TRIS BIO FUISA AND BIO ACTIVE ACCELERATED STABILITY REPORT 2017

Overview

The purpose of this report is to analyze the data obtained from the accelerated stability of Tris Bio FUISA Grade and Bio Active Grade manufactured in API Suite 3, Room E04 of BioSpectra's Bangor, PA facility. Samples were initially placed on the stability program in May 2016 consisting of one Tris Bio Active Process Validation batch and four Tris Bio FUISA Process Validation batches with each lot contained in one pail. In July and August 2016, questionably high Loss on Drying results were noted, refer to BLI16-14 and BLI16-16 respectively. It was found that the pails were being opened inside of the accelerated stability chamber thus subjecting the samples to additional moisture. New stability samples of all four lots were entered into the accelerated stability chamber on 07/29/16 and the previous stability samples were removed on 8/2/16. These new samples were packaged into pails designated for each time period containing all four lots to be pulled at one time. This would prevent opening the packaging within the stability chamber. Analysis was conducted on a monthly basis for a total of six months in order to assure that the manufactured product remains stable under the specified conditions and for the specified interval of time.

The data was analyzed utilizing an I Chart and a Moving Range Chart. The I and Moving Range Charts show process performance using continuous data, in this case, time in months. 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. The data can be found in the Accelerated Stability Program binder, the individual Analytical Summary Sheets for analysis of the product, as well as attached to this report.

This accelerated Stability analysis assesses the stability of one Tris Bio Active Grade lot and four lots of Tris Bio FUISA Grade that came off accelerated stability in February of 2017. The study included the following analysis: Absorbance (40%) @ 290 nm, Assay, Identification (IR), pH (5%), and Loss on Drying as determined by the stability indicating report. All Identification (IR) results met requirements. These results will not be analyzed as they are qualitative.

References

ICH Q1E§; 2.4.1 No significant change at accelerated condition

Definitions

CL: Control Limit, the average

UCL: Upper control limit, 3 sigma above the CL

LCL: Lower control limit, 3 sigma below the CL
OOL: Point(s) that fall outside the UCL or LCL
OOT: Out Of Trend, this means that the material still meets control limits but was not in trend with the rest of the material.
OOS: Out of Specification, for the purpose of this stability analysis, OOS will mean that there is a point(s) that fall outside of the UCL or LCL.

Sample Designation

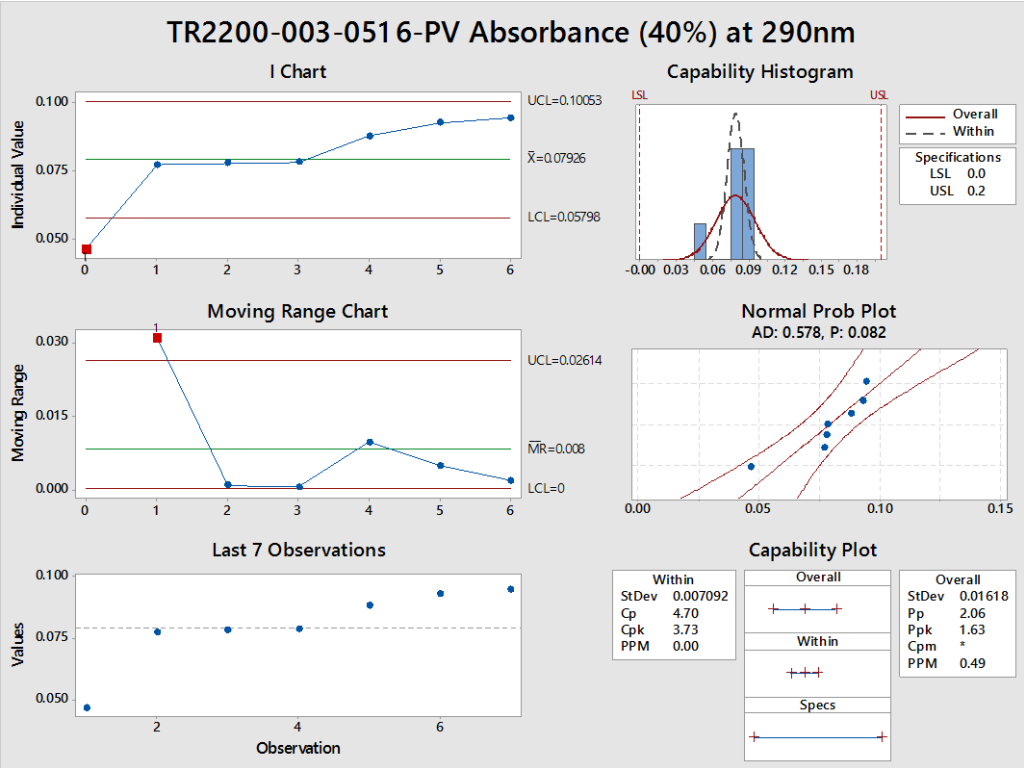
Samples initially placed on the stability program consisted of one Tris Bio Active Process Validation batch and four Tris Bio FUISA Process Validation batches. Stability samples from each of the batches were put into a round poly pail lined with two poly liners (P/P), with the outer liner being goose-neck tied closed. These batches were placed on stability in the Darwin Accelerated Stability Chamber located in the BioSpectra Bangor, PA facility. The type of packaging utilized in the accelerated stability samples was based on BioSpectra packaging.

