. This study will be used to establish shelf life for all product codes of Bis-Tris. The following product codes are commercially available:

- BTRI-3250
- BTRI-4250

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:

Samples placed on the stability program in 2023 consisted of five validation lots of Bis-Tris. Stability samples from these lots were put into P/P and Labline packaging configuration. The samples were packaged in accordance with the Stability Inventory SOP. Reference Table 1, below, for packaging configuration and description. The type of packaging utilized in this stability study was equivalent to the finished product packaging.

TABLE 2: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Poly/Poly (P/P)	Samples are packaged into small LLDPE bags and sealed with a zip tie. All individual samples are then placed into a HDPE pail.
Labline (HDPE Bottle)	Samples are packaged into a HDPE Lab Screw-Top Bottle.

4. STORAGE:

4.1. The Packaging and Storage requirements for Bis-Tris are to be in tightly closed container, and stored in a dry, well-ventilated area away from incompatible substances. For this study, the samples were stored in the Real Time Stability Chamber H03SC01 at the Bangor, PA facility from April 2023 until the last sample time point in May 2025. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (23-27°C) and humidity (55-65%RH). Maximum and minimum values that are outside limits for temperature and humidity are due to opening the door of the chamber as explained in Temperature and Humidity Monitoring Assessments for the chambers. The storage conditions for the time period of this study are detailed in Table 3. Section 5 will include any excursions from these conditions that resulted in an investigation.

TABLE 3: STORAGE CONDITIONS

Condition	Specification	Value
Minimum Temperature	25°C ±2°C	21.81°C
Maximum Temperature		26.20°C
Average Temperature		25.35°C
Mean Kinetic Temperature	Monitor	25.35°C
Minimum Humidity	60%RH ±5%RH	43.6%
Maximum Humidity		80.5%
Average Humidity		61.5%

5. INVESTIGATIONS:

5.1. BDI24-13, Out of range humidity for the Real Time Stability Chamber H03SC01 caused by improper work order completion to prevent water leaking from the stability chamber. On 1/15/24 while conducting a maintenance walkthrough of the Bangor facility water was observed on the floor of room H03RM01. 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 humidity and temperature for H03SC01 occurred on 8/15/24 with a humidity reading of 54.4% and a temperature of 21.81°C. It was discovered that a 20-amp fuse had blown. The fuse was replaced and the chamber went back into specification on 8/16/24 with a humidity reading of 62.3%. There is no impact on the stability samples as this excursion lasted less than 24 hours.

6. LOT EVALUATION:

TABLE 4: BTRI-0123-00003-PV P/P

Time Point	Analyses/Specifications								
	Absorbance 0.1M		Appearance and Color	Assay (Dried)	Identification (IR)	LOD	Melting Point	pH (1%)	pKa
	280 nm	340 nm	White Crystalline Powder	99.0 – 101.0%	Conforms to Reference Standard	≤1.0%	100 – 105°C	8.8 – 9.8	6.3 – 6.7
	≤0.04 a.u.	≤0.02 a.u.							
T_0	0.0096	0.0002	White Crystalline Powder	99.97%	Conforms to Reference Standard	<0.0144%	103.5°C	9.33 @ 25.3°C	6.564
T_3	0.0091	0.0003	White Crystalline Powder	99.87%	Conforms to Reference Standard	0.0277%	103.4°C	9.48 @ 23.0°C	6.653
T_6	0.0097	0.0003	White/ Crystals	100.05%	Conforms to Reference Standard	0.0160%	103.5°C	9.45 @ 23.2°C	6.579
T_9	0.0105	0.0004	White Crystalline Powder	100.11%	Conforms to Reference Standard	<0.0079%	104.2°C	9.49 @ 25.5°C	6.562
T_{12}	0.0128	0.0021	White Crystalline Powder	100.03%	Conforms to Reference Standard	0.0804%	104.2°C	9.28 @ 23.1°C	6.603
T_{18}	0.0101	0.0040	White Crystalline Powder	100.21%	Conforms to Reference Standard	0.1140%	104.2°C	9.46 @ 24.4°C	6.562
T_{24}	0.0111	0.0004	White/ Crystals	100.12%	Conforms to Reference Standard	0.0697%	103.3°C	9.42 @ 24.7°C	6.568

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 36; Scheduled for March 30, 2026
  - T = 48; Scheduled for March 30, 2027
  - T = 60; Scheduled for March 30, 2028

