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TRIS HYDROCHLORIDE LONG TERM STABILITY REPORT: 2017 LOTS

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the Real-Time Stability of Tris Hydrochloride manufactured at BioSpectra's Stroudsburg, PA facility. Samples were placed on the Stability Testing Program in October of 2017 to fulfil the requirements of placing all manufactured Validation lots on the Stability Testing Program. Testing intervals are designated by T_n, where n represents the number of months on stability. 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 for a total of three years 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 be used to re-evaluate the retest period for future lots of manufactured material.

This Real-Time Stability report assesses the stability of three lots of Tris Hydrochloride. The study includes the following analyses: Absorbance (1M), Appearance and Color, Assay (Dried Basis), Identification (IR), Loss on Drying (105°C), Melting Range, and pH (0.5M). Results from all analyses are summarized in Table 2 and Shelf-Life Plot determinations have been created for quantitative analyses. 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, i.e. the Predicted Shelf Life. This allows BioSpectra to ensure that the product will be stable for the time period in which it is part of the Stability Testing Program.

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 Hydrochloride. The following Product Codes are commercially available:

THCL-3203	THCL-3256
THCL-3220	THCL-3257
THCL-3221	THCL-3258
THCL-3250	THCL-3259
THCL-3251	THCL-3260
THCL-3252	THCL-4220
THCL-3253	THCL-4221
THCL-3254	THCL-7202
THCL-3255	

2. REFERENCES:

- 2.1. Current USP
- 2.2. ICH Q1
- 2.3. BSI-SOP-0136, Stability Testing Program
- 2.4. BSI-SOP-0146, Stability Inventory

3. SAMPLE DESIGNATION:

Samples placed on the Stability Testing Program consisted of three lots of Tris Hydrochloride. Stability samples from this batch were put into four different packaging configurations. These samples were

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packaged in accordance with the Stability Inventory SOP. Reference Table 1, below, for packaging configurations and descriptions. The type of packaging utilized in this stability study were based on BioSpectra final packaging.

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.
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.
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.
Labline	Samples are packaged into lab screw-top bottles.

4. STORAGE:

Samples were placed on stability in BioSpectra's Stroudsburg, PA facility Stability Area, located in the quarantine area of the Warehouse. Although there are no storage requirements for Tris Hydrochloride, storage conditions were continuously monitored and recorded utilizing MadgeTech data loggers, with regulated conditions for temperature (15-30°C) and humidity (monitor). The maximum temperature of the warehouse during the stability study was 28.14°C and the minimum temperature of the warehouse was 14.10°C. See Section 5 for the discrepancy investigations initiated for temperature excursions.

5. INVESTIGATIONS:

- 5.1. SDI18-01 was initiated for temperatures dropping below the minimum storage temperature of 15°C on 1/7/18. The temperature excursion had no impact on the Tris Hydrochloride stability samples, as the next time point, T₃, was pulled and tested and all lots met specifications.
- 5.2. SDI18-45 was initiated for MadgeTech data loggers not being replaced before the calibration due date. This had no impact on the Tris Hydrochloride stability samples, as the next time point, T₁₈, was pulled and tested and all lots met specifications.
- 5.3. SDI19-49 was initiated for a MadgeTech data logger that stopped recording temperature and humidity data. This had no impact on the Tris Hydrochloride stability samples, as the next time point, T₂₄, was pulled and tested and all lots met specifications.
- 5.4. SDI19-103 was initiated for the battery dying in a MadgeTech logger, therefore the logger stopped recording temperature and humidity data until it was replaced. This had no impact on the Tris Hydrochloride stability samples, as the next time point, T₃₆, was pulled and tested and all lots met specification.
- 5.5. SDI20-33 was initiated for four MadgeTech loggers in use past the calibration due date. This had no impact on the Tris Hydrochloride stability samples, as the next time point, T₃₆, was pulled and tested and all lots met specification.
- 5.6. SLI20-50 was initiated for OOS Assay for TH3200-139-1017-PV Labline at T₃₆. All retests met specification, therefore, there is no impact to the quality of this lot.

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6. LOT EVALUATION:

TABLE 2: ALL-INCLUSIVE STABILITY DATA

Tris Hydrochloride Stability Data										
Lot Number	Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆
TH3200-137-1017-PV (PP)	Absorbance (1M)	0.01 a.u max @ 400 nm	0.0005	0.0017	0.0018	0.0050	0.0028	0.0019	0.0043	0.0055
		0.06 a.u max @ 280 nm	0.0015	0.0053	0.0052	0.0129	0.0078	0.0054	0.0122	0.0151
		0.06 a.u max @ 260 nm	0.0010	0.0060	0.0065	0.0162	0.0096	0.0059	0.0146	0.0180
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.25%	99.70%	99.91%	99.72%	99.65%	100.08%	100.04%	99.60%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.0476%	0.0334%	0.0673%	0.0607%	0.0444%	<0.0067%	0.0665%	0.0625%
	Melting Range	147 - 153°C	150.5-151.2°C	150.9-152.1°C	150.5-151.6°C	150.1-151.3°C	150.3-151.3°C	150.5-151.6°C	150.0-151.5°C	150.6-151.8°C
	pH (0.5M)	3.5 – 5.0	4.212 @ 23.85°C	4.232 @ 20.69°C	4.155 @ 22.49°C	4.195 @ 22.89°C	4.163 @ 25.89°C	4.243 @ 24.87°C	4.186 @ 23.41°C	4.160 @ 25.6°C
TH3200-137-1017-PV (PF)	Absorbance (1M)	0.01 a.u max @ 400 nm	0.0005	0.0042	0.0032	0.0052	0.0022	0.0019	0.0037	0.0045
		0.06 a.u max @ 280 nm	0.0015	0.0111	0.0076	0.0132	0.0069	0.0059	0.0114	0.0143
		0.06 a.u max @ 260 nm	0.0010	0.0127	0.0091	0.0162	0.0083	0.0064	0.0137	0.0172
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.25%	99.72%	99.77%	99.75%	99.63%	100.08%	99.79%	99.58%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.0476%	0.0539%	0.0776%	0.0285%	0.0592%	0.0146%	0.0695%	0.0766%
	Melting Range	147 - 153°C	150.5-151.2°C	150.9-152.1°C	150.5-151.6°C	150.1-151.3°C	150.4-151.4°C	150.6-151.8°C	150.3-151.8°C	150.6-151.8°C
	pH (0.5M)	3.5 – 5.0	4.212 @ 23.85°C	4.226 @ 20.99°C	4.150 @ 22.73°C	4.183 @ 23.59°C	4.166 @ 25.62°C	4.239 @ 25.00°C	4.186 @ 23.25°C	4.162 @ 24.9°C
TH3200-137-1017-PV (TP)	Absorbance (1M)	0.01 a.u max @ 400 nm	0.0005	0.0010	< 0.003	0.0009	0.0018	0.0010	0.0011	0.0017
		0.06 a.u max @ 280 nm	0.0015	0.0043	0.0045	0.0055	0.0070	0.0047	0.0055	0.0090
		0.06 a.u max @ 260 nm	0.0010	0.0049	0.0053	0.0072	0.0083	0.0050	0.0067	0.0104
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.25%	99.74%	99.93%	99.76%	99.56%	100.15%	100.06 %	99.69%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.0476%	0.0268%	0.0745%	0.0357%	0.0416%	<0.0067%	0.0224%	0.0211%

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Tris Hydrochloride Stability Data

Lot Number	Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆
	Melting Range	147 - 153°C	150.5-151.2°C	150.9-152.1°C	150.5-151.6°C	150.1-151.3°C	150.4-151.4°C	150.6-151.8°C	150.2-151.6°C	150.9-152.0°C
	pH (0.5M)	3.5 – 5.0	4.212 @ 23.85°C	4.241 @ 20.74°C	4.178 @ 22.26°C	4.191 @ 23.24°C	4.170 @ 25.52°C	4.247 @ 24.61°C	4.193 @ 23.42°C	4.147 @ 26.3°C
TH3200-137-1017-PV (Labline)	Absorbance (1M)	0.01 a.u max @ 400 nm	0.0005	0.0002	< 0.003	0.0015	0.0019	0.0009	0.0005	0.0007
		0.06 a.u max @ 280 nm	0.0015	0.0042	0.0098	0.0051	0.0056	0.0039	0.0031	0.0043
		0.06 a.u max @ 260 nm	0.0010	0.0048	0.0100	0.0069	0.0069	0.0040	0.0037	0.0051
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.25%	99.64%	99.60%	99.67%	99.67%	99.99%	99.86%	99.71%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.0476%	0.0446%	0.2178%	0.1641%	0.1174%	0.0887%	0.1496%	0.0361%
	Melting Range	147 - 153°C	150.5-151.2°C	150.9-152.1°C	150.5-151.6°C	150.0-151.1°C	150.4-151.4°C	150.3-151.5°C	150.1-151.5°C	151.3-152.5°C
	pH (0.5M)	3.5 – 5.0	4.212 @ 23.85°C	4.267 @ 20.69°C	4.144 @ 22.69°C	4.168 @ 23.34°C	4.182 @ 25.04°C	4.250 @ 24.46°C	4.216 @ 23.46°C	4.182 @ 24.6°C
TH3200-138-1017-PV (PP)	Absorbance (1M)	0.01 a.u max @ 400 nm	< 0.003	0.0028	0.0032	0.0031	0.0030	0.0020	0.0035	0.0036
		0.06 a.u max @ 280 nm	< 0.003	0.0071	0.0065	0.0080	0.0075	0.0048	0.0101	0.0098
		0.06 a.u max @ 260 nm	< 0.003	0.0087	0.0071	0.0097	0.0096	0.0054	0.0127	0.0118
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.26%	99.77%	99.84%	99.66%	99.69%	100.15%	100.23%	99.57%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.1428%	0.0467%	0.0855%	0.0471%	0.0396%	<0.0067%	0.0707%	0.0547%
	Melting Range	147 - 153°C	150.8-151.9°C	150.8-152.0°C	150.8-151.8°C	150.6-151.8°C	150.2-151.2°C	150.6-151.7°C	149.8-151.3°C	151.0-152.0°C
	pH (0.5M)	3.5 – 5.0	4.209 @ 23.34°C	4.227 @ 21.21°C	4.191 @ 20.85°C	4.201 @ 23.09°C	4.181 @ 24.80°C	4.243 @ 24.31°C	4.194 @ 24.88°C	4.122 @ 26.7°C
TH3200-138-1017-PV (PF)	Absorbance (1M)	0.01 a.u max @ 400 nm	< 0.003	0.0020	0.0044	0.0066	0.0024	0.0016	0.0027	0.0042
		0.06 a.u max @ 280 nm	< 0.003	0.0056	0.0090	0.0144	0.0067	0.0043	0.0084	0.0107
		0.06 a.u max @ 260 nm	< 0.003	0.0068	0.0100	0.0171	0.0087	0.0048	0.0106	0.0129
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.26%	99.70%	99.84%	99.71%	99.64%	100.08%	100.07%	98.97%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.1428%	0.0968%	0.0529%	0.0455%	0.0710%	0.0163%	0.0480%	0.0442%