Storage

Storage conditions have been continuously monitored and recorded. The temperature and humidity was monitored continuously utilizing a chart recorder and MadgeTech data loggers located on the Darwin Accelerated Stability Chamber. The temperature is set to 40°C + 2°C and 75% Relative Humidity + 5% Relative Humidity. There was one significant deviation from the set values for humidity noted on 10/03/16. BDI16-52 was initiated to investigate the low humidity that was noted. The sample pull dates were adjusted by seven days to allow additional time in the Stability chamber upon reaching proper humidity.

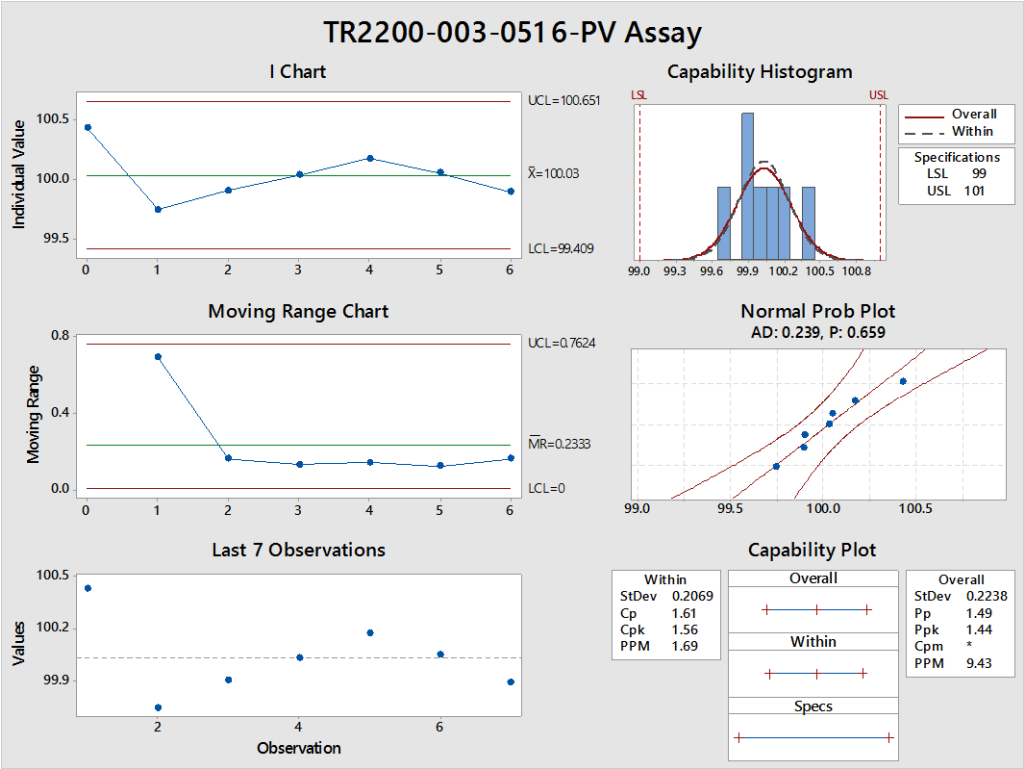
Lot Evaluation:

Graph 1: TR2200-003-0516-PV Absorbance (40%) at 290 nm



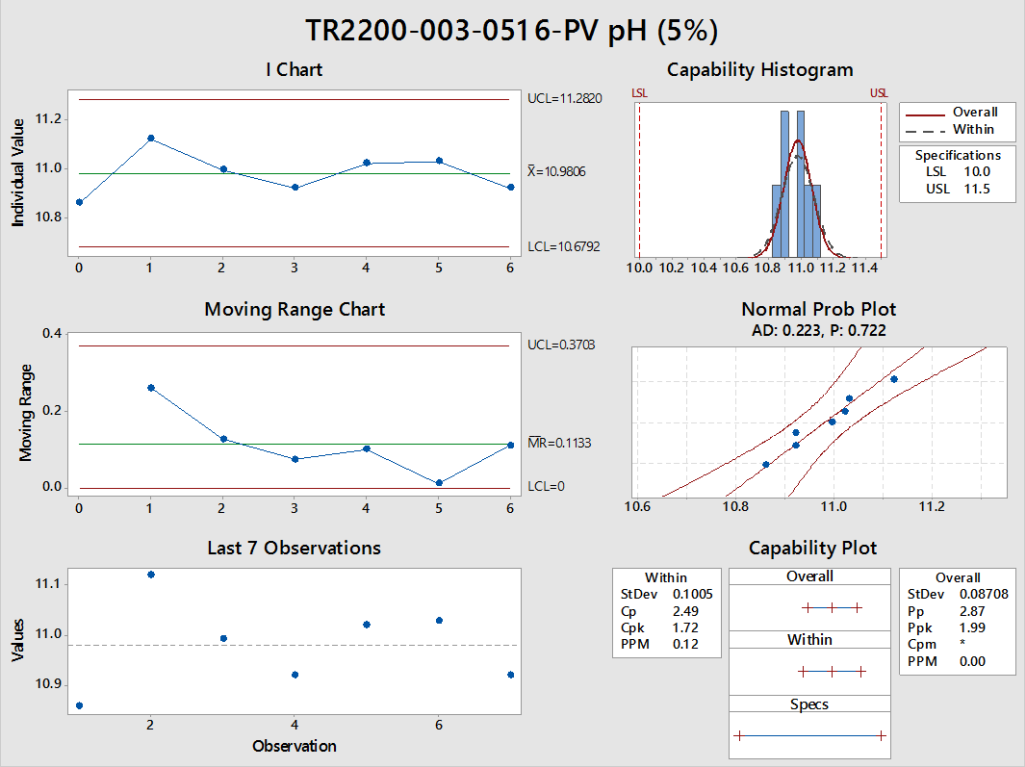
One OOL is noted for the T=0 data point. This will be considered acceptable since the data meets the specification of 0.2 a.u. maximum @ 290nm and is the baseline for this data set.

