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

TRIS BIO EXCIPIENT GRADE 2022 LONG-TERM STABILITY REPORT

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 Tris Bio Excipient Grade material manufactured at the Stroudsburg, PA facility. 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.

This long-term stability analysis will assess the stability of three batches of Tris Bio Excipient Grade material lot TRIS-0222-00042 and TRIS-0222-00013 that completed 24-months (24) of long-term stability in July 2024 and TRIS-0222-00168 that completed eighteen (18) months of long-term stability in April 2024. The stability study included the following analyses: Absorbance (1M) at 400 nm, Absorbance (1M) at 280 nm, Absorbance (1M) at 260 nm, Assay, Appearance and Color, Loss on Drying, Identification (IR) and Melting Range. Results from all analyses are summarized in Table 2 through 9. 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 specifications for the stability indicating analyses are established in accordance with the Stability Indication Protocol, BSI-SOP-0289, when a new product is manufactured. 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. This study will be used to establish shelf life for all product codes of Tris Bio Excipient Grade material. The following product codes are commercially available.

- TRIS-3201
- TRIS-3220
- TRIS-3251
- TRIS-3252
- TRIS-3254
- TRIS-3255
- TRIS-3257
- TRIS-4220
- TRIS-5201
- TRIS-5203
- TRIS-5204
- TRIS-5207
- TRIS-5220
- TRIS-7201
- TRIS-7202

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 Testing Program consisted of three Tris Bio Excipient Grade batches. Stability samples from the batches were put in up to three different packaging configurations. The samples were packaged in accordance with the Stability Inventory SOP. Reference Table 1 for packaging configuration and description. The type of packaging utilized in this stability study were based on BioSpectra's packaging configurations offered to the customer.

TABLE 1: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Poly/Fiber (P/F)	Samples are packaged into small poly bags and sealed with a zip tie. All individual samples are then placed into a fiber drum, along with a 4-unit desiccant.
Poly/Poly (P/P) with EziDock Poly Bag	Samples are packaged into EziDock Poly bags. All individual samples are then placed into a poly drum.
Labline	Samples are packaged into a HDPE Lab Screw-Top Bottle

4. STORAGE:

Samples were placed on stability in BioSpectra's Stroudsburg, PA facility stability area, located in the warehouse. Although there are no storage requirements for Tris Bio Excipient Grade material, storage conditions were continuously monitored and recorded utilizing MadgeTech data loggers for temperature (specification: 15-30°C), humidity (specification: monitor) and Mean Kinetic Temperature (specification: ≤25°C). The samples were stored in the Stroudsburg warehouse from July 2022 through July 2024. The maximum temperature of the warehouse during this time was 29.75°C and the minimum temperature of the warehouse during this time was 11.73°C the average temperature was 20.76°C. The average mean kinetic temperature was 20.85°C. See Section 5 for the discrepancy investigations initiated for temperature excursions.

5. INVESTIGATIONS:

5.1. **SLI22-07** was initiated due to out of specification result of 0.7445% obtained for Loss on Drying for TRIS-0222-00042 at the T=0 timepoint. A resampling of the batch was performed with 6 replicates and the results confirmed the original result.

5.2. **SDI22-100** was initiated due to out of specification on a Loss on Drying for a result of 0.7445% obtained for TRIS-0222-00042 for the T=0 timepoint. The cause of the OOS for the LOD can likely be attributed to the moisture found in the finished good crystal from the individual drums at the time of packaging in the poly/poly packaging configuration.

5.3. **BDI22-275** was initiated for not completing the July 2022 temperature and humidity assessments within the specified time frame. The root cause was due to time management and not prioritizing the time sensitive job. This had no impact on the stability samples as the temperature and humidity assessments were completed.

5.4. **SDI22-184** was initiated due to out of specification low temperature readings. Multiple loggers recorded OOS low temperatures with the lowest reading of 13.40°C due to the AC being turned on instead of the heat and for the issue with heating unit number 3. This had no impact on the stability samples as the excursions lasted only a few hours during the nights and early mornings.

5.5. **SLI23-09** was initiated for an out of specification for 1M Absorbance results at 260 nm and 280 nm for batch TRIS-0222-00196 T=3 P/F and Labline. Six retests were performed and the results confirmed the initial results.