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Tris Hydrochloride Stability Data

Lot Number	Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆
	Melting Range	147 - 153°C	150.8-151.9°C	150.8-151.8°C	150.8-151.6°C	150.8-151.8°C	150.3-151.3°C	150.8-152.0°C	150.1-151.5°C	151.0-151.8°C
	pH (0.5M)	3.5 – 5.0	4.209 @ 23.34°C	4.224 @ 21.31°C	4.204 @ 21.07°C	4.215 @ 22.85°C	4.186 @ 24.31°C	4.258 @ 24.40°C	4.182 @ 23.97°C	4.158 @ 25.2°C
TH3200-138-1017-PV (TP)	Absorbance (1M)	0.01 a.u max @ 400 nm	< 0.003	0.0017	0.0013	0.0004	0.0039	0.0009	0.0009	0.0008
		0.06 a.u max @ 280 nm	< 0.003	0.0060	0.0043	0.0038	0.0105	0.0036	0.0050	0.0060
		0.06 a.u max @ 260 nm	< 0.003	0.0076	0.0047	0.0050	0.0132	0.0040	0.0067	0.0073
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.26%	99.81%	99.82%	99.63%	99.67%	100.17%	100.12%	99.76%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.1428%	0.0541%	0.0446%	0.0472%	0.0285%	0.0215%	0.0356%	0.0477%
	Melting Range	147 - 153°C	150.8-151.9°C	151.0-152.1°C	150.8-151.8°C	150.8-151.8°C	150.4-151.4°C	150.8-152.0°C	150.1-151.6°C	151.1-152.1°C
	pH (0.5M)	3.5 – 5.0	4.209 @ 23.34°C	4.230 @ 21.00°C	4.183 @ 20.88°C	4.160 @ 23.00°C	4.166 @ 25.49°C	4.243 @ 24.39°C	4.179 @ 24.87°C	4.151 @ 25.2°C
TH3200-138-1017-PV (Labline)	Absorbance (1M)	0.01 a.u max @ 400 nm	< 0.003	0.0007	0.0016	0.0004	0.0043	0.0010	0.0009	0.0020
		0.06 a.u max @ 280 nm	< 0.003	0.0037	0.0036	0.0035	0.0095	0.0031	0.0035	0.0056
		0.06 a.u max @ 260 nm	< 0.003	0.0047	0.0039	0.0048	0.0120	0.0035	0.0046	0.0070
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.26%	99.63%	99.63%	99.68%	99.52%	100.08%	100.08%	99.50%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.1428%	0.0406%	0.1735%	0.0832%	0.0548%	0.0871%	0.0723%	0.0768%
	Melting Range	147 - 153°C	150.8-151.9°C	151.0-152.1°C	150.6-151.6°C	150.8-151.6°C	150.3-151.3°C	150.6-152.0°C	150.1-151.3°C	151.1-152.0°C
	pH (0.5M)	3.5 – 5.0	4.209 @ 23.34°C	4.245 @ 20.62°C	4.220 @ 20.84°C	4.172 @ 22.89°C	4.208 @ 25.18°C	4.244 @ 24.73°C	4.205 @ 23.80°C	4.157 @ 25.3°C
TH3200-139-1017-PV (PP)	Absorbance (1M)	0.01 a.u max @ 400 nm	0.0023	0.0022	0.0040	0.0042	0.0050	0.0024	0.0041	0.0061
		0.06 a.u max @ 280 nm	0.0085	0.0072	0.0115	0.0104	0.0115	0.0069	0.0131	0.0160
		0.06 a.u max @ 260 nm	0.0097	0.0087	0.0135	0.0124	0.0140	0.0078	0.0164	0.0188
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.78%	99.82%	99.79%	99.63%	99.61%	100.07%	100.06%	100.33%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.1234%	0.0573%	0.0480%	0.0252%	<0.0067%	0.0197%	0.0435%	0.0272%

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Tris Hydrochloride Stability Data

