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

TRIS BIO EXCIPIENT GRADE REAL-TIME STABILITY REPORT 2020

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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 Tris Bio Excipient Grade material manufactured at the Rockdale, 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 Tris Bio Excipient Grade material lot TR3200-553-0120 and validation lot TR3200-561-0220-PV packaged in poly/fiber, poly/poly, Tyvek/poly and Labline that completed thirty-six (36) months of long-term stability in February 2023. The stability study included the following analyses: Absorbance at 400 nm, Absorbance at 280 nm, Absorbance at 260 nm, Assay, Loss on Drying and Melting Range. Appearance and color were added into the stability study mid study. 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 SOP, BSI-SOP-0136. The specifications for the stability indicating analyses are established in accordance with the Stability Indication Protocol SOP, 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. Shelf life plots determine 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. 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 one Tris Bio Excipient Process Validation batch and one routine stability batch. Stability samples from these batches were put into four different packaging configurations. 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 based on BioSpectra's final 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)	Samples are packaged into small poly bags and sealed with a zip tie. All individual samples are then placed into a poly drum.
Tyvek/Poly (T/P)	Samples are packaged into small Tyvek bags and sealed with a zip tie. All individual samples are then placed into a poly drum, along with a 5x8-unit desiccant.
Labline	Samples are packaged into a HDPE Lab Screw-Top Bottle

4. STORAGE:

Samples were placed on stability in BioSpectra's Rockdale, 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 (specifications: monitor) and Mean Kinetic temperature (≤25°C). The samples were stored in the Rockdale warehouse from January 2020 through February 2023. The maximum temperature of the warehouse during this time was 28.24°C and the minimum temperature of the warehouse during this time was 11.73°C. The average mean kinetic temperature was 20.47°C. See Section 5 for the discrepancy investigations initiated for temperature excursions.

5. INVESTIGATIONS:

5.1 **SDI20-33** was initiated for four MadgeTech loggers in use past the calibration due date. This had no impact on the Tris Bio Excipient Grade material stability samples, as the next time point was pulled and tested and all lots met specification.

5.2 **SLI20-52** was initiated for an apparent OOS for Assay with a result of 97.27% for Tris stability lot TR3200-561-0220-PV, T=9 T/P. Six retests were performed and all results were passing. The root cause for the out of specification result was attributed to sample loss during sample preparation due to analyst error. The average of the six results will be reported.

5.3 **SDI20-107** was initiated for the MadgeTech August temperature and humidity assessment not being complete due to missing data. This had no impact on the Tris Bio Excipient Grade material stability samples as some data from six out of the seven data loggers was auto downloaded on the software. The data still available was used to perform a partial assessment of the Rockdale warehouse for 08/03/20-09/02/20.

5.4 **SDI21-27** was initiated for MadgeTech data logger 2 not downloading data. This had no impact on the Tris Bio Excipient Grade material stability samples as all other data was within specification.

5.5 **SDI21-35** was initiated for the MadgeTech data logger STRD-R malfunctioning. This had no impact on the Tris Bio Excipient Grade material stability samples as the other six loggers did not fall outside of the specified temperature range of 15 – 30°C during the missing timeframe.

5.6 **SDI21-88** was initiated for a MadgeTech logger that was calibrated and found to be out of specification whit respect to relative humidity. This had no impact on the Tris Bio Excipient Grade material stability samples although the data logger was found to be out of specifications the warehouse relative humidity is only monitored and still found to be within specification with respect to temperature.

5.7 **SDI22-03** was initiated for four MadgeTech loggers in use past the calibration due date. This had no impact on the Tris Bio Excipient Grade material stability samples, as the next time point was pulled and tested and all lots met specification.

5.8 **SDI22-184** was initiated due to an out of specification low temperature readings 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. Additionally, at no time were all seven loggers out of specification. This had no impact on the stability samples as because the excursions lasted only a few hours during the nights and early mornings.

5.9 **SDI23-07** was initiated for MadgeTech STRD-4 data logger being damaged and unavailable to provide data. This had no impact on the Tris Bio Excipient Grade material stability samples as all other loggers recorded temperatures within specification.

