BIOSPECTRA
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TRIS API 2022
LONG TERM STABILITY REPORT
TRIS-0122-00135

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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 API manufactured at the Bangor, 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 API lot TRIS-0122-00135 packaged in poly/poly that completed twenty-four (24) months of long-term stability in June 2024. The stability study included the following analyses: Absorbance (40%), Assay, Appearance and Color, Formaldehyde, Identification (IR), Karl Fischer (Water), Loss on Drying, Micro, and pH (5%). Organic impurities were tested starting at the 6-month time point, at the 18-month timepoint the new GC method for unspecified impurities was used and at the 24 month timepoint an Assay by GC-FID was incorporated into the testing program (BCC24-31). Results from all analyses are summarized in Table 2.

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 API Material. The following Product Codes are commercially available.

- TRIS-2255

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 API batch. Stability samples from this batch were put into one packaging configuration. 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 was based on BioSpectra's packaging configurations offered to the customer.

TABLE 1: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Poly/Poly (P/P)	Samples are packaged into small poly bags and sealed with a ziptie. All individual samples are then placed into a poly drum.

4. STORAGE:

4.1. For this study, Tris API samples were stored in the Long-Term Stability Chamber H03SC01 at the Bangor, PA facility. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25°C ± 2°C), Mean Kinetic Temperature (monitored) and relative humidity (60% ± 5%). For the time period of June 2022 to June 2024 the samples were located in the Long-Term Stability Chamber, and all future time point samples remain at this condition. The maximum temperature recorded was 25.80°C, the minimum temperature was 24.77°C, the average temperature was 25.44°C, and the average Mean Kinetic Temperature was 25.44°C. The maximum relative humidity recorded was 80.5%, the minimum relative humidity was 43.6%, and the average relative humidity was 61.4%. 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. Section 5 will include any excursions from these conditions that resulted in an investigation.

5. INVESTIGATIONS:

5.1. **BDI22-264**: No results were reported for the Organic Impurity analysis for the T=3 testing Interval. This was due to the instrument not meeting system suitability due to issues with the current method. An update to the method and a validation was performed before the six months' time pull. All subsequent data met the specification requirements so there was no impact to the stability data.

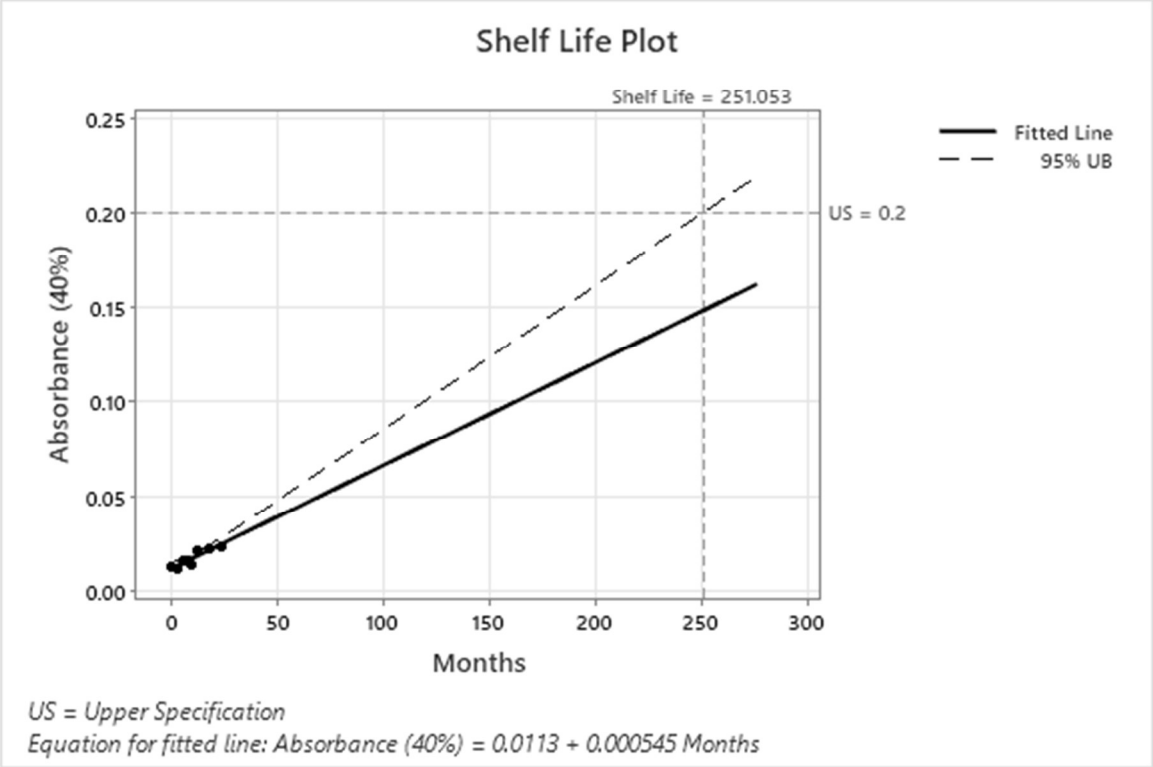
5.2. **BDI24-13**: Out of range humidity for the Long-Term Stability Chamber H03SC01 caused by improper work order completion to prevent water leaking from the stability chamber. On 1/15/24 while conducting a maintenance walkthrough of the Bangor facility water was observed on the floor of room H03RM01. 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.