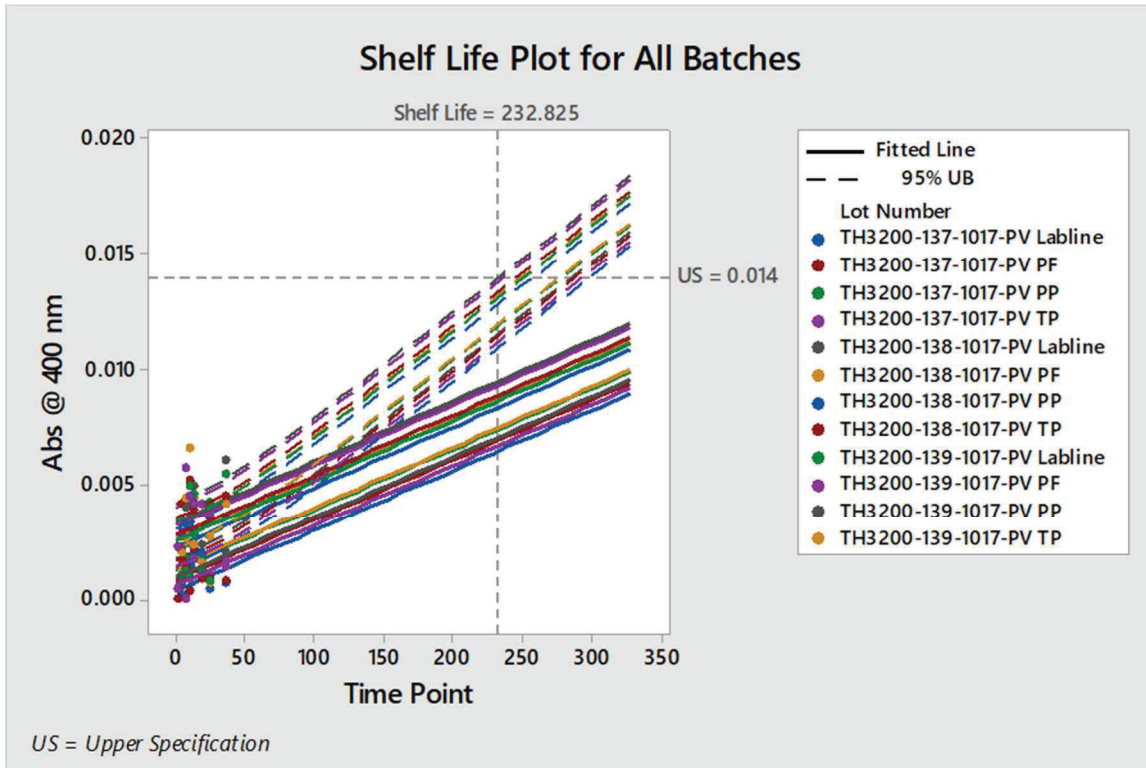
Lot Number	Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆
	Melting Range	147 - 153°C	150.7-151.7°C	151.0-152.0°C	150.6-151.6°C	150.6-151.5°C	150.6-151.6°C	150.6-151.8°C	150.0-150.8°C	151.0-151.8°C
	pH (0.5M)	3.5 – 5.0	4.210 @ 23.01°C	4.228 @ 21.49°C	4.192 @ 21.33°C	4.173 @ 22.79°C	4.148 @ 26.75°C	4.262 @ 23.76°C	4.187 @ 23.51°C	4.162 @ 24.7°C
TH3200-139-1017-PV (PF)	Absorbance (1M)	0.01 a.u max @ 400 nm	0.0023	0.0029	0.0057	0.0045	0.0042	0.0042	0.0037	0.0014
		0.06 a.u max @ 280 nm	0.0085	0.0078	0.0141	0.0117	0.0111	0.0096	0.0126	0.0064
		0.06 a.u max @ 260 nm	0.0097	0.0095	0.0166	0.0138	0.0138	0.0108	0.0159	0.0081
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.78%	99.77%	99.82%	99.58%	99.69%	100.11%	100.07%	99.64%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.1234%	0.0748%	0.0356%	0.0360%	0.0457%	0.0154%	0.0856%	<0.0074%
	Melting Range	147 - 153°C	150.7-151.7°C	150.6-151.6°C	150.8-151.6°C	150.8-151.6°C	150.5-151.5°C	150.8-152.0°C	150.4-151.6°C	151.1-152.1°C
	pH (0.5M)	3.5 – 5.0	4.210 @ 23.01°C	4.223 @ 21.57°C	4.180 @ 21.15°C	4.175 @ 22.77°C	4.151 @ 26.86°C	4.258 @ 24.39°C	4.202 @ 23.41°C	4.166 @ 25.0°C
TH3200-139-1017-PV (TP)	Absorbance (1M)	0.01 a.u max @ 400 nm	0.0023	0.0012	0.0026	0.0004	0.0044	0.0012	0.0007	0.0014
		0.06 a.u max @ 280 nm	0.0085	0.0058	0.0078	0.0059	0.0109	0.0055	0.0062	0.0083
		0.06 a.u max @ 260 nm	0.0097	0.0069	0.0092	0.0074	0.0130	0.0061	0.0082	0.0100
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.78%	99.79%	99.87%	99.65%	99.68%	100.19%	100.08%	99.83%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.1234%	0.0467%	0.0315%	< 0.0067%	0.0138%	0.0142%	0.0141%	0.0315%
	Melting Range	147 - 153°C	150.7-151.7°C	151.1-152.3°C	150.6-151.6°C	150.6-151.6°C	150.6-151.6°C	150.5-151.8°C	150.4-151.5°C	151.0-151.8°C
	pH (0.5M)	3.5 – 5.0	4.210 @ 23.01°C	4.221 @ 21.74°C	4.207 @ 20.94°C	4.181 @ 22.86°C	4.167 @ 25.96°C	4.257 @ 24.35°C	4.204 @ 23.43°C	4.155 @ 25.0°C
TH3200-139-1017-PV (Labline)	Absorbance (1M)	0.01 a.u max @ 400 nm	0.0023	0.0011	0.0012	0.0010	0.0046	0.0012	0.0008	0.0014
		0.06 a.u max @ 280 nm	0.0085	0.0053	0.0055	0.0061	0.0103	0.0049	0.0053	0.0058
		0.06 a.u max @ 260 nm	0.0097	0.0065	0.0064	0.0077	0.0129	0.0057	0.0075	0.0064
	Appearance and Color	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay	99.0 – 103.0%	99.78%	99.73%	99.84%	99.56%	99.57%	100.05%	100.00%	99.69%
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
	Loss on Drying (105°C)	0.5% max.	0.1234%	0.0411%	0.1075%	0.0321%	0.0526%	0.0507%	0.0851%	0.0232%