6. LOT EVALUATION:

TABLE 2: TR3200-553-0120 P/P									
Analysis	**Specification**	**T0**	**T3**	**T6**	**T9**	**T12**	**T18**	**T24**	**T36**
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0000	0.0023	0.0027	0.0029	0.0027	0.0036	0.0034	0.0033
	0.06 a.u. max @ 280 nm	0.0060	0.0121	0.0112	0.0142	0.0154	0.0176	0.0182	0.0201
	0.06 a.u. max @ 260 nm	0.0073	0.0137	0.0134	0.0163	0.0168	0.0197	0.0199	0.0218
Assay	99.0-101.0%	100.15%	100.41%	99.86%	100.00%	100.25%	99.98%	99.91%	99.97%
Appearance and Color	White / Crystals	Not Tested	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Loss on Drying	0.5% max.	0.2347%	0.0702%	0.0751%	0.0848%	0.0366%	0.2900%	0.0898%	0.0561%
Melting Range	168-172°C	169.7 - 171.3°C	169.8- 171.5°C	169.7 - 171.6°C	170.0 - 171.1°C	168.3 - 170.3°C	170.0 - 171.2°C	170.2 - 171.1°C	169.3 - 171.1°C

TABLE 3: TR3200-553-0120 P/F									
Analysis	**Specification**	**T0**	**T3**	**T6**	**T9**	**T12**	**T18**	**T24**	**T36**
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0000	0.0028	0.0047	0.0026	0.0031	0.0044	0.0045	0.0043
	0.06 a.u. max @ 280 nm	0.0060	0.0128	0.0158	0.0131	0.0146	0.0178	0.0212	0.0221
	0.06 a.u. max @ 260 nm	0.0073	0.0143	0.0189	0.0149	0.0159	0.0203	0.0233	0.0237
Assay	99.0-101.0%	100.15%	100.32%	99.83%	100.00%	100.28%	99.89%	99.90%	99.92%
Appearance and Color	White / Crystals	Not Tested	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Loss on Drying	0.5% max.	0.2347%	0.0628%	0.1057%	0.1088%	0.0314%	0.0776%	0.0813%	0.0404%
Melting Range	168-172°C	169.7 - 171.3°C	169.9- 171.5°C	169.8 - 171.8°C	170.2 - 171.4°C	170.3 - 171.7°C	169.1 - 170.9°C	170.2 - 171.1°C	169.9 - 170.5°C

TABLE 4: TR3200-553-0120 T/P									
Analysis	**Specification**	**T0**	**T3**	**T6**	**T9**	**T12**	**T18**	**T24**	**T36**
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0000	0.0004	0.0008	0.0024	0.0016	0.0013	0.0015	0.0005
	0.06 a.u. max @ 280 nm	0.0060	0.0117	0.0128	0.0149	0.0140	0.0130	0.0127	0.0118
	0.06 a.u. max @ 260 nm	0.0073	0.0126	0.0149	0.0165	0.0151	0.0168	0.0168	0.0169
Assay	99.0-101.0%	100.15%	100.26%	99.83%	99.97%	100.20%	99.90%	99.92%	99.93%
Appearance and Color	White / Crystals	Not Tested	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Loss on Drying	0.5% max.	0.2347%	0.0832%	0.0879%	0.0601%	0.0251%	0.0665%	0.0915%	0.0476%
Melting Range	168-172°C	169.7 - 171.3°C	170.0- 171.5°C	170.1 - 171.8°C	169.8 - 171.5°C	170.6 - 171.6°C	170.4 - 171.6°C	169.8 - 171.0°C	170.8 - 171.9°C