6. LOT EVALUATION:

TABLE 2: TRIS-0122-00135 P/P

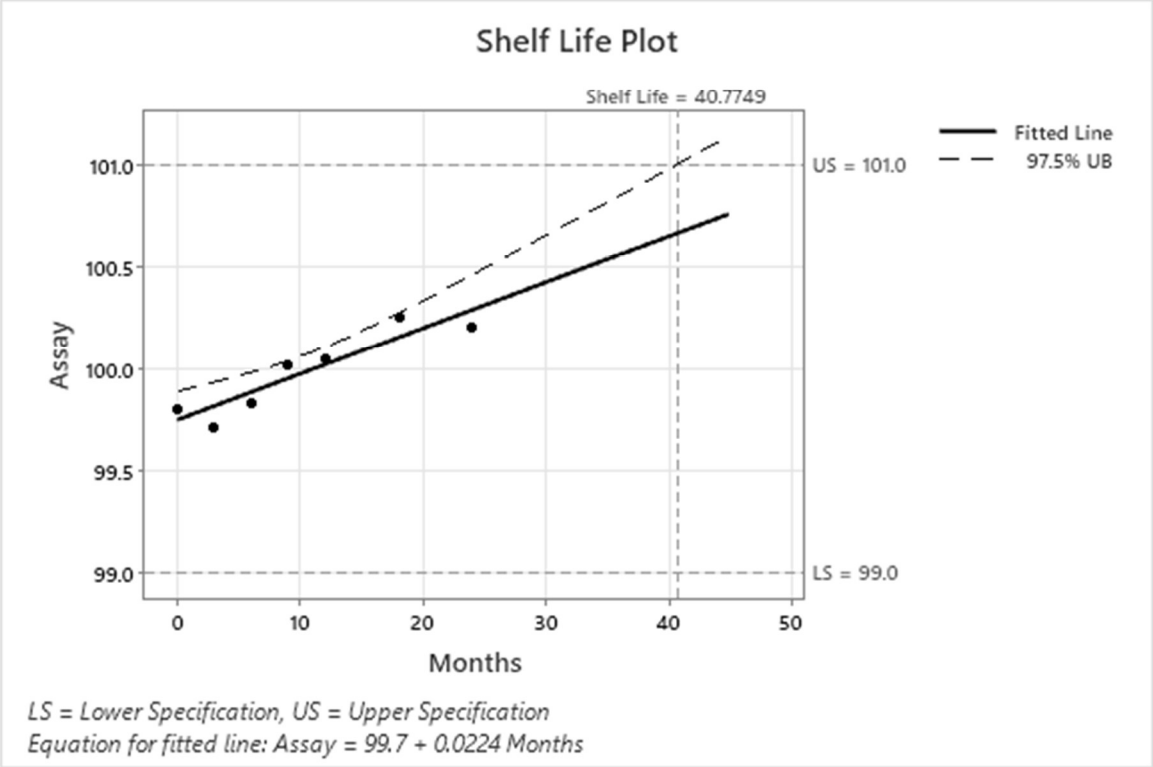
Analysis		Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}
Absorbance (40%)		0.20 a.u. max @ 290 nm	0.0122 a.u.	0.0109 a.u.	0.0158 a.u.	0.0136 a.u.	0.0209 a.u.	0.0219 a.u.	0.0233 a.u.
Assay		99.0-101.0%	99.80%	99.71%	99.83%	100.01%	100.04%	100.25%	100.20%
Assay (GC-FID)		98.0-102.0%	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	100.2%
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
Loss on Drying		1.0% max.	0.1116%	0.2064%	0.2389%	0.1606%	0.1615%	0.2541%	0.0898%
KF (Water)		2.0% max.	0.20%	0.20%	0.24%	0.28%	0.27%	0.36%	0.28%
pH (5%)		10.0 – 11.5	10.87	10.91	10.78	10.91	10.75	10.83	10.82
Micro	TAMC	100 CFU/g max.	<10 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g
	TYMC	10 CFU/g max.	<10 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g
	Staphylococcus Aureus	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Salmonella	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Escherichia Coli	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Pseudomonas Aeruginosa	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Organic Impurities	2-Nitropropane-1,3-diol	NMT 1 ppm	<1 ppm	Not tested	<1 ppm	<1 ppm	<1 ppm	<1 ppm	<1 ppm
	Tris(hydroxymethyl) nitromethane	NMT 1 ppm	<1 ppm	Not tested	<1 ppm	<1 ppm	<1 ppm	<1 ppm	<1 ppm
	2-Nitroethanol	NMT 1 ppm	<1 ppm	Not tested	<1 ppm	<1 ppm	<1 ppm	<1 ppm	<1 ppm
	Formaldehyde	NMT 15 ppm	0.89 ppm	0.68 ppm	0.41 ppm	0.72 ppm	1.09 ppm	0.86 ppm	0.79 ppm
	Unspecified Impurities	NMT 300 ppm	<300 ppm	Not tested	<300 ppm	<300 ppm	<300 ppm	<300 ppm	<300 ppm
	Total Impurities	NMT 300 ppm	<300 ppm	Not tested	<300 ppm	<300 ppm	<300 ppm	<300 ppm	<300 ppm