5.6. **SDI23-07** was initiated because one of the MadgeTech data loggers fell from its bracket and stopped collecting data. This had no impact on the stability samples as the other six data loggers did not fall outside the specified temperature range of 15 – 30°C during the missing time frame.

5.7. **SDI23-76** was initiated due to an out of specification low temperature reading. This was due to an empty propane tank. This had no impact on the stability samples as the other six data loggers did not fall outside the specified temperature range of 15 – 30°C during the missing time.

5.8. **SDI23-98** was initiated for an out of specification for 1M Absorbance results at 260 nm and 280 nm for batch TRIS-0222-00196 T=3 P/F and Labline. These failures were confirmed through SLI23-09. The investigation discovered that the absorbances from certain batches of raw material from Angus were getting worse over time. The raw material was the root cause of the failures.

5.9. **SDI23-128** was initiated due to a data logger not able to download temperature and humidity data for the month of June 2023. This was due to the logger being damaged during the movement of materials. This had no impact on the stability samples as the other six data loggers did not fall outside the specified temperature range of 15 – 30°C during the missing time.

5.10. **SDI23-159** was initiated due to a data logger to able to download temperature and humidity data for the month of July 2023. This was due to the logger being damaged during the movement of materials. This had no impact on the stability samples as the other six data loggers did not fall outside the specified temperature range of 15 – 30°C during the missing time.

5.11. **SDI24-17** was initiated due to missing data points from a logger from 1/17/24 to 1/30/24. The logger sustained damage when it fell from the bracket at the top of the racking. This had no impact on the stability samples as the other data loggers did not fall outside the specified temperature range of 15 – 30°C during the missing time.

6. LOT EVALUATION:

TABLE 2: TRIS-0222-00013 P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0010 a.u.	<0.003 a.u.	<0.003 a.u.	0.0001 a.u.	<0.003 a.u.	0.0004 a.u.	0.0001 a.u.
	0.06 a.u. max @ 280 nm	0.0054 a.u.	0.0039 a.u.	0.0043 a.u.	0.0042 a.u.	0.0041 a.u.	0.0053 a.u.	0.0053 a.u.
	0.06 a.u. max @ 260 nm	0.0065 a.u.	0.0044 a.u.	0.0049 a.u.	0.0049 a.u.	0.0047 a.u.	0.0061 a.u.	0.0064 a.u.
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Assay (USP)	99.0-101.0%	99.93%	99.92%	99.97%	99.60%	99.67%	100.31%	100.32%
Loss on Drying	0.5% max.	0.0711%	0.0721%	0.0437%	0.0434%	0.0360%	0.0768%	0.0411%
Melting Range	168-172°C	170.5°C – 171.6°C	170.5°C – 171.6°C	170.7°C – 171.8°C	170.6°C – 171.8°C	170.6°C – 172.1°C	171.3°C – 172.4°C	170.8°C – 171.8°C

- **Remaining Testing Interval pull Dates**
  - T = 36; Scheduled for July 21, 2025
  - T = 48; Scheduled for July 21, 2026
  - T = 60; Scheduled for July 21, 2027

TABLE 3: TRIS-0222-00013 P/F

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0010 a.u.	0.0000 a.u.	<0.003 a.u.	<0.003 a.u.	0.0001 a.u.	0.0006 a.u.	<0.003 a.u.
	0.06 a.u. max @ 280 nm	0.0054 a.u.	0.0039 a.u.	0.0045 a.u.	0.0037 a.u.	0.0047 a.u.	0.0063 a.u.	0.0052 a.u.
	0.06 a.u. max @ 260 nm	0.0065 a.u.	0.0045 a.u.	0.0051 a.u.	0.0043 a.u.	0.0054 a.u.	0.0071 a.u.	0.0064 a.u.
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Assay (USP)	99.0-101.0%	99.93%	99.94%	99.92%	99.41%	99.72%	99.98%	100.12%
Loss on Drying	0.5% max.	0.0711%	0.0743%	0.0706%	<0.0064%	<0.0064%	0.0463%	0.0682%
Melting Range	168-172°C	170.5°C – 171.6°C	170.4°C – 171.6°C	170.5°C – 171.7°C	170.4°C – 171.6°C	171.2°C – 172.3°C	171.3°C – 172.4°C	170.8°C – 171.8°C