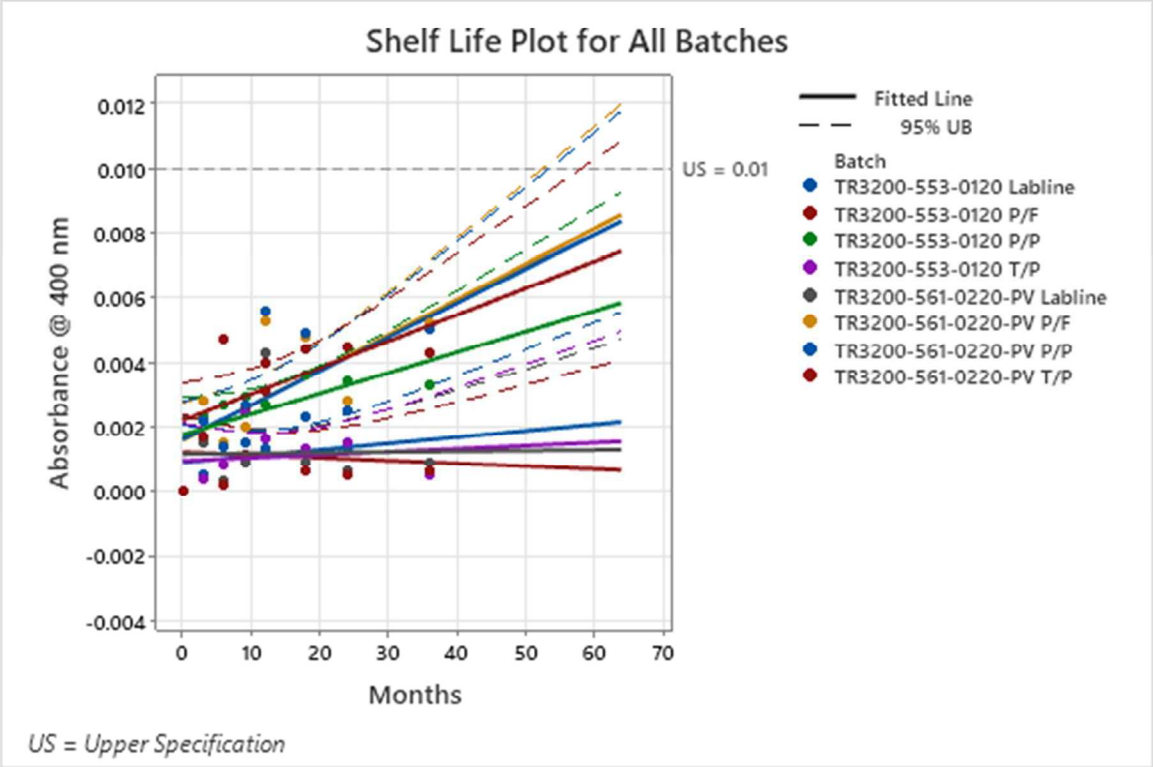
TABLE 5: TR3200-553-0120 LABLINE									
Analysis	**Specification**	**T0**	**T3**	**T6**	**T9**	**T12**	**T18**	**T24**	**T36**
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0000	0.0005	0.0014	0.0015	0.0013	0.0023	0.0013	0.0009
	0.06 a.u. max @ 280 nm	0.0060	0.0100	0.0111	0.0119	0.0130	0.0156	0.0154	0.0162
	0.06 a.u. max @ 260 nm	0.0073	0.0101	0.0125	0.0130	0.0141	0.0182	0.0174	0.0187
Assay	99.0-101.0%	100.15%	100.26%	99.88%	100.03%	100.19%	99.97%	99.90%	100.00%
Appearance and Color	White / Crystals	Not Tested	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Loss on Drying	0.5% max.	0.2347%	0.0634%	0.1086%	0.0384%	0.0614%	0.0608%	0.0905%	0.0462%
Melting Range	168-172°C	169.7 - 171.3°C	169.3- 171.1°C	170.2 - 171.7°C	170.4 - 171.6°C	170.1 - 171.3°C	170.2 - 171.5°C	170.2 - 171.1°C	170.2 - 171.4°C

TABLE 6: TR3200-561-0220-PV P/P									
Analysis	**Specification**	**T0**	**T3**	**T6**	**T9**	**T12**	**T18**	**T24**	**T36**
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0000	0.0022	0.0014	0.0027	0.0056	0.0049	0.0025	0.0050
	0.06 a.u. max @ 280 nm	0.0064	0.0111	0.0103	0.0136	0.0170	0.0178	0.0159	0.0222
	0.06 a.u. max @ 260 nm	0.0077	0.0130	0.0119	0.0157	0.0192	0.0205	0.0173	0.0243
Assay	99.0-101.0%	99.95%	100.74%	100.28%	100.62%	99.92%	99.68%	99.78%	99.83%
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Loss on Drying	0.5% max.	0.1177%	0.0702%	0.1025%	0.1254%	0.0558%	0.0460%	0.0743%	0.0260%
Melting Range	168-172°C	169.8 - 171.5°C	169.9- 171.5°C	169.8 - 171.5°C	168.8 - 171.1°C	170.1 - 171.2°C	170.1 - 171.2°C	169.8 - 170.5°C	170.4 - 171.6°C