TABLE 5: BTRI-0123-00003-PV LABLINE

Time Point	Analyses/Specifications								
	Absorbance 0.1M		Appearance and Color	Assay (Dried)	Identification (IR)	LOD	Melting Point	pH (1%)	pKa
	280 nm	340 nm	White Crystalline Powder	99.0 – 101.0%	Conforms to Reference Standard	≤1.0%	100 – 105°C	8.8 – 9.8	6.3 – 6.7
	≤0.04 a.u.	≤0.02 a.u.							
T_0	0.0096	0.0002	White Crystalline Powder	99.97%	Conforms to Reference Standard	<0.0144%	103.5°C	9.33 @ 25.3°C	6.564
T_3	0.0086	0.0002	White Crystalline Powder	100.05%	Conforms to Reference Standard	0.0484%	103.3°C	9.51 @ 23.9°C	6.634
T_6	0.0096	<0.003	White/ Crystals	100.09%	Conforms to Reference Standard	0.0732%	103.5°C	9.55 @ 23.2°C	6.577
T_9	0.0096	0.0003	White Crystalline Powder	100.04%	Conforms to Reference Standard	0.0195%	104.3°C	9.50 @ 23.6°C	6.563
T_{12}	0.0128	0.0021	White Crystalline Powder	100.08%	Conforms to Reference Standard	0.0342%	104.2°C	8.95 @ 23.1°C	6.593
T_{18}	0.0089	0.0031	White Crystalline Powder	100.11%	Conforms to Reference Standard	0.0579%	104.1°C	9.49 @ 23.3°C	6.562
T_{24}	0.0099	0.0002	White/ Crystals	100.00%	Conforms to Reference Standard	0.0639%	104.4°C	9.45 @ 24.7°C	6.572

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 36; Scheduled for March 30, 2026
  - T = 48; Scheduled for March 30, 2027
  - T = 60; Scheduled for March 30, 2028

TABLE 6: BTRI-0123-00004-PV P/P

Time Point	Analyses/Specifications								
	Absorbance 0.1M		Appearance and Color	Assay (Dried)	Identification (IR)	LOD	Melting Point	pH (1%)	pKa
	280 nm ≤0.04 a.u.	340 nm ≤0.02 a.u.	White Crystalline Powder	99.0 – 101.0%	Conforms to Reference Standard	≤1.0%	100 – 105°C	8.8 – 9.8	6.3 – 6.7
T_0	0.0100	0.0003	White Crystalline Powder	99.90%	Conforms to Reference Standard	<0.0193%	103.5°C	9.08 @ 25.6°C	6.547
T_3	0.0093	0.0011	White Crystalline Powder	100.02%	Conforms to Reference Standard	0.0547%	103.3°C	9.39 @ 24.1°C	6.627
T_6	0.0100	0.0010	White/ Crystals	100.10%	Conforms to Reference Standard	0.0433%	103.5°C	9.53 @ 23.2°C	6.582
T_9	0.0120	0.0013	White Crystalline Powder	100.39%	Conforms to Reference Standard	0.0230%	104.2°C	9.44 @ 26.2°C	6.565
T_{12}	0.0141	0.0029	White Crystalline Powder	100.18%	Conforms to Reference Standard	0.0610%	104.2°C	9.45 @ 23.1°C	6.603
T_{18}	0.0110	0.0041	White Crystalline Powder	99.93%	Conforms to Reference Standard	0.1427%	104.1°C	9.47 @ 23.6°C	6.565
T_{24}	0.0117	0.0010	White/ Crystals	99.98%	Conforms to Reference Standard	0.0416%	104.3°C	9.46 @ 25.1°C	6.560

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 36; Scheduled for March 30, 2026
  - T = 48; Scheduled for March 30, 2027
  - T = 60; Scheduled for March 30, 2028

TABLE 7: BTRI-0123-00004-PV LABLINE

Time Point	Analyses/Specifications								
	Absorbance 0.1M		Appearance and Color	Assay (Dried)	Identification (IR)	LOD	Melting Point	pH (1%)	pKa
	280 nm	340 nm	White Crystalline Powder	99.0 – 101.0%	Conforms to Reference Standard	≤1.0%	100 – 105°C	8.8 – 9.8	6.3 – 6.7
	≤0.04 a.u.	≤0.02 a.u.							
T_0	0.0100	0.0003	White Crystalline Powder	99.90%	Conforms to Reference Standard	<0.0193%	103.5°C	9.08 @ 25.6°C	6.547
T_3	0.0095	0.0010	White Crystalline Powder	100.15%	Conforms to Reference Standard	0.0418%	103.4°C	9.52 @ 25.1°C	6.633
T_6	0.0101	0.0008	White/ Crystals	100.16%	Conforms to Reference Standard	0.0404%	103.4°C	9.50 @ 23.2°C	6.581
T_9	0.0142	0.0018	White Crystalline Powder	100.27%	Conforms to Reference Standard	0.0295%	104.1°C	9.42 @ 26.3°C	6.570
T_{12}	0.0142	0.0026	White Crystalline Powder	100.07%	Conforms to Reference Standard	<0.0076%	104.2°C	9.37 @ 23.1°C	6.602
T_{18}	0.0101	0.0039	White Crystalline Powder	99.93%	Conforms to Reference Standard	0.0850%	104.2°C	9.47 @ 23.1°C	6.567
T_{24}	0.0101	0.0006	White/ Crystals	100.11%	Conforms to Reference Standard	0.0838%	104.4°C	9.49 @ 23.0°C	6.566