Graph 2: TR2200-003-0516-PV Assay



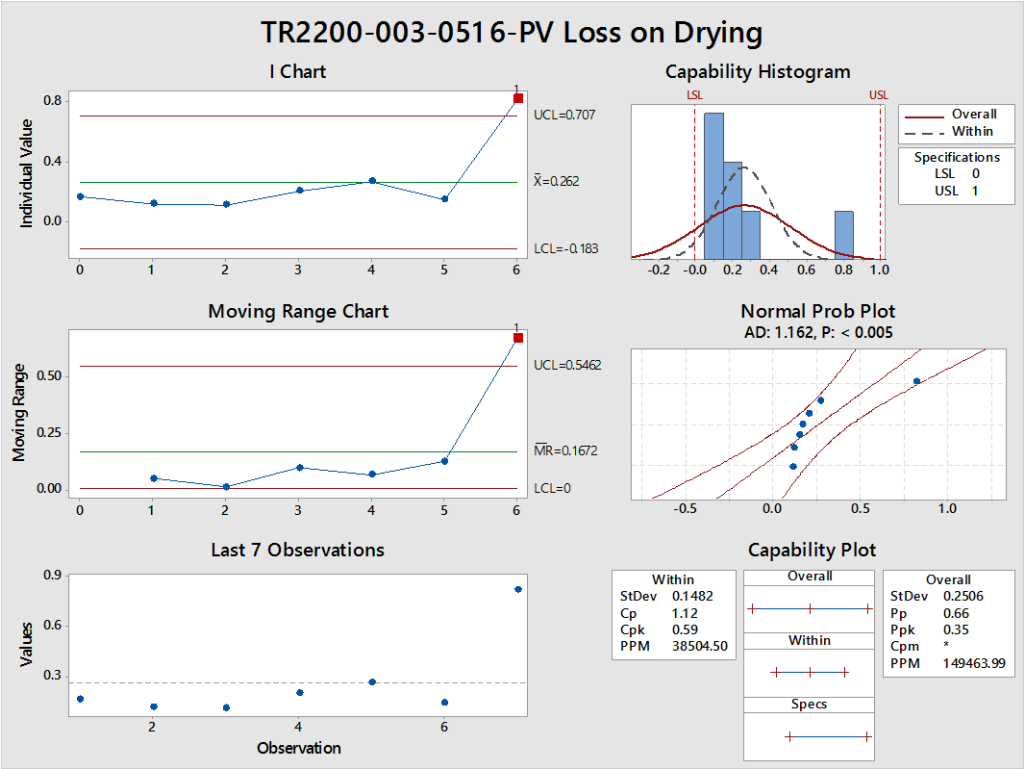
No OOL data points are shown for TR2200-003-0516-PV for Assay analysis. Variation may be attributed to the nature of the assay being performed under different pH calibrations and being standardized on different days.

Graph 3: TR2200-003-0516-PV pH (5%)



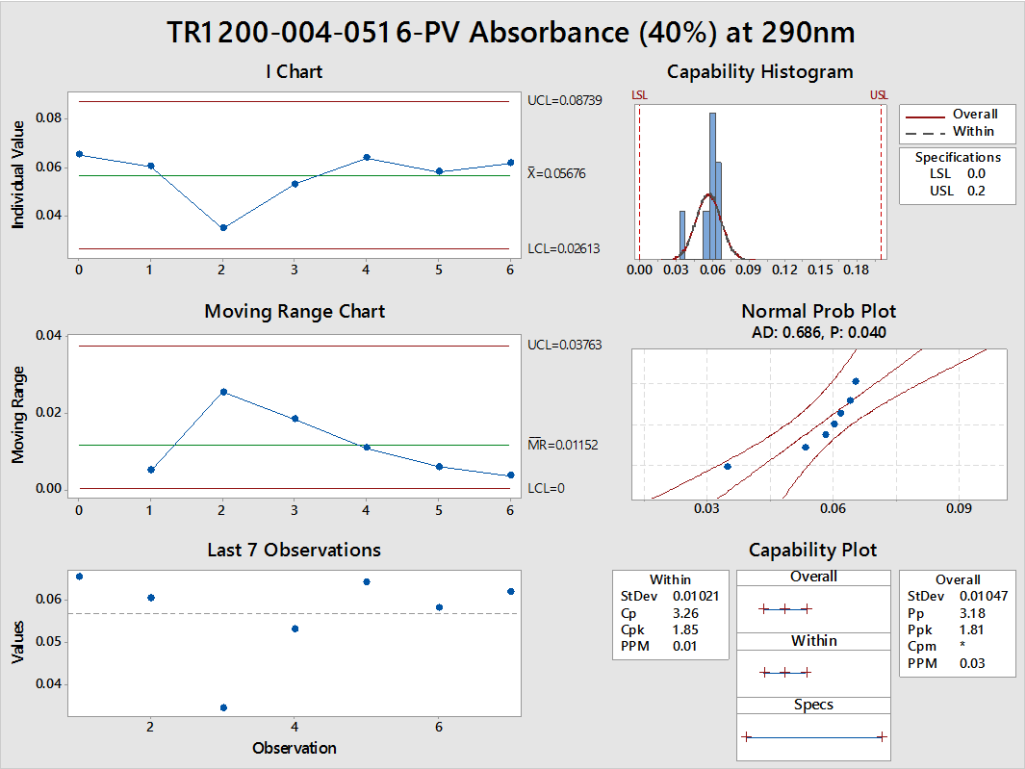
There are no OOL data points shown for pH 5% for TR2200-003-0516-PV. Variation may be attributed to pH calibrations being performed on different days. The higher pH of the T=1 sample would cause the Assay value to be lower since the titration uses hydrochloric acid. A more acidic sample would require less titrant, resulting in a lower assay.