- **Remaining Testing Interval pull Dates**
  - T = 36; Scheduled for July 21, 2025
  - T = 48; Scheduled for July 21, 2026
  - T = 60; Scheduled for July 21, 2027

TABLE 4: TRIS-0222-00013 LABLINE

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0010 a.u.	0.0002 a.u.	<0.003 a.u.	0.0013 a.u.	0.0002 a.u.	0.0009 a.u.	<0.003 a.u.
	0.06 a.u. max @ 280 nm	0.0054 a.u.	0.0039 a.u.	0.0039 a.u.	0.0063 a.u.	0.0042 a.u.	0.0057 a.u.	0.0042 a.u.
	0.06 a.u. max @ 260 nm	0.0065 a.u.	0.0044 a.u.	0.0046 a.u.	0.0077 a.u.	0.0053 a.u.	0.0070 a.u.	0.0056 a.u.
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Assay (USP)	99.0-101.0%	99.93%	99.90%	99.76%	99.86%	99.75%	100.23%	100.54%
Loss on Drying	0.5% max.	0.0711%	0.0490%	0.0364%	<0.0062%	0.0600%	0.1108%	0.0363%
Melting Range	168-172°C	170.5°C – 171.6°C	170.5°C – 171.6°C	170.6°C – 171.8°C	170.6°C – 171.7°C	171.2°C – 172.3°C	171.4°C – 172.3°C	170.7°C – 171.4°C

- **Remaining Testing Interval pull Dates**
  - T = 36; Scheduled for July 21, 2025
  - T = 48; Scheduled for July 21, 2026
  - T = 60; Scheduled for July 21, 2027

TABLE 5: TRIS-0222-00042 P/F

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0012 a.u	0.0021 a.u.	0.0022 a.u.	0.0098 a.u.	0.0024 a.u.	0.0024 a.u.	0.0028 a.u.
	0.06 a.u. max @ 280 nm	0.0130 a.u.	0.0206 a.u.	0.0208 a.u.	0.0366 a.u.	0.0218 a.u.	0.0236 a.u.	0.0263 a.u.
	0.06 a.u. max @ 260 nm	0.0142 a.u.	0.0195 a.u.	0.0204 a.u.	0.0398 a.u.	0.0227 a.u.	0.0249 a.u.	0.0274 a.u.
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Assay (USP)	99.0-101.0%	99.91%	99.86%	99.95%	100.10%	99.71%	99.89%	99.92%
Loss on Drying	0.5% max.	0.7445%[1]	0.1644%	0.1097%	0.0328%	0.1043%	0.1761%	0.1360%
Melting Range	168-172°C	169.6°C – 171.0°C	170.0°C – 171.4°C	170.2°C – 171.5°C	170.0°C – 171.5°C	170.9°C – 172.1°C	170.9°C – 172.1°C	169.9°C – 171.1°C

[1] See; STOI22-64

- **Remaining Testing Interval pull Dates**
  - T = 36; Scheduled for June 17, 2025
  - T = 48; Scheduled for June 17, 2026
  - T = 60; Scheduled for June 17, 2027

TABLE 6: TRIS-0222-00042 LABLINE

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0012 a.u.	0.0016 a.u.	0.0014 a.u.	0.0104 a.u.	0.0018 a.u.	0.0019 a.u.	0.0032 a.u.
	0.06 a.u. max @ 280 nm	0.0130 a.u.	0.0148 a.u.	0.0176 a.u.	0.0431 a.u.	0.0265 a.u.	0.0376 a.u.	0.0281 a.u.
	0.06 a.u. max @ 260 nm	0.0142 a.u.	0.0146 a.u.	0.0162 a.u.	0.0441 a.u.	0.0216 a.u.	0.0309 a.u.	0.0307 a.u.
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Assay (USP)	99.0-101.0%	99.91%	99.86%	99.88%	99.86%	99.75%	99.82%	99.88%
Loss on Drying	0.5% max.	0.7445%[1]	0.5102%[1]	0.5695%[1]	0.5405%[1]	0.5076%[1]	0.3643%	0.1326%
Melting Range	168-172°C	169.6°C – 171.0°C	169.9°C – 171.3°C	170.1°C– 171.4°C	170.0°C – 171.4°C	170.6°C – 171.9°C	170.8°C – 171.9°C	169.8°C – 170.9°C