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 36; Scheduled for March 30, 2026
  - T = 48; Scheduled for March 30, 2027
  - T = 60; Scheduled for March 30, 2028

TABLE 8: BTRI-0123-00005-PV P/P

Time Point	Analyses/Specifications								
	Absorbance 0.1M		Appearance and Color	Assay (Dried)	Identification (IR)	LOD	Melting Point	pH (1%)	pKa
	280 nm ≤0.04 a.u.	340 nm ≤0.02 a.u.	White Crystalline Powder	99.0 – 101.0%	Conforms to Reference Standard	≤1.0%	100 – 105°C	8.8 – 9.8	6.3 – 6.7
T_0	0.0105	0.0002	White Crystalline Powder	100.20%	Conforms to Reference Standard	0.0456%	103.4°C	9.42 @ 24.9°C	6.547
T_3	0.0092	0.0003	White Crystalline Powder	99.86%	Conforms to Reference Standard	0.0415%	103.4°C	9.38 @ 23.8°C	6.624
T_6	0.0092	0.0004	White/ Crystals	100.04%	Conforms to Reference Standard	0.0114%	103.5°C	9.52 @ 23.2°C	6.581
T_9	0.0126	0.0018	White Crystalline Powder	100.18%	Conforms to Reference Standard	0.0309%	104.2°C	9.45 @ 25.4°C	6.572
T_{12}	0.0137	0.0032	White Crystalline Powder	100.01%	Conforms to Reference Standard	0.0295%	104.3°C	9.42 @ 23.1°C	6.608
T_{18}	0.0092	0.0033	White Crystalline Powder	99.91%	Conforms to Reference Standard	<0.0061%	103.5°C	9.51 @ 23.2°C	6.566
T_{24}	0.0103	0.0006	White/ Crystals	99.93%	Conforms to Reference Standard	0.0411%	104.4°C	9.49 @ 24.2°C	6.565

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 36; Scheduled for March 30, 2026
  - T = 48; Scheduled for March 30, 2027
  - T = 60; Scheduled for March 30, 2028

TABLE 9: BTRI-0123-00005-PV LABLINE

Time Point	Analyses/Specifications								
	Absorbance 0.1M		Appearance and Color	Assay (Dried)	Identification (IR)	LOD	Melting Point	pH (1%)	pKa
	280 nm	340 nm	White Crystalline Powder	99.0 – 101.0%	Conforms to Reference Standard	≤1.0%	100 – 105°C	8.8 – 9.8	6.3 – 6.7
	≤0.04 a.u.	≤0.02 a.u.							
T_0	0.0105	0.0002	White Crystalline Powder	100.20%	Conforms to Reference Standard	0.0456%	103.4°C	9.42 @ 24.9°C	6.547
T_3	0.0096	0.0003	White Crystalline Powder	99.82%	Conforms to Reference Standard	0.0498%	103.4°C	9.49 @ 23.7°C	6.634
T_6	0.0098	0.0004	White/ Crystals	100.20%	Conforms to Reference Standard	0.0505%	103.6°C	9.48 @ 23.2°C	6.581
T_9	0.0117	0.0014	White Crystalline Powder	100.04%	Conforms to Reference Standard	0.0299%	104.2°C	9.46 @ 25.1°C	6.570
T_{12}	0.0146	0.0033	White Crystalline Powder	100.11%	Conforms to Reference Standard	0.0147%	104.4°C	9.45 @ 23.1°C	6.601
T_{18}	0.0099	0.0035	White Crystalline Powder	100.03%	Conforms to Reference Standard	0.0243%	103.9°C	9.54 @ 23.3°C	6.564
T_{24}	0.0099	0.0004	White/ Crystals	99.97%	Conforms to Reference Standard	0.0431%	104.3°C	9.49 @ 23.3°C	6.557

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 36; Scheduled for March 30, 2026
  - T = 48; Scheduled for March 30, 2027
  - T = 60; Scheduled for March 30, 2028

TABLE 10: BTRI-0123-00006-PV P/P

Time Point	Analyses/Specifications								
	Absorbance 0.1M		Appearance and Color	Assay (Dried)	Identification (IR)	LOD	Melting Point	pH (1%)	pKa
	280 nm	340 nm	White Crystalline Powder	99.0 – 101.0%	Conforms to Reference Standard	≤1.0%	100 – 105°C	8.8 – 9.8	6.3 – 6.7
	≤0.04 a.u.	≤0.02 a.u.							
T_0	0.0090	<0.003	White Crystalline Powder	99.91%	Conforms to Reference Standard	0.0614%	103.6°C	9.32 @ 24.9°C	6.573
T_3	0.0131	0.0014	White Crystalline Powder	99.54%	Conforms to Reference Standard	0.0573%	103.4°C	9.51 @ 24.4°C	6.578
T_6	0.0105	0.0011	White Crystalline Powder	99.99%	Conforms to Reference Standard	0.0298%	103.5°C	9.44 @ 23.0°C	6.559
T_9	0.0149	0.0035	White Crystalline Powder	100.27%	Conforms to Reference Standard	0.0704%	104.2°C	9.53 @ 23.1°C	6.599
T_{12}	0.0110	0.0013	White/ Crystals	100.29%	Conforms to Reference Standard	0.0213%	104.3°C	9.29 @ 24.3°C	6.596
T_{18}	0.0109	0.0025	White Crystalline Powder	99.80%	Conforms to Reference Standard	0.0634%	104.2°C	9.50 @ 23.0°C	6.533
T_{24}	0.0105	0.0011	White Crystalline Powder	99.71%	Conforms to Reference Standard	0.0745%	104.4°C	9.43 @ 23.0°C	6.579