Graph 4: TR2200-003-0516-PV Loss on Drying



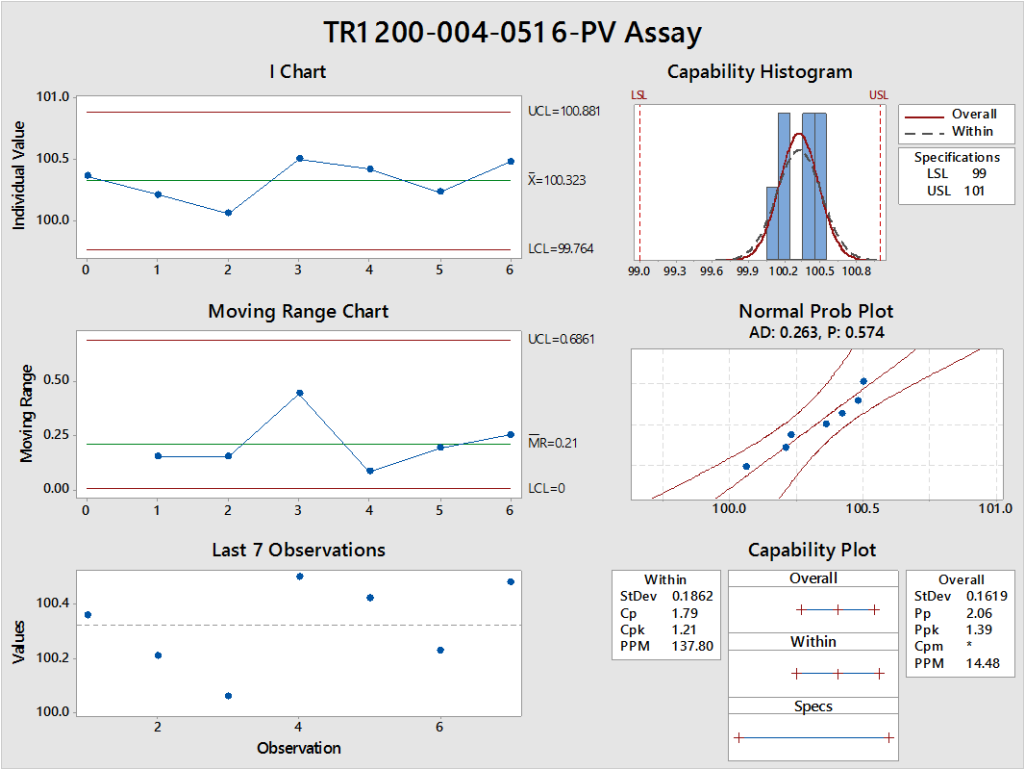
There is one OOL data point noted for the Loss on Drying for the T=6 sample. The neoprene gasket on the T=6 pail was kinked in multiple areas. This allowed for moisture to enter the pail thus increasing the Loss on Drying. SCR17-04 and SCR17-06 were initiated to evaluate the application of pail lids and supplier of the pails. All data are still within specification.