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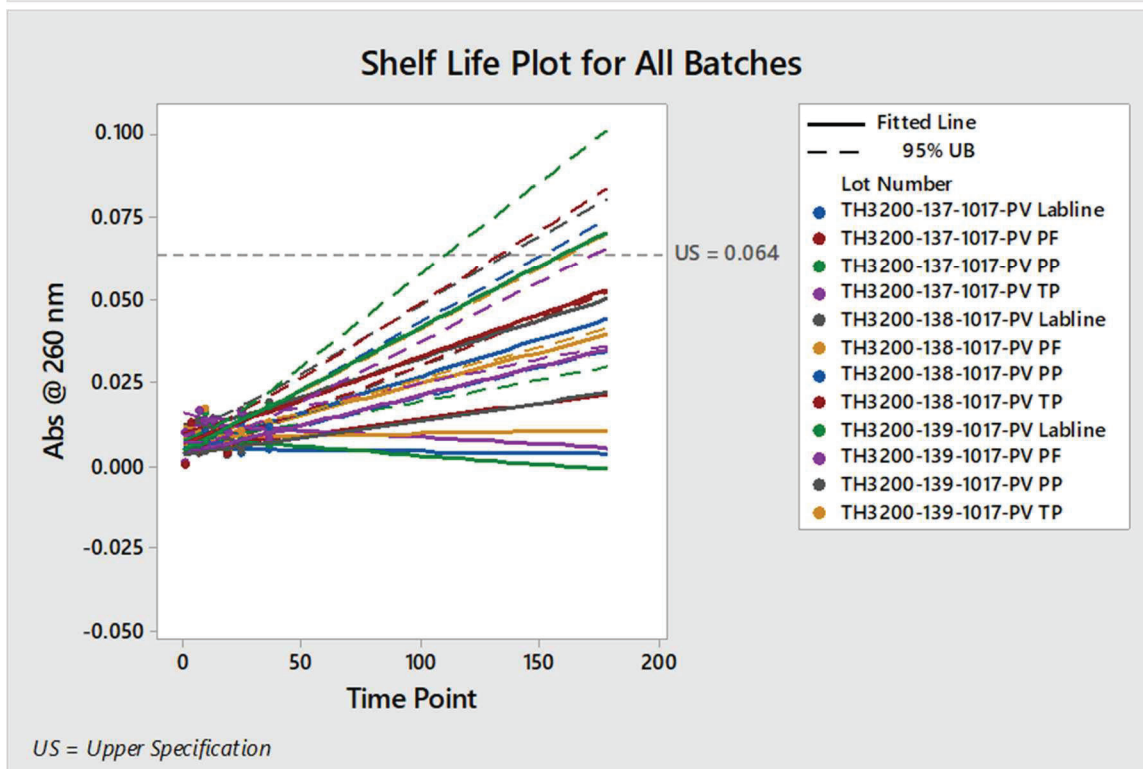
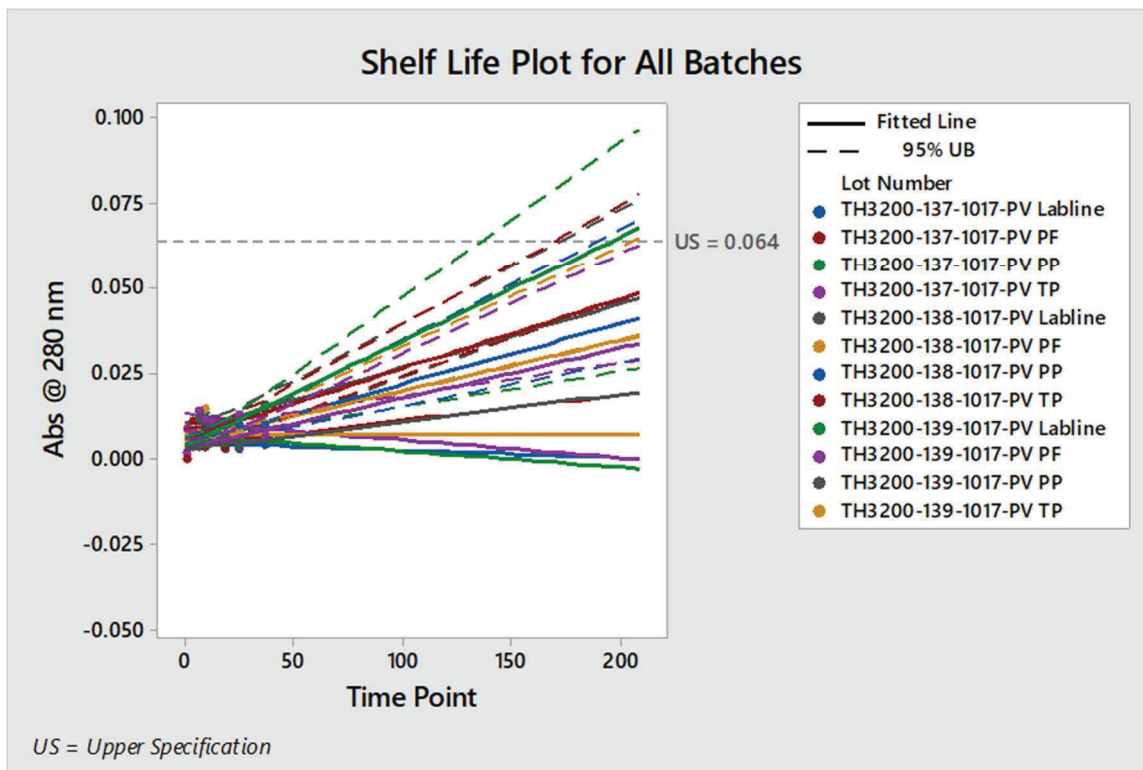
Tris Hydrochloride Stability Data