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 36; Scheduled for April 14, 2026
  - T = 48; Scheduled for April 14, 2027
  - T = 60; Scheduled for April 14, 2028

TABLE 11: BTRI-0123-00006-PV LABLINE

Time Point	Analyses/Specifications								
	Absorbance 0.1M		Appearance and Color	Assay (Dried)	Identification (IR)	LOD	Melting Point	pH (1%)	pKa
	280 nm	340 nm	White Crystalline Powder	99.0 – 101.0%	Conforms to Reference Standard	≤1.0%	100 – 105°C	8.8 – 9.8	6.3 – 6.7
	≤0.04 a.u.	≤0.02 a.u.							
T_0	0.0090	<0.003	White Crystalline Powder	99.91%	Conforms to Reference Standard	0.0614%	103.6°C	9.32 @ 24.9°C	6.573
T_3	0.0104	0.0006	White Crystalline Powder	99.84%	Conforms to Reference Standard	0.0111%	103.4°C	9.57 @ 24.3°C	6.593
T_6	0.0105	0.0010	White Crystalline Powder	100.26%	Conforms to Reference Standard	0.0379%	103.5°C	9.46 @ 23.1°C	6.580
T_9	0.0121	0.0021	White Crystalline Powder	99.86%	Conforms to Reference Standard	0.0607%	104.2°C	9.52 @ 23.1°C	6.599
T_{12}	0.0141	0.0042	White/ Crystals	100.04%	Conforms to Reference Standard	0.0220%	104.3°C	9.41 @ 24.1°C	6.600
T_{18}	0.0104	0.0007	White Crystalline Powder	100.21%	Conforms to Reference Standard	0.1136%	104.2°C	9.44 @ 23.0°C	6.536
T_{24}	0.0131	0.0008	White Crystalline Powder	99.85%	Conforms to Reference Standard	0.0512%	104.3°C	9.46 @ 23.0°C	6.577

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 36; Scheduled for April 14, 2026
  - T = 48; Scheduled for April 14, 2027
  - T = 60; Scheduled for April 14, 2028

TABLE 12: BTRI-0123-00045-PV P/P

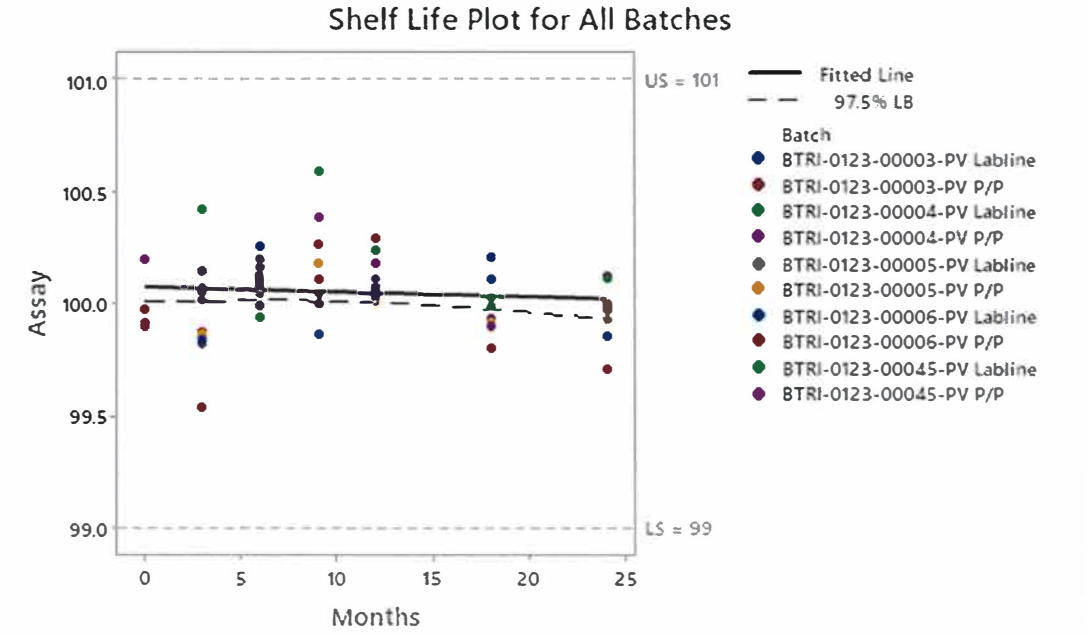
Time Point	Analyses/Specifications								
	Absorbance 0.1M		Appearance and Color	Assay (Dried)	Identification (IR)	LOD	Melting Point	pH (1%)	pKa
	280 nm	340 nm	White Crystalline Powder	99.0 – 101.0%	Conforms to Reference Standard	≤1.0%	100 – 105°C	8.8 – 9.8	6.3 – 6.7
	≤0.04 a.u.	≤0.02 a.u.							
T_0	0.0089	0.0002	White Crystalline Powder	100.20%	Conforms to Reference Standard	0.0739%	104.0°C	9.43 @ 23.0°C	6.607
T_3	0.0096	0.0002	White Crystalline Powder	100.07%	Conforms to Reference Standard	0.0761%	104.0°C	9.43 @ 23.3°C	6.619
T_6	0.0108	0.0005	White Crystalline Powder	100.13%	Conforms to Reference Standard	0.0388%	104.0°C	9.49 @ 23.3°C	6.579
T_9	0.0108	0.0005	White Crystalline Powder	100.00%	Conforms to Reference Standard	0.0263%	104.0°C	9.34 @ 23.1°C	6.558
T_{12}	0.0108	0.0011	White Crystalline Powder	100.07%	Conforms to Reference Standard	0.0158%	104.3°C	9.53 @ 24.2°C	6.583
T_{18}	0.0101	0.0009	White Crystalline Powder	99.90%	Conforms to Reference Standard	0.1352%	104.3°C	9.57 @ 23.1°C	6.570