TABLE 7: TR3200-561-0220-PV P/F									
Analysis	**Specification**	**T0**	**T3**	**T6**	**T9**	**T12**	**T18**	**T24**	**T36**
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0000	0.0028	0.0015	0.0020	0.0053	0.0048	0.0028	0.0052
	0.06 a.u. max @ 280 nm	0.0064	0.0120	0.0103	0.0121	0.0156	0.0260	0.0171	0.0253
	0.06 a.u. max @ 260 nm	0.0077	0.0138	0.0119	0.0137	0.0179	0.0260	0.0188	0.0269
Assay	99.0-101.0%	99.95%	100.63%	100.36%	100.60%	99.78%	99.76%	99.72%	99.99%
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Loss on Drying	0.5% max.	0.1177%	0.0931%	0.0590%	0.0729%	0.1307%	0.0755%	0.1128%	0.0414%
Melting Range	168-172°C	169.8 - 171.5°C	170.0- 171.6°C	170.0 - 171.5°C	169.5 - 171.3°C	170.3 - 171.3°C	169.9 - 171.1°C	169.9 - 171.3°C	170.3 - 171.4°C

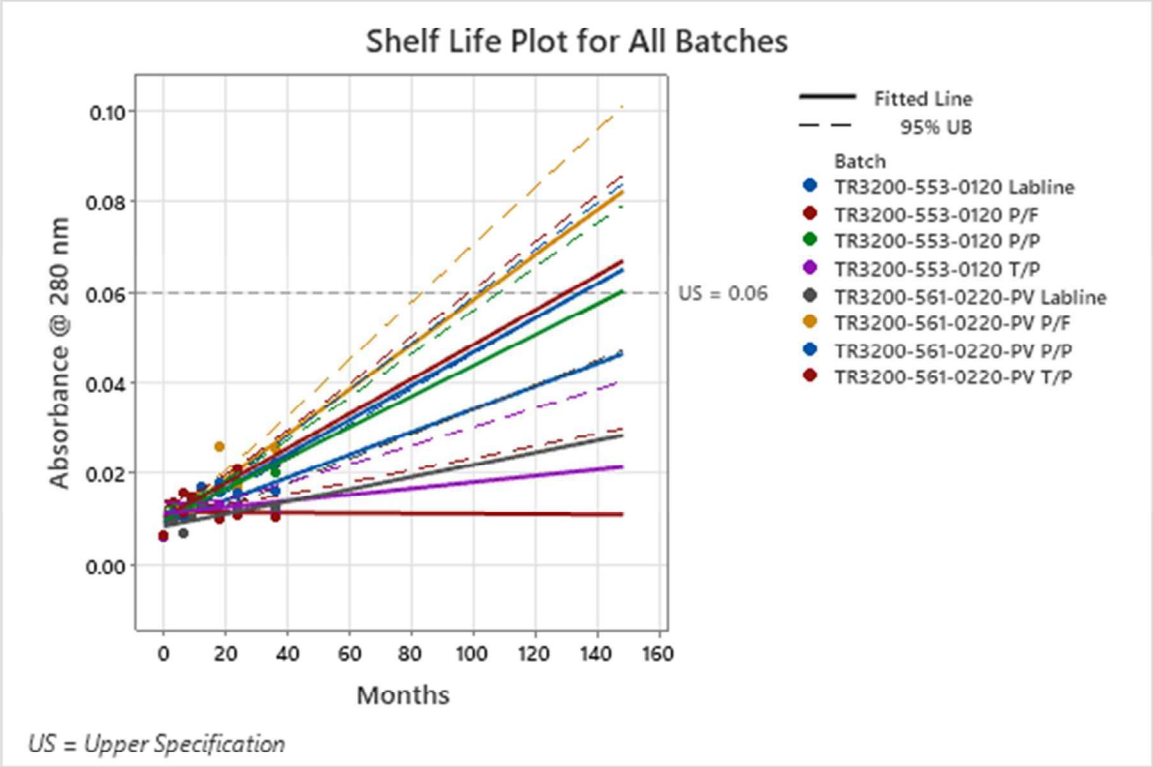
TABLE 8: TR3200-561-0220-PV T/P									
Analysis	**Specification**	**T0**	**T3**	**T6**	**T9**	**T12**	**T18**	**T24**	**T36**
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0000	0.0017	0.0002	0.0011	0.0040	0.0006	0.0005	0.0006
	0.06 a.u. max @ 280 nm	0.0064	0.0133	0.0112	0.0150	0.0146	0.0102	0.0110	0.0104
	0.06 a.u. max @ 260 nm	0.0077	0.0146	0.0129	0.0159	0.0172	0.0144	0.0153	0.0156
Assay	99.0-101.0%	99.95%	100.63%	99.84%	99.85%	99.95%	99.89%	99.90%	99.88%
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Loss on Drying	0.5% max.	0.1177%	0.0478%	0.0912%	0.1049%	0.0773%	0.1107%	0.0296%	0.0617%
Melting Range	168-172°C	169.8 - 171.5°C	170.0- 171.8°C	170.1 - 171.6°C	170.5 - 171.6°C	170.4 - 171.5°C	170.0 - 171.4°C	169.6 - 171.1°C	169.9 - 171.8°C