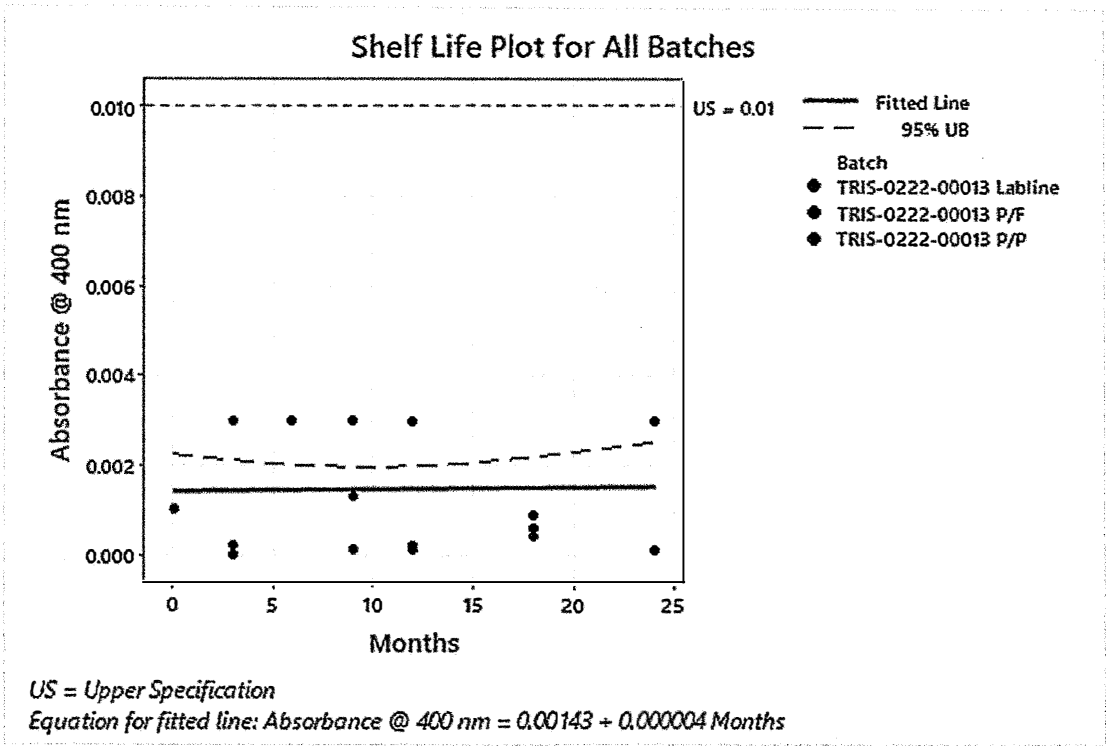
[1] See; STOI22-64

- **Remaining Testing Interval pull Dates**
  - T = 36; Scheduled for June 17, 2025
  - T = 48; Scheduled for June 17, 2026
  - T = 60; Scheduled for June 17, 2027