- **Remaining testing interval pull dates**
  - T = 36; Scheduled for June 15, 2025
  - T = 48: Scheduled for June 15, 2026
  - T = 60; Scheduled for June 15, 2027



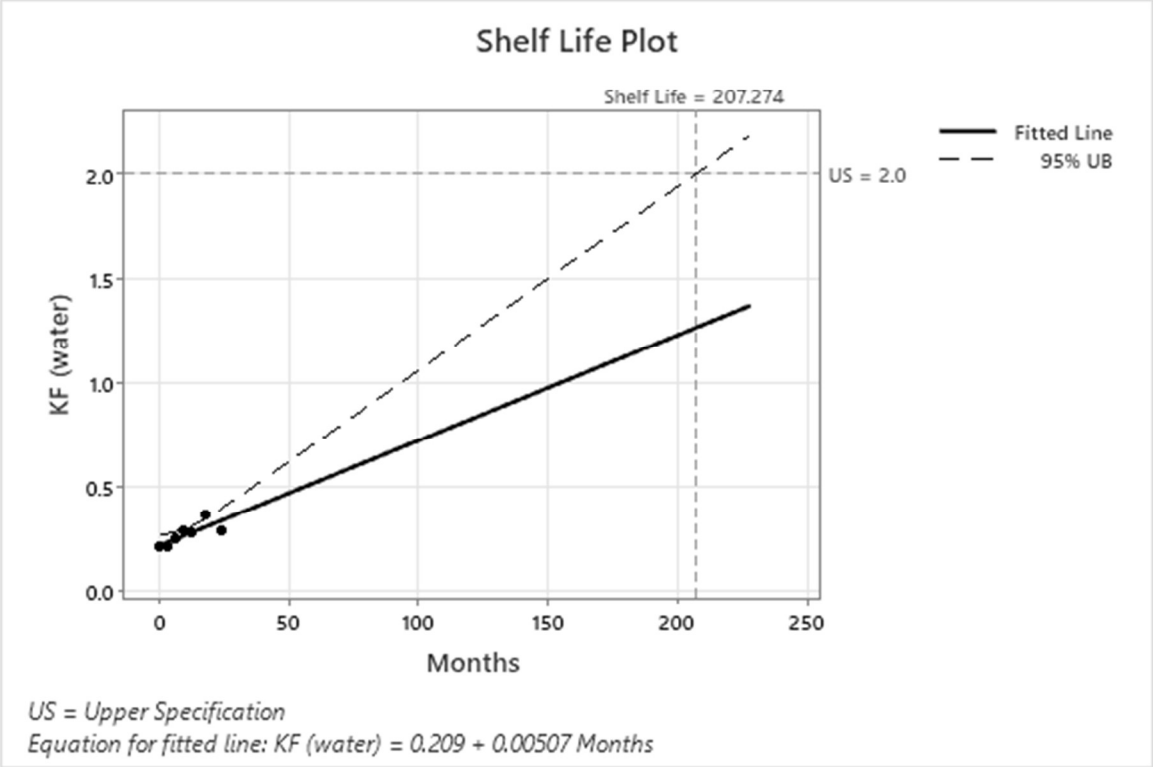
GRAPH 1: ABSORBANCE (40%) AT 290 NM

The predicted Shelf-Life for Absorbance (40%) at 290 nm was determined to be 251.053 months as of the T=24-month time interval. There is no impact to the product or currently