TABLE 9: TR3200-561-0220-PV LABLINE									
Analysis	**Specification**	**T0**	**T3**	**T6**	**T9**	**T12**	**T18**	**T24**	**T36**
Absorbance (1M)	0.01 a.u. max @ 400 nm	0.0000	0.0015	0.0000	0.0009	0.0043	0.0009	0.0006	0.0009
	0.06 a.u. max @ 280 nm	0.0064	0.0101	0.0071	0.0107	0.0136	0.0101	0.0113	0.0127
	0.06 a.u. max @ 260 nm	0.0077	0.0108	0.0085	0.0118	0.0153	0.0119	0.0134	0.0153
Assay	99.0-101.0%	99.95%	100.64%	99.97%	100.69%	99.89%	99.98%	99.79%	99.81%
Appearance and Color	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals	White / Crystals
Loss on Drying	0.5% max.	0.1177%	0.0738%	0.0961%	0.0580%	0.0695%	0.1081%	0.0617%	0.0183%
Melting Range	168-172°C	169.8 - 171.5°C	169.8- 171.5°C	170.1 - 171.6°C	170.3 - 171.6°C	170.6 - 171.9°C	168.9 - 170.8°C	169.9 - 171.3°C	169.8 - 170.7°C



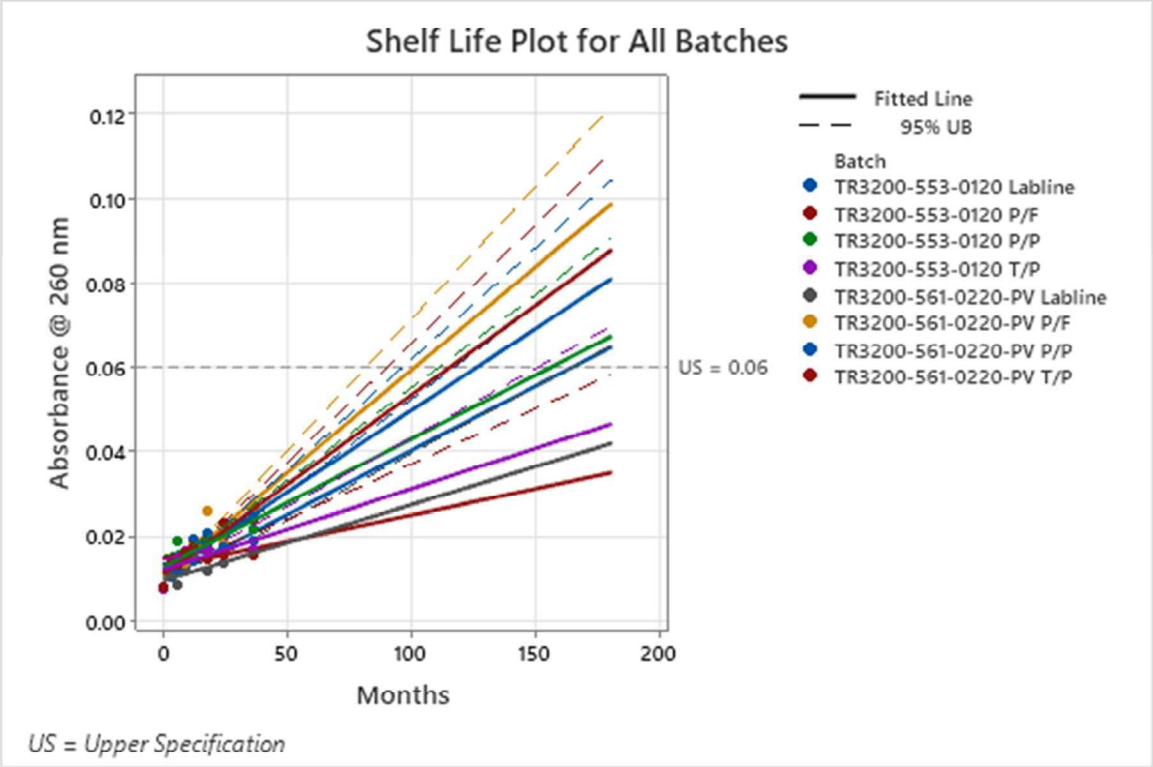
GRAPH 1: ABSORBANCE (1M) AT 400 NM

The predicted Shelf-Life for Absorbance at 400 nm was determined to be 54.788 months for batch TR3200-553-0120 and 52.263 months for TR3200-561-0220-PV as of the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material, as this is significantly beyond the end of the study.



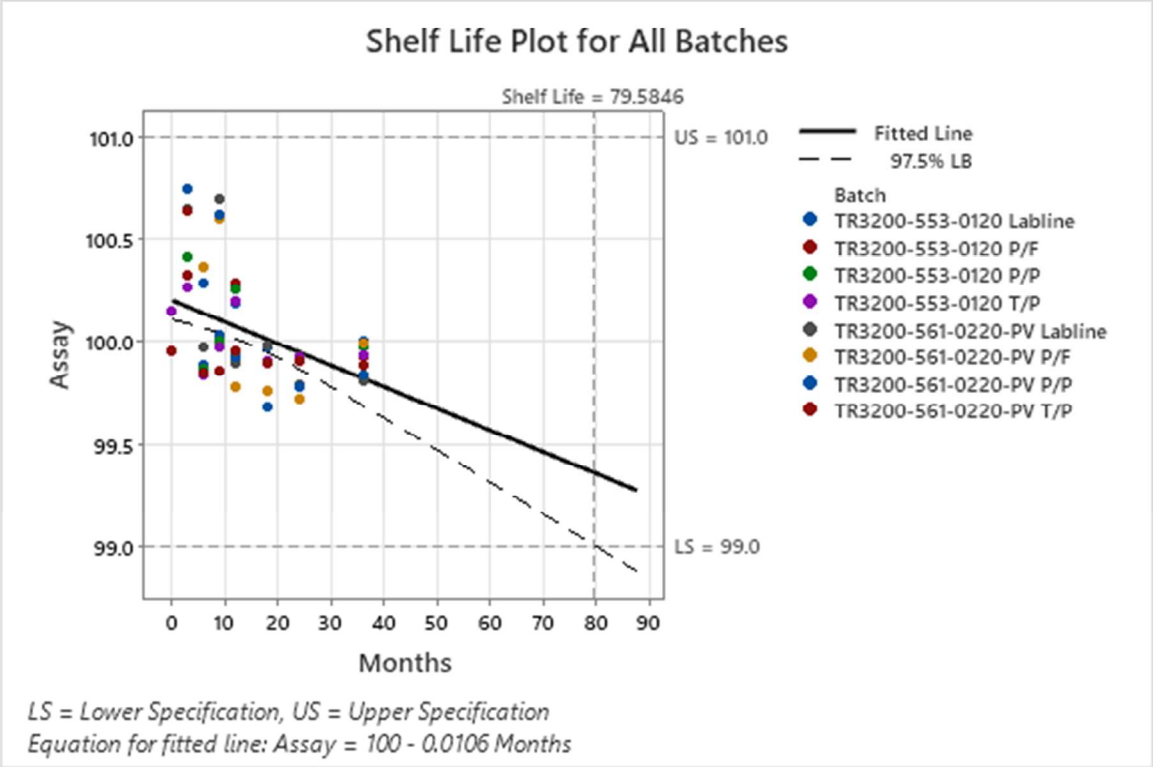
GRAPH 2: ABSORBANCE (1M) AT 280 NM

The predicted Shelf-Life for Absorbance at 280 nm was determined to be 83.318 months for TR3200-561-0220-PV and 98.706 months for TR3200-553-0120 as of the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material, as this is significantly beyond the end of the study.