TABLE 7: TRIS-0222-00168 P/P EZ/DOCK BAG

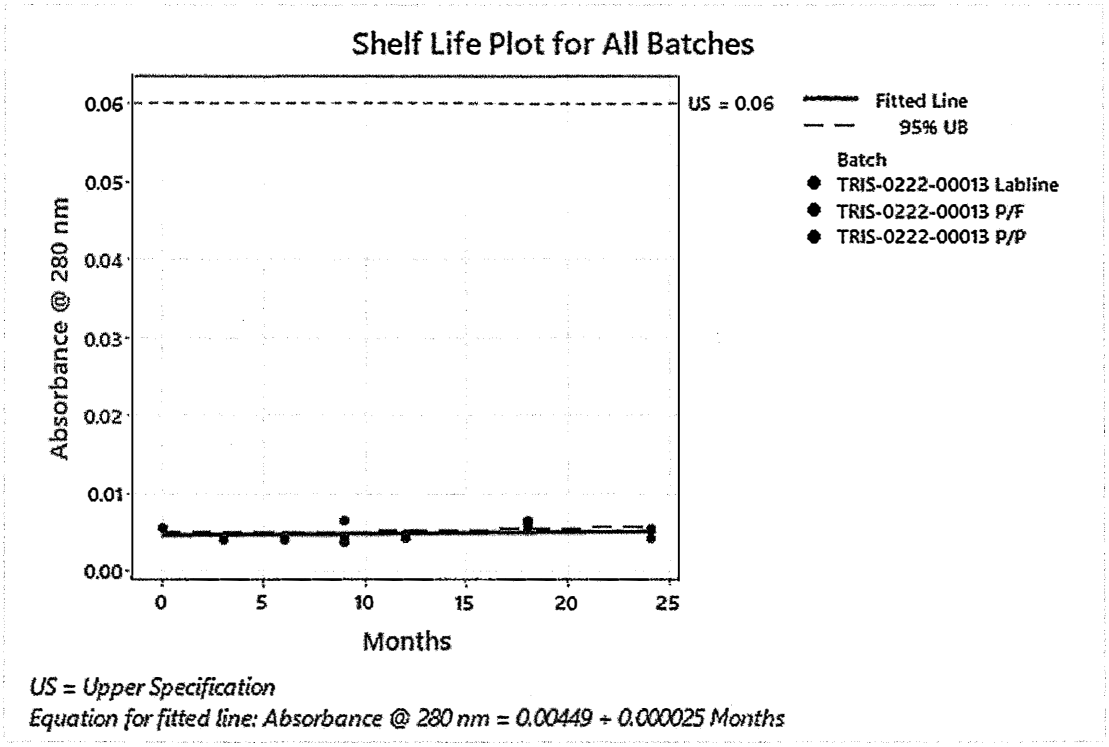
Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0011 a.u.	0.0007 a.u.	0.0013 a.u.	<0.003 a.u.	0.0043 a.u.	0.0048 a.u.
	0.06 a.u. max @ 280 nm	0.0209 a.u.	0.0424 a.u.	0.0568 a.u.	0.0657 a.u.	0.0738 a.u.	0.0700 a.u.
	0.06 a.u. max @ 260 nm	0.0207 a.u.	0.0350 a.u.	0.0481 a.u.	0.0614 a.u.	0.0782 a.u.	0.0794 a.u.
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Assay (USP)	99.0-101.0%	99.79%	99.67%	99.26%	99.70%	100.46%	100.51%
Loss on Drying	0.5% max.	0.2522%	0.2520%	0.1814%	0.0508%	0.1069%	0.0689%
Melting Range	168-172°C	169.8°C – 171.1°C	169.6°C – 171.1°C	169.1°C – 170.8°C	170.4°C – 171.8°C	169.4°C – 171.6°C	169.8°C – 171.7°C

- **Remaining Testing Interval pull Dates**
  - T = 24; Scheduled for October 3, 2024
  - T = 36; Scheduled for October 3, 2025
  - T = 48; Scheduled for October 3, 2026
  - T = 60; Scheduled for October 3, 2027