Graph 5: TR1200-004-0516-PV Absorbance (40%) at 290nm



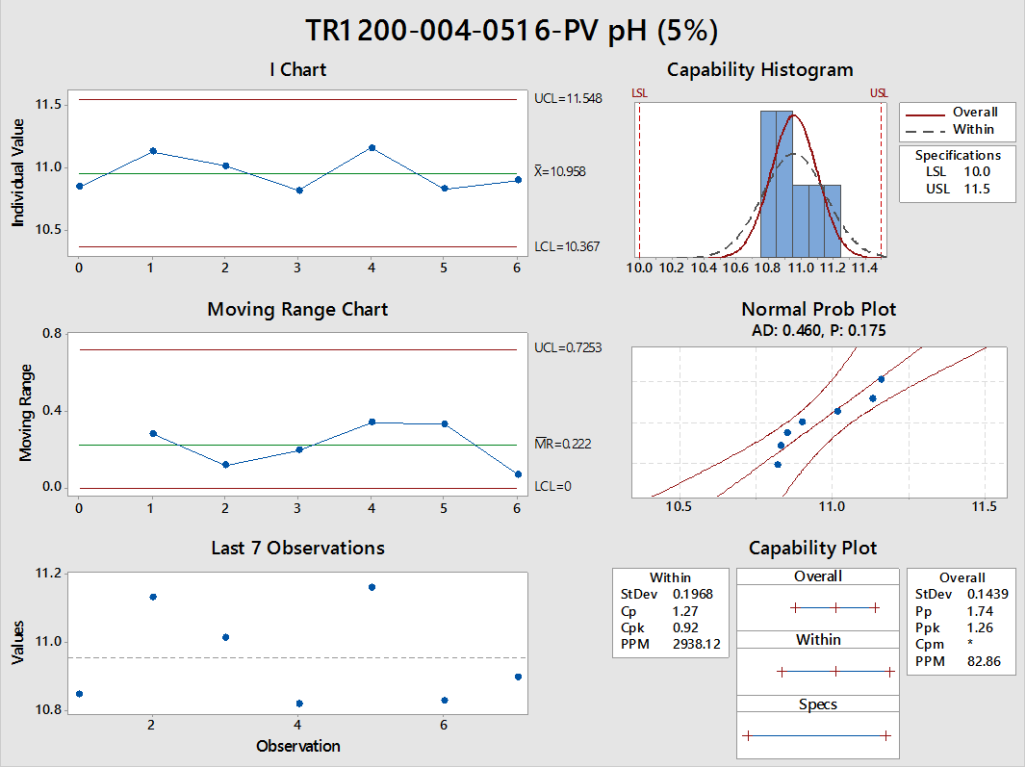
There are no OOL data points noted for Absorbance, however there is one OOT data point at T=2. This is likely due to analyst preparation of the sample or cuvettes. All data are within specification and considered acceptable.

Graph 6: TR1200-004-0516-PV Assay



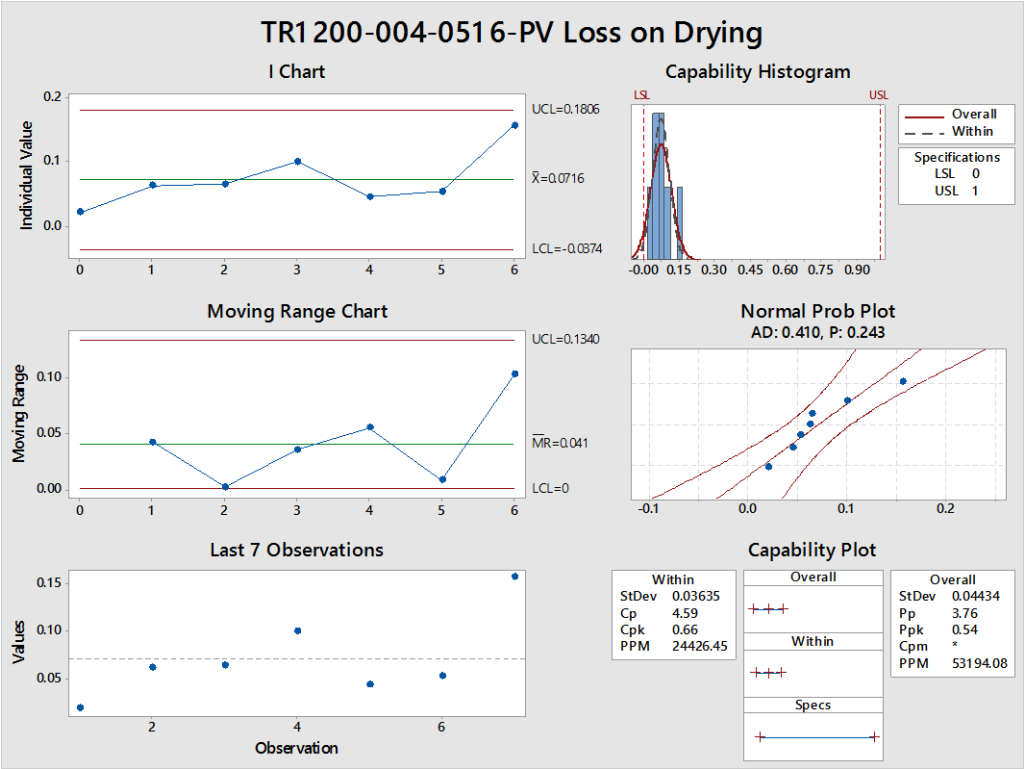
There are no OOL data points noted for Assay. As noted under Graph 2, variations in Assay may be attributed to pH calibrations and standardizations being performed on different days.