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 24; Scheduled for November 20, 2025
  - T = 36; Scheduled for November 20, 2026
  - T = 48; Scheduled for November 20, 2027
  - T = 60; Scheduled for November 20, 2028

TABLE 13: BTRI-0123-00045-PV LABLINE

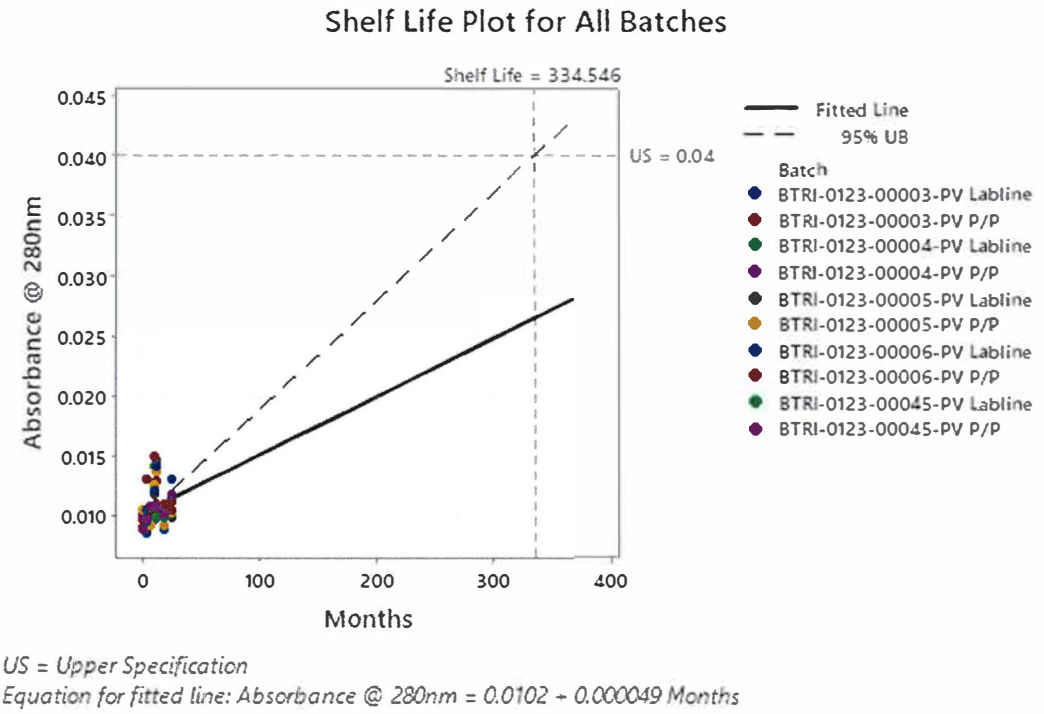
Time Point	Analyses/Specifications								
	Absorbance 0.1M		Appearance and Color	Assay (Dried)	Identification (IR)	LOD	Melting Point	pH (1%)	pKa
	280 nm ≤0.04 a.u.	340 nm ≤0.02 a.u.	White Crystalline Powder	99.0 – 101.0%	Conforms to Reference Standard	≤1.0%	100 – 105°C	8.8 – 9.8	6.3 – 6.7
T_0	0.0089	0.0002	White Crystalline Powder	100.20%	Conforms to Reference Standard	0.0739%	104.0°C	9.43 @ 23.0°C	6.607
T_3	0.0095	0.0001	White Crystalline Powder	100.42%	Conforms to Reference Standard	0.1094%	104.1°C	9.45 @ 23.3°C	6.599
T_6	0.0106	0.0002	White Crystalline Powder	99.94%	Conforms to Reference Standard	<0.0071%	104.0°C	9.41 @ 23.6°C	6.588
T_9	0.0108	0.0005	White Crystalline Powder	100.59%	Conforms to Reference Standard	0.2179%	104.0°C	9.58 @ 23.1°C	6.592
T_{12}	0.0099	0.0002	White Crystalline Powder	100.24%	Conforms to Reference Standard	0.0344%	104.3°C	9.46 @ 24.5°C	6.582
T_{18}	0.0098	0.0006	White Crystalline Powder	99.99%	Conforms to Reference Standard	0.0152%	104.2°C	9.53 @ 23.0°C	6.572