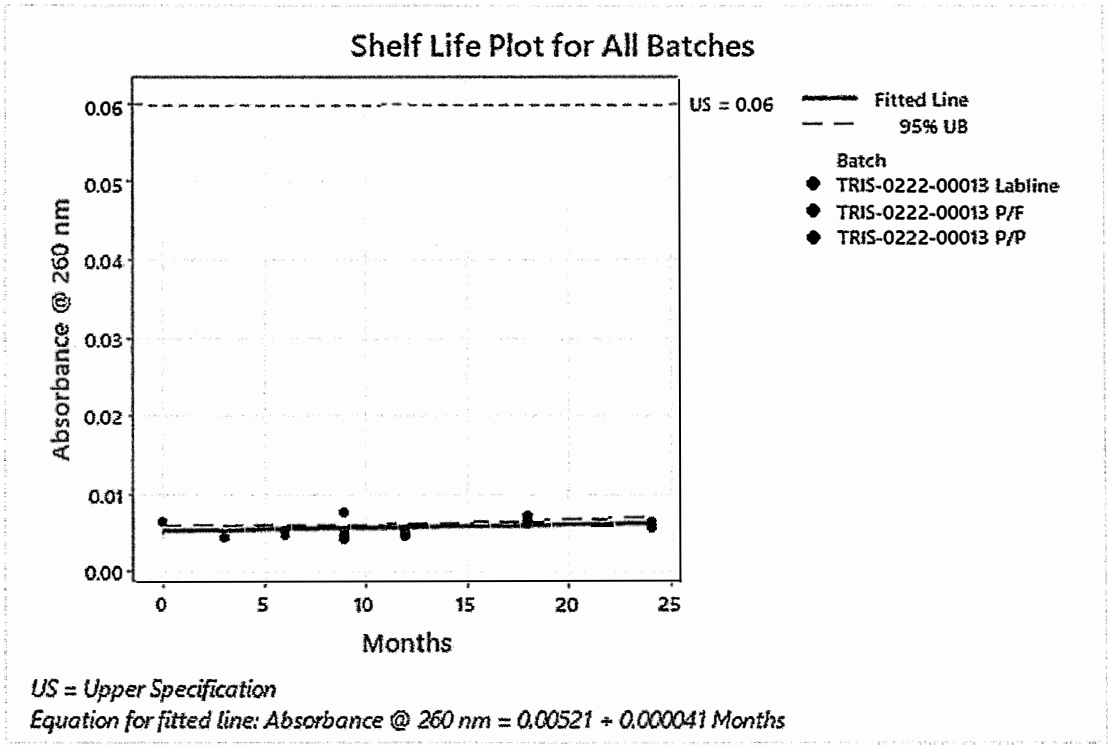
GRAPH 1: ABSORBANCE (1M) AT 400 NM

As TRIS-0222-00042 failed for LOD and TRIS-0222-00168 failed for absorbance at 280 nm and 260 nm they will not be included in the shelf-life predictions. No Shelf-Life was able to be determined for Absorbance at 400 nm at the 24-month time point for TRIS-0222-00013, 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.



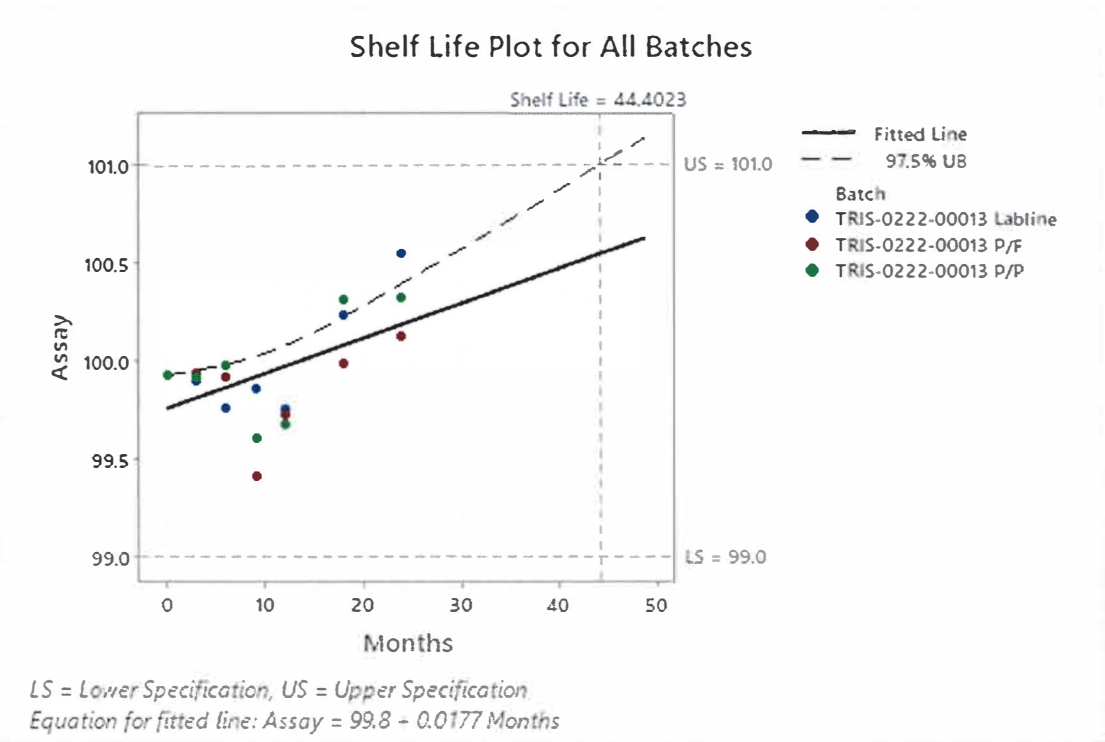
GRAPH 2: ABSORBANCE (1M) AT 280 NM

As TRIS-0222-00042 failed for LOD and TRIS-0222-00168 failed for absorbance at 280 nm and 260 nm they will not be included in the shelf-life predictions. No Shelf-Life was able to be determined for Absorbance at 280 nm at the 24-month time point for TRIS-0222-00013, 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.