Graph 7: TR1200-004-0516-PV pH (5%)



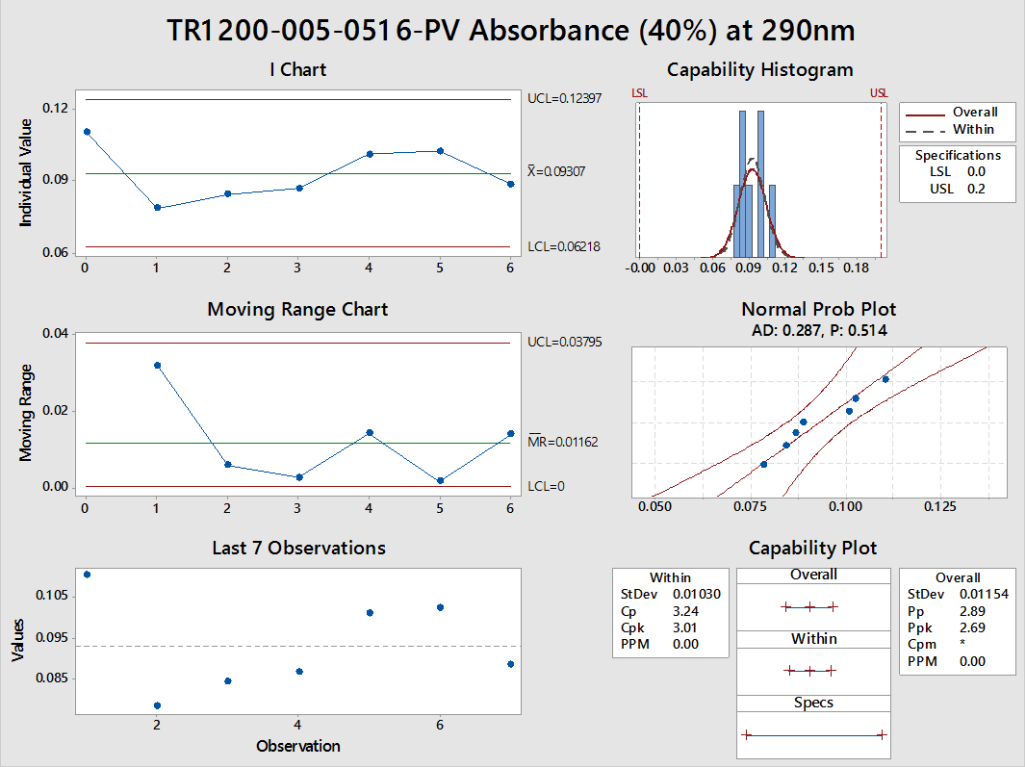
There are no noted OOL data points for pH. As noted under Graph 3, variation may be attributed to pH calibrations being performed on different days. The pH and Assay results show a correlation between acidic pH of the sample and a higher assay value.

Graph 8: TR1200-004-0516-PV Loss on Drying