- **REMAINING TESTING INTERVAL PULL DATES**
  - T = 24; Scheduled for November 20, 2025
  - T = 36; Scheduled for November 20, 2026
  - T = 48; Scheduled for November 20, 2027
  - T = 60; Scheduled for November 20, 2028



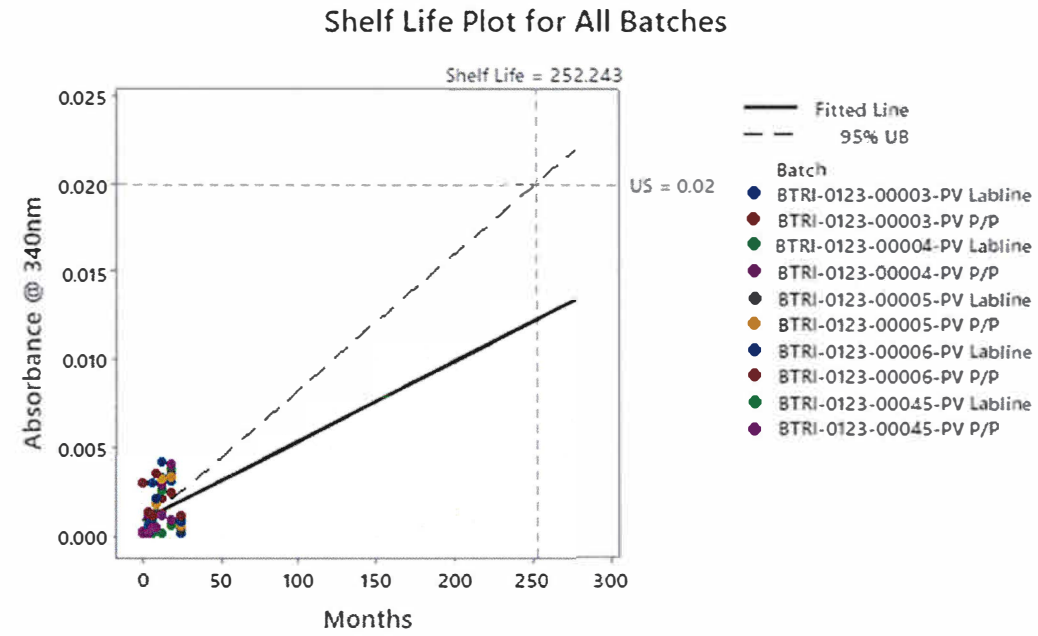
GRAPH 1: ASSAY

No Shelf-Life was able to be determined for Assay 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 2: ABSORBANCE @ 280 NM

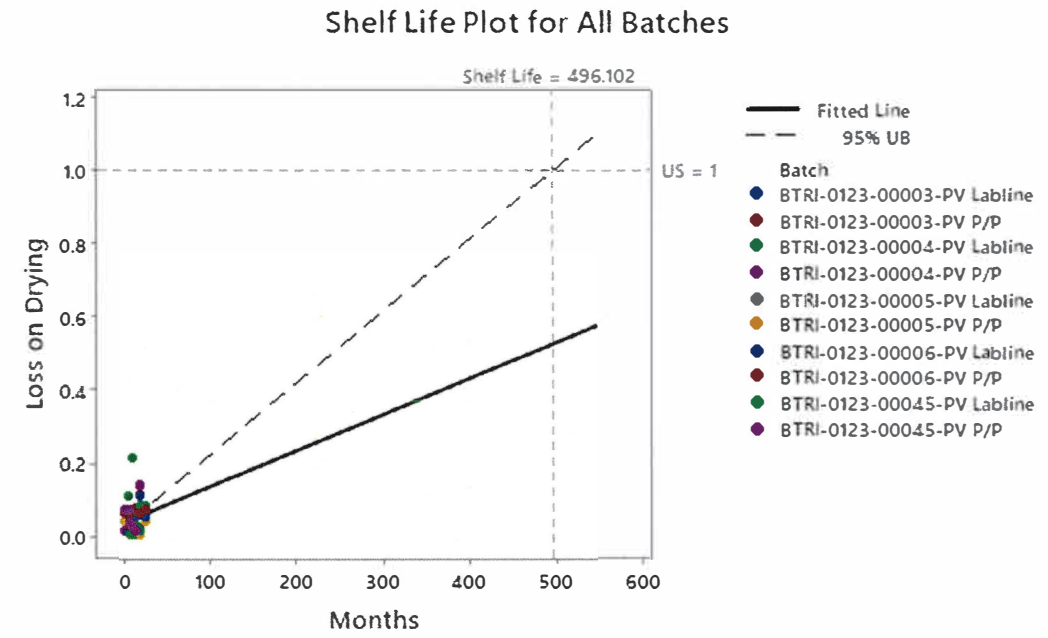
The predicted Shelf-Life for Absorbance @ 280 nm was determined to be 334.546 months as of the 24-month time interval. There is no impact to the product or currently assigned retest period of this material.