Lot Number	Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆
	Melting Range	147 - 153°C	150.7-151.7°C	151.0-152.3°C	150.6-151.6°C	150.3-151.3°C	150.4-151.4°C	150.6-151.8°C	150.5-151.5°C	151.0-151.8°C
	pH (0.5M)	3.5 – 5.0	4.210 @ 23.01°C	4.227 @ 22.66°C	4.225 @ 20.88°C	4.197 @ 22.90°C	4.171 @ 25.72°C	4.253 @ 24.37°C	4.213 @ 23.52°C	4.129 @ 25.4°C

GRAPHS 1, 2 AND 3: SHELF LIFE PLOTS FOR ABSORBANCE @ 400 NM, 280 NM AND 260 NM



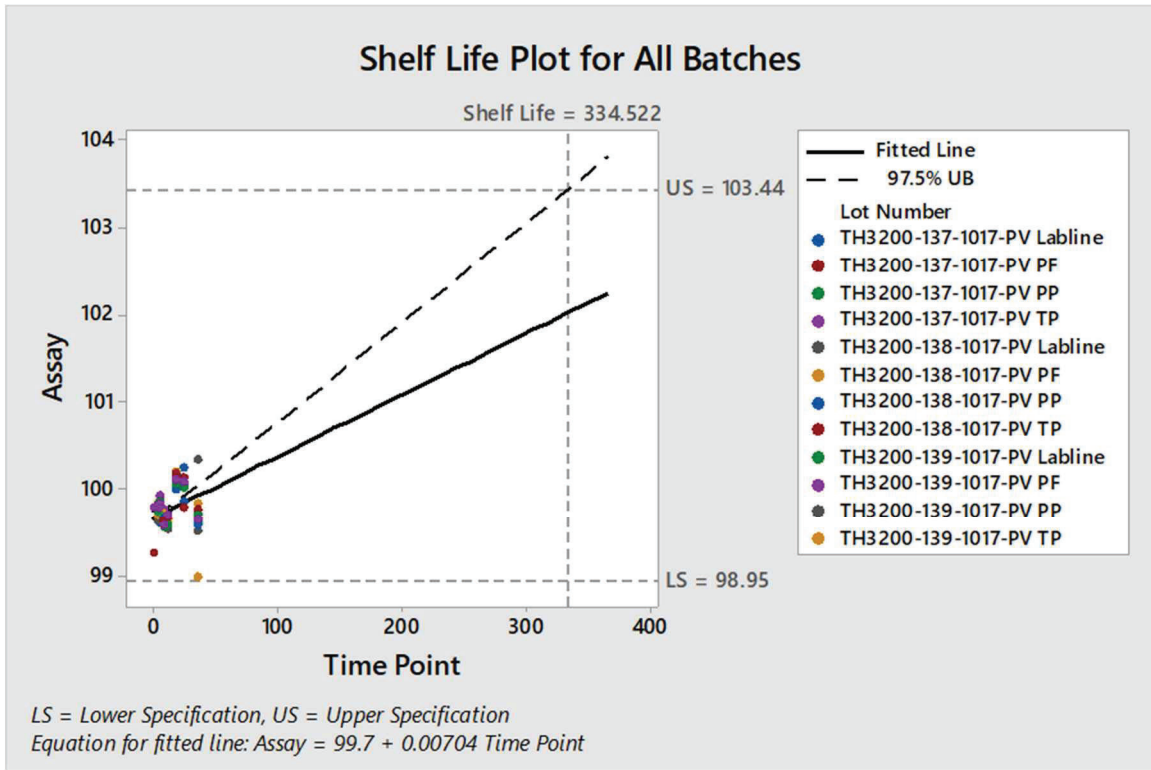
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The Shelf Lives for Absorbance were predicted to be 232.825 months at 400 nm, 136.46 months at 280 nm, and 111.21 months at 260nm. The overall Shelf Life for Absorbance is predicted to be 111.93 months. This is well beyond the 36-month stability study, and shows no indication of an issue to the product of the current shelf life.

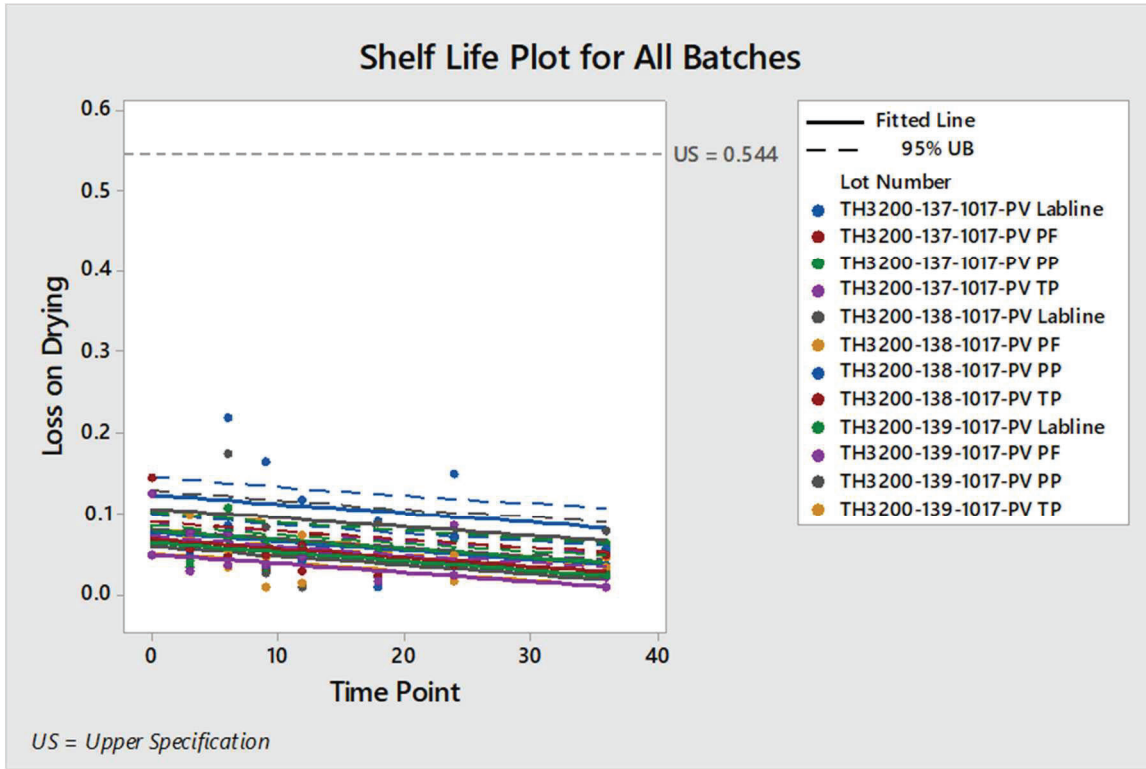
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GRAPH 4: SHELF LIFE PLOT FOR ASSAY