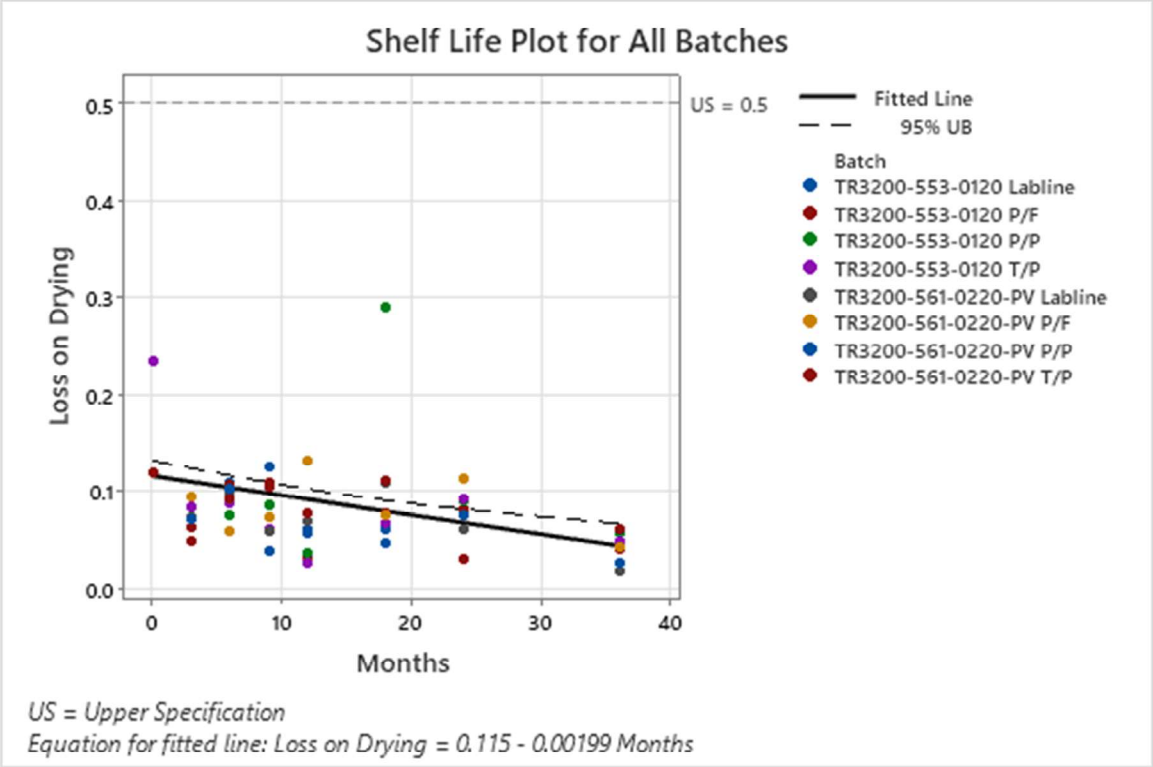
GRAPH 3: ABSORBANCE (1M) AT 260 NM

The predicted Shelf-Life for Absorbance at 260 nm was determined to be 81.606 months for TR3200-561-0220-PV and 90.071 months for TR3200-553-0120 as of the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material, as this is significantly beyond the end of the study.