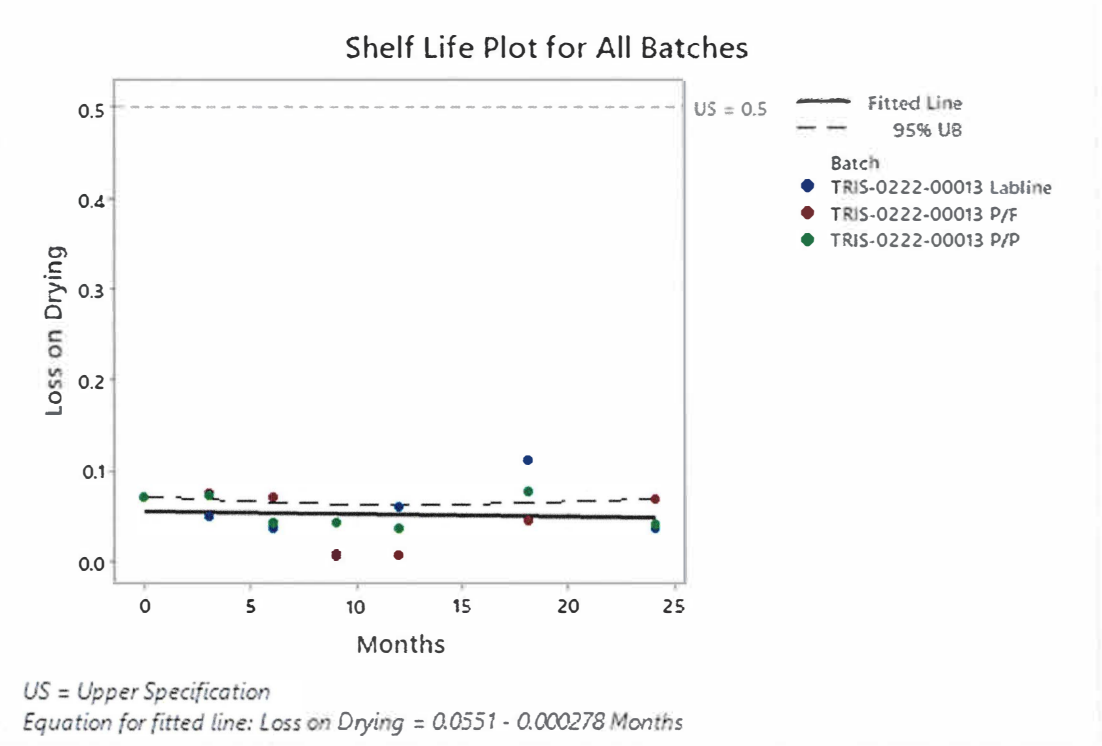
GRAPH 3: ABSORBANCE (1M) AT 260 NM

As TRIS-0222-00042 failed for LOD and TRIS-0222-00168 failed for absorbance at 280 nm and 260 nm they will not be included in the shelf-life predictions. No Shelf-Life was able to be determined for Absorbance at 260 nm at the 24-month time point for TRIS-0222-00013, 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.