US = Upper Specification
Equation for fitted line: Absorbance @ 340nm = 0.000883 + 0.000045 Months

GRAPH 3: ABSORBANCE @ 340 NM

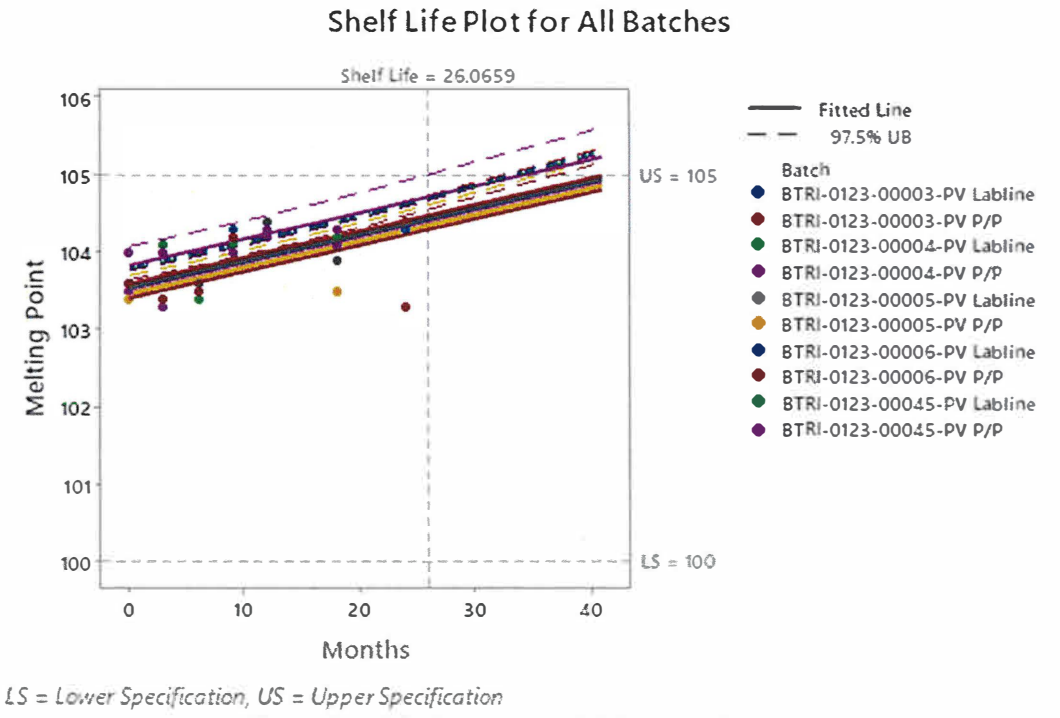
The predicted Shelf-Life for Absorbance @ 340 nm was determined to be 252.243 months as of the 24-month time interval. There is no impact to the product or currently assigned retest period of this material.



US = Upper Specification
Equation for fitted line: Loss on Drying = 0.0397 + 0.000981 Months