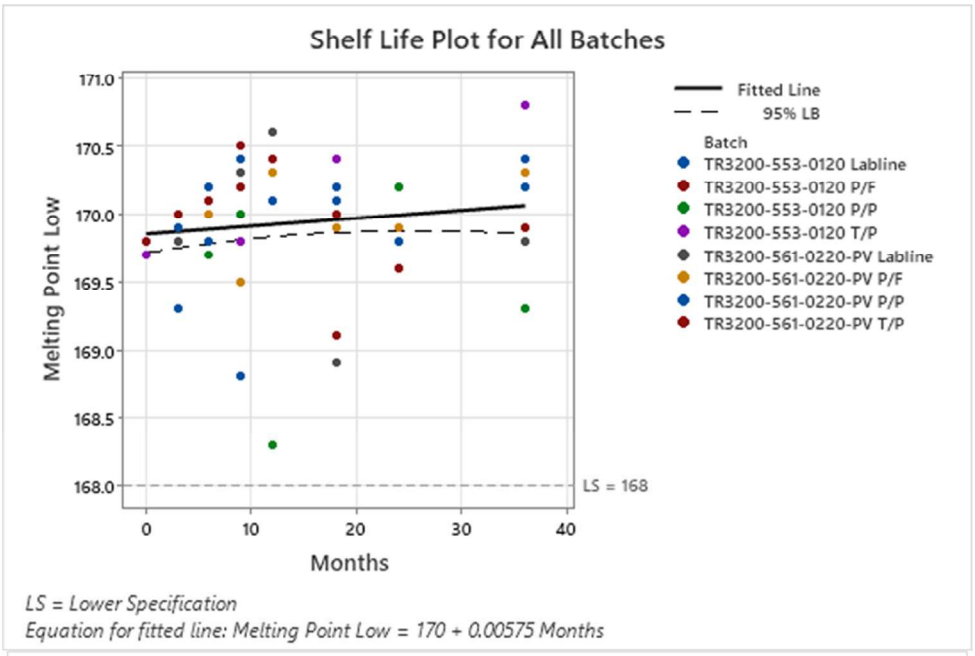
GRAPH 4: ASSAY (%)

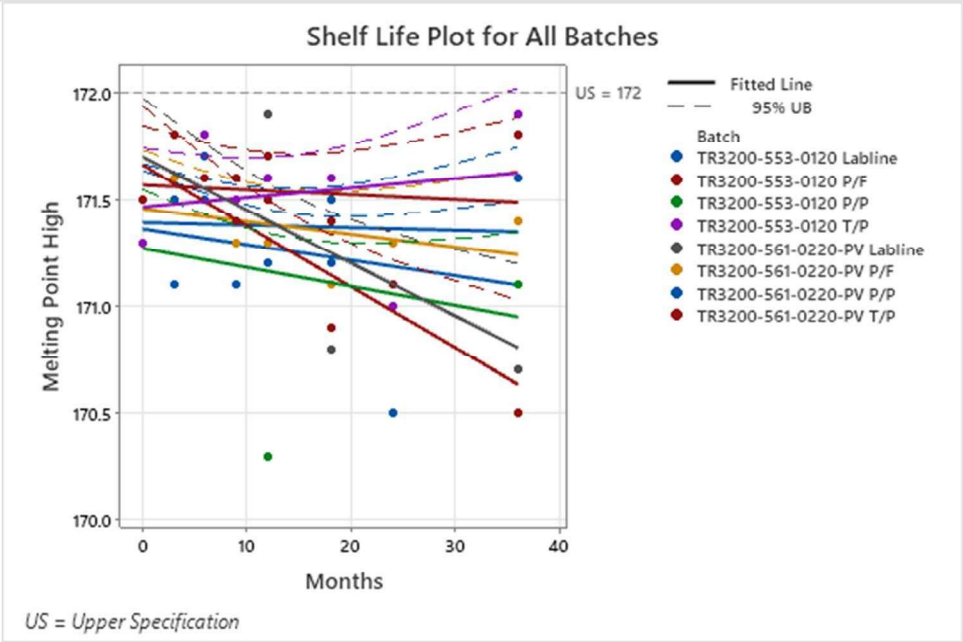
The predicted Shelf-Life for Assay was determined to be 79.5846 months as of the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material, as this is significantly beyond the end of the study.



GRAPH 5: 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. There is no impact to the product or currently assigned retest period of this material.





GRAPH 6: MELTING POINT

No Shelf-Life was able to be determined for Melting Point Low and High, 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.

7. CONCLUSION:

In regards to the Real Time 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 real time conditions (warehouse conditions of 15 – 30°C). The Real Time Stability Study data, along with the predicted shelf-life plots, supports a retest date of 24 months for each lot of Tris Bio Excipient Grade Material manufactured at BioSpectra in the Rockdale, 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.