assigned retest or expiry period of this material, as this is beyond the end of the study.



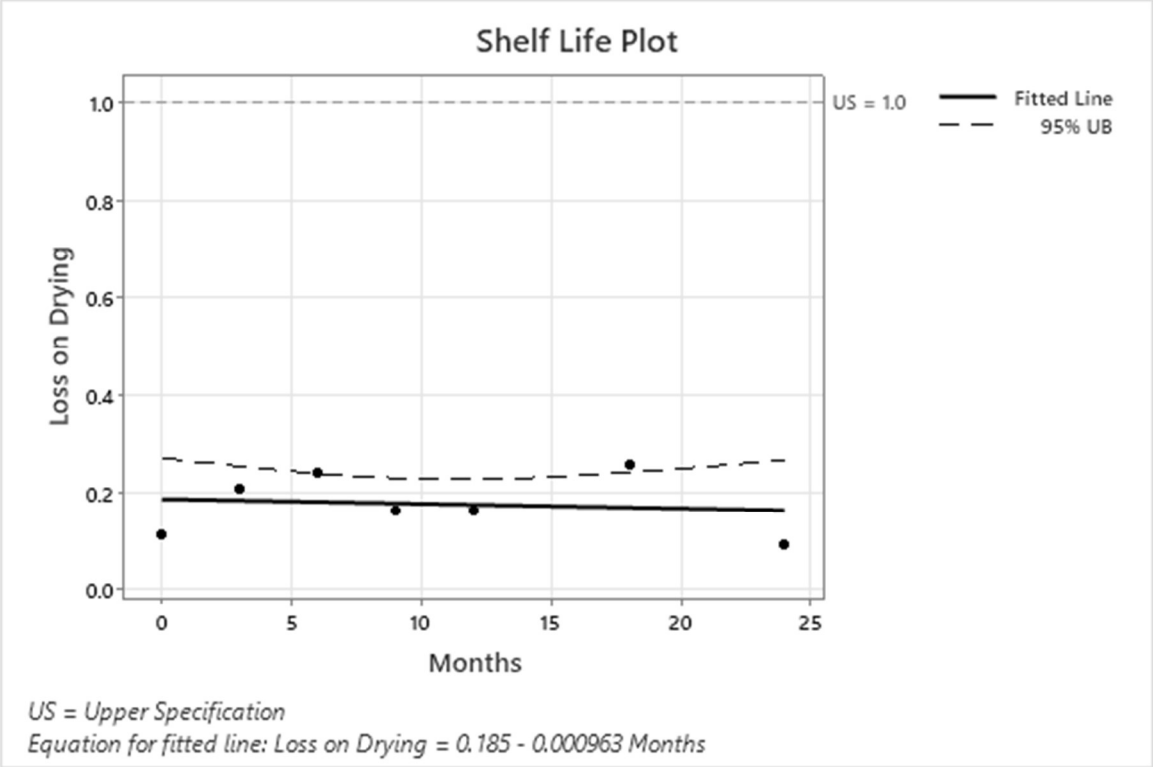
GRAPH 2: ASSAY

The predicted Shelf-Life for Assay was determined to be 40.7749 months as of the T=24-month time interval. There is no impact to the product or currently assigned retest or expiry period of this material, as this is past the currently assigned retest and expiry period.