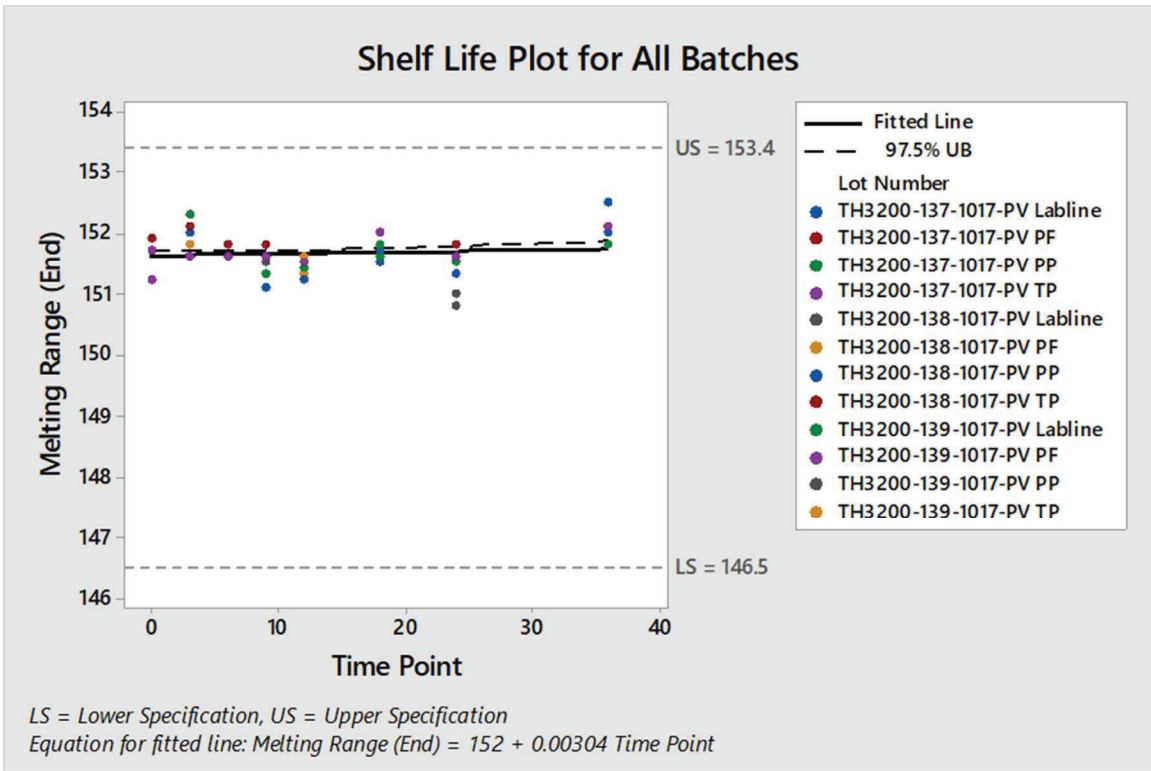
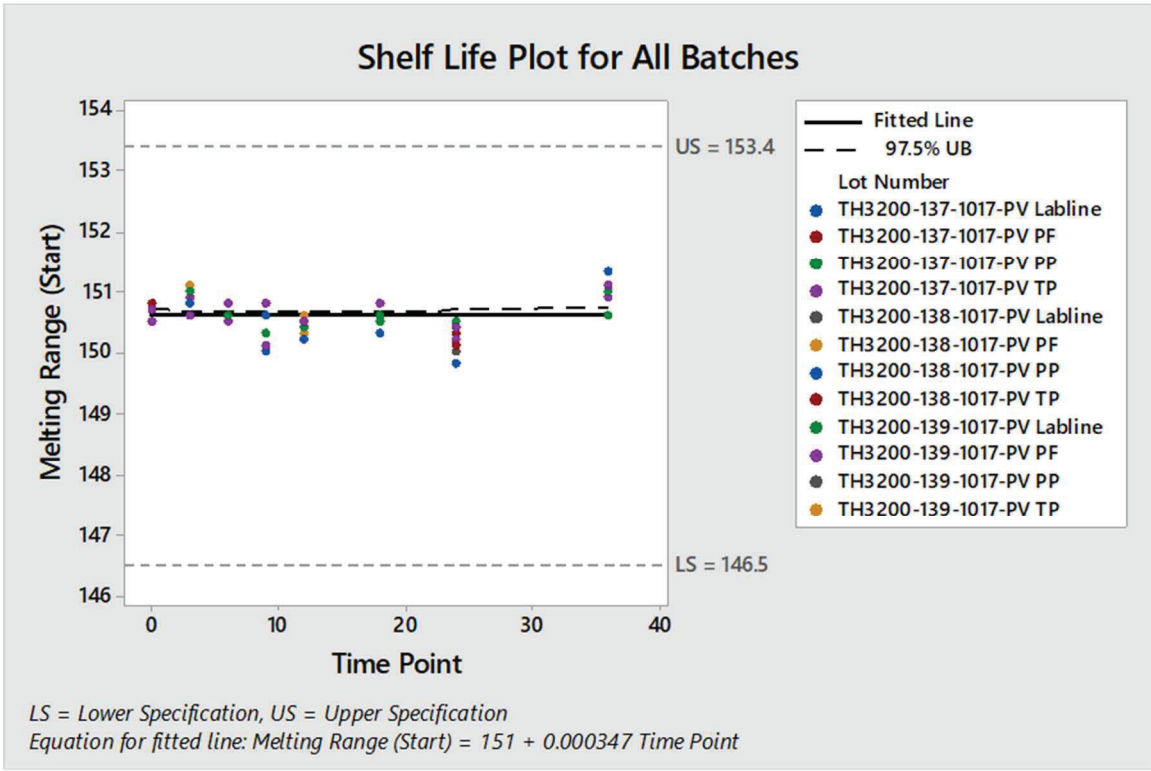
The Shelf Live for Assay was predicted to be 334.522 months. This is well beyond the 36-month stability study, and shows no indication of an issue to the product of the current shelf life.