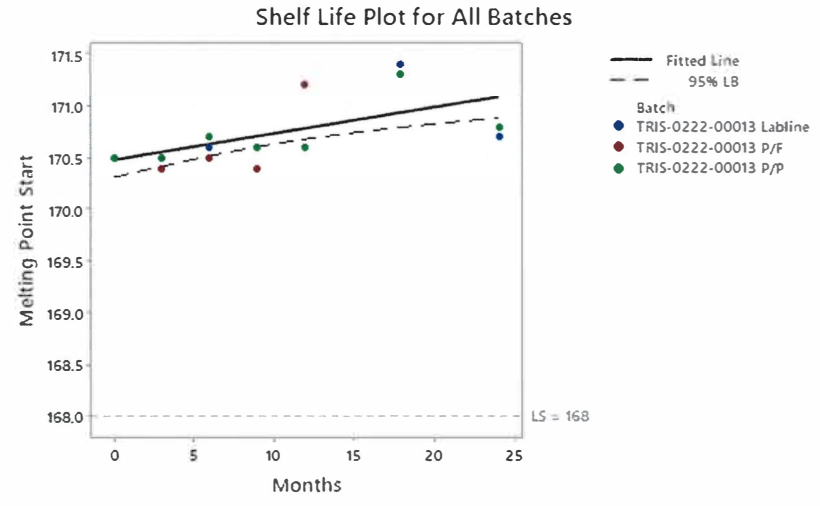
GRAPH 4: ASSAY (%)

As TRIS-0222-00042 failed for LOD and TRIS-0222-00168 failed for absorbance at 280 nm and 260 nm they will not be included in the shelf-life predictions. The predicted Shelf-Life for Assay was determined to be 44.4023 months as of the T=24-month time interval. There is no impact to the product or currently assigned retest period of this material.

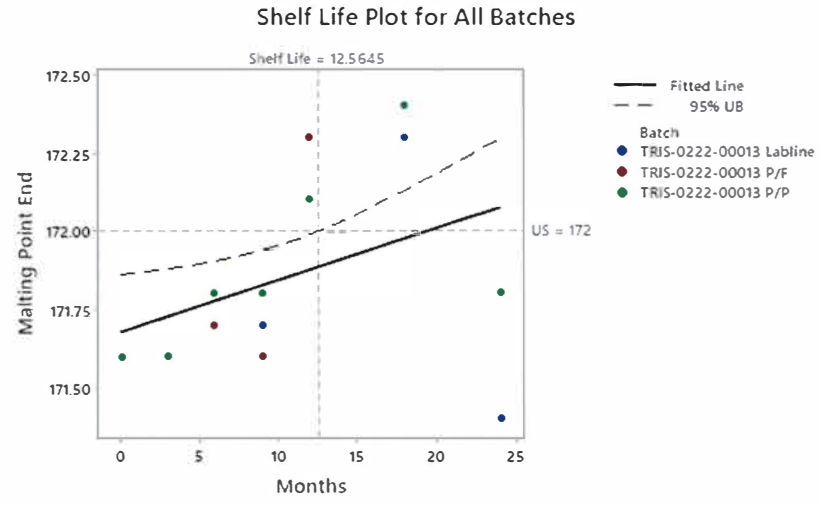


GRAPH 5: LOSS ON DRYING

As TRIS-0222-00042 failed for LOD and TRIS-0222-00168 failed for absorbance at 280 nm and 260 nm they will not be included in the shelf-life predictions. No Shelf-Life was able to be determined for Loss on Drying at the 24-month time point for TRIS-0222-00013, 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.



LS = Lower Specification
Equation for fitted line: Melting Point Start = 170 + 0.0250 Months



US = Upper Specification
Equation for fitted line: Melting Point End = 172 + 0.0165 Months

GRAPH 6: MELTING POINT

As TRIS-0222-00042 failed for LOD and TRIS-0222-00168 failed for absorbance at 280 nm and 260 nm they will not be included in the shelf-life predictions. No Shelf-Life was able to be determined for Melting Point Start at the 24-month time point for batch TRIS-0222-00013, 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. The predicted Shelf-Life for Melting Point End was determined to be 12.5645 months as of the T=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 in within the required limits of specifications. All data up to the 24-month time point has met the required specification.

7. CONCLUSION:

In regards to the Long-Term Stability Study for Tris Bio Excipient Grade Material, all data met the specifications set forth in the Stability Testing Program for lot stored at the recommended real time condition. 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 long-term conditions (warehouse conditions of 15 – 30°C). The Long-Term Stability Study data, along with the predicted shelf-life plots, supports a retest date of 24 months for lot TRIS-0222-00013 of Tris Bio Excipient Grade Material manufactured at BioSpectra in the Stroudsburg, PA facility. The other lots in this report failed specifications and do not have a shelf-life determined. Process improvements have been made as a result of the failing results and investigative work to aid in the shelf life of Tris Bio Excipient.

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.