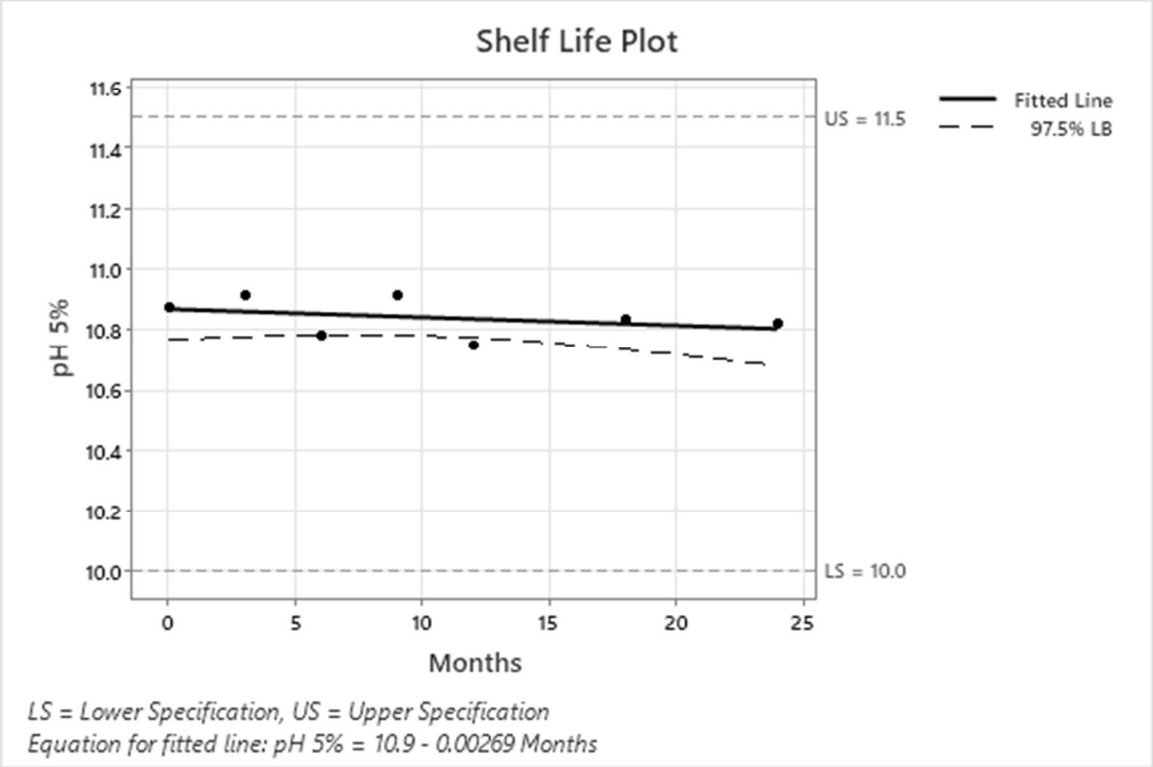
GRAPH 3 KARL FISCHER (WATER)

The predicted Shelf-Life for Karl Fischer (Water) was determined to be 207.274 months as of the T=24-month time interval. There is no impact to the product or currently assigned retest or expiry period of this material, as this is beyond the end of the study.



GRAPH 4: 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 or expiry period of this material. The shelf-life will continue to be monitored at the 36-month timepoint.



GRAPH 5: pH (5%)

No Shelf-Life was able to be determined for pH (5%), 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 or expiry period of this material. The shelf-life will continue to be monitored at the 36-month timepoint.

7. CONCLUSION:

In regards to the Long-Term Stability Study for Tris API, all data met the specifications set forth in the Stability Testing Program for a lot stored at the recommended long-term 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 (Temperature: 25°C ± 2°C and Relative Humidity: 60% ± 5%). The Long-Term Stability Study data for Tris API, along with the predicted shelf-life plots, supports a 24-month retest date with the possibility of an extension to a 36-months expiry date at customer request.

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.