GRAPH 5: SHELF LIFE PLOT FOR LOSS ON DRYING



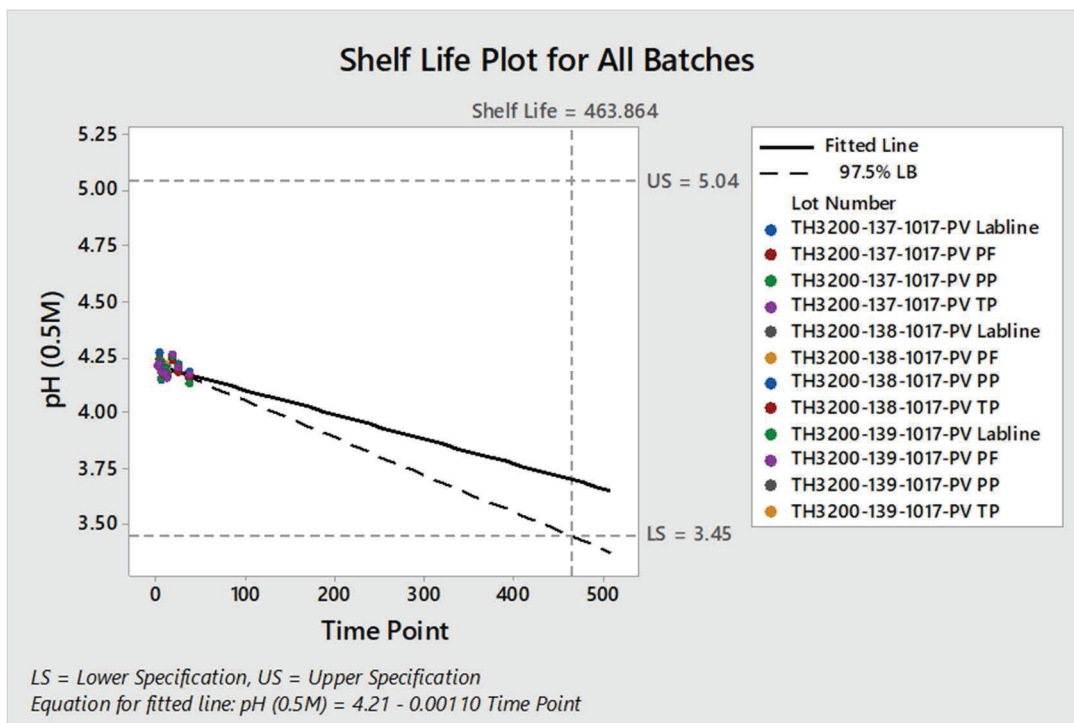
The Shelf Live for Loss on Drying could not be predicted based on this statistical model due to the mean response slope not being significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

GRAPHS 6 AND 7: SHELF LIFE PLOTS FOR MELTING RANGE



The Shelf Live for Melting Range could not be predicted based on this statistical model due to the mean response slope not being significantly different from zero for both Melting Range Start and Melting Range End. There is no impact to the product or currently assigned expiration of this material.

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GRAPH 8: SHELF LIFE PLOT FOR PH

The Shelf Live for pH was predicted to be 463.864 months. This is well beyond the 36-month stability study, and shows no indication of an issue to the product of the current shelf life.

7. CONCLUSION:

All data met the specifications set forth in the Stability Program. In accordance with ICH Q1E 2.4.2.1, 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 the last testing interval. All known predicted Shelf Life estimates exceeded a Shelf Life of 36 months. The expiration date will be assigned as 36 months. As the historical data and predicted Shelf Life plots indicate that the material is stable at 36 months in the following packaging configurations P/P, P/F, T/P and Labline.

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.
 - 8.1.1.1. 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.

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