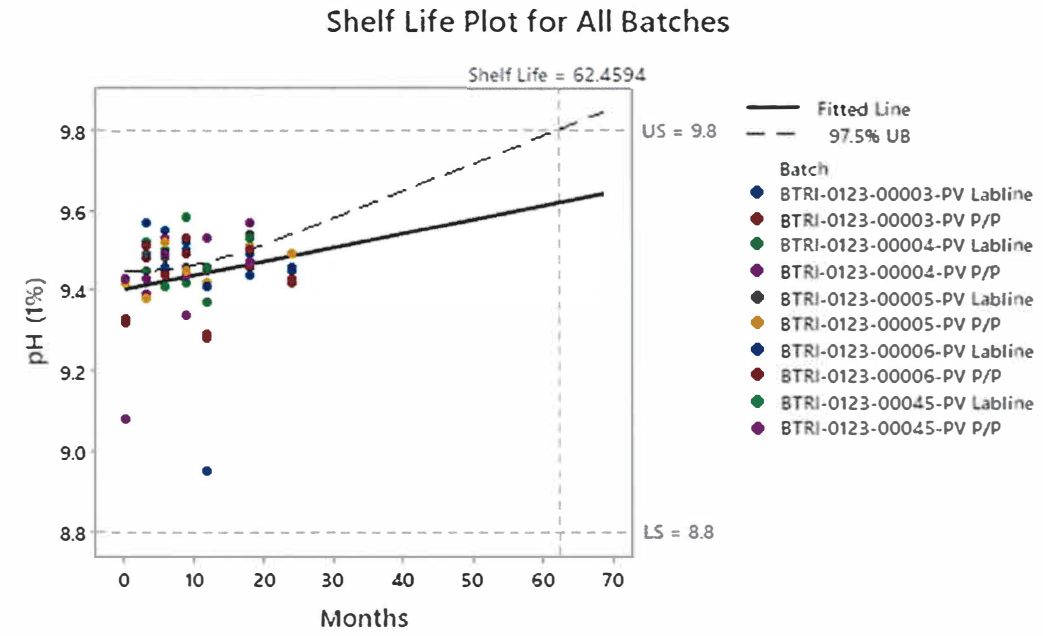
GRAPH 4: LOSS ON DRYING

The predicted Shelf-Life for Loss on Drying was determined to be 496.102 months as of the 24-month time interval. There is no impact to the product or currently assigned retest period of this material.



GRAPH 5: MELTING POINT

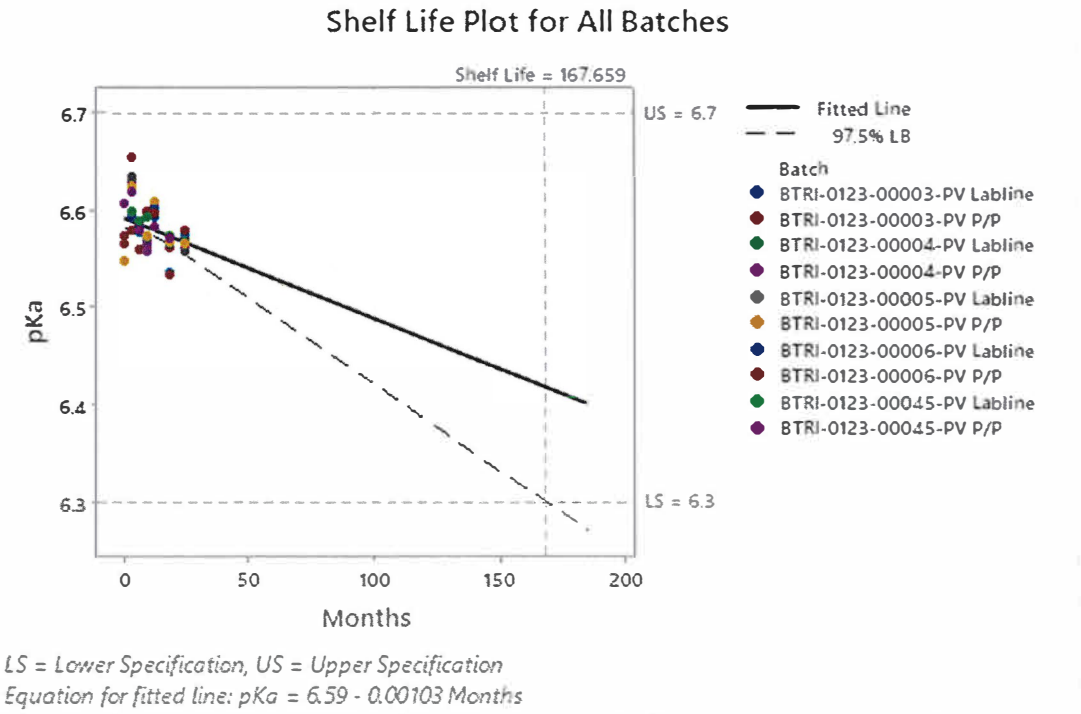
The predicted Shelf-Life for Melting Point was determined to be 26.0659 months as of the 24-month time interval. The shelf-life is defined as the time period in which you may be 95% confident that at least 50% of the response is within the required limits of specifications. All data regardless of the predicted model up to the current time point (18-month and 24-month) has met the required specification. There is no impact to the product or currently assigned retest period of this material.



LS = Lower Specification, US = Upper Specification
Equation for fitted line: pH (1%) = 9.40 + 0.00344 Months

GRAPH 6: PH (1%)

The predicted Shelf-Life for pH 1% was determined to be 62.4594 months as of the 24-month time interval. There is no impact to the product or currently assigned retest period of this material.



GRAPH 7: PKA

The predicted Shelf-Life for pKa was determined to be 167.659 months as of the 24-month time interval. There is no impact to the product or currently assigned retest period of this material.

7. CONCLUSION:

7.1. 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. Long-Term Stability Data displayed in this report, along with the predicted shelf-life plots, supports a retest date of 24 months for Bis-Tris manufactured at BioSpectra in the 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 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, the batch will be withdrawn from the market through communication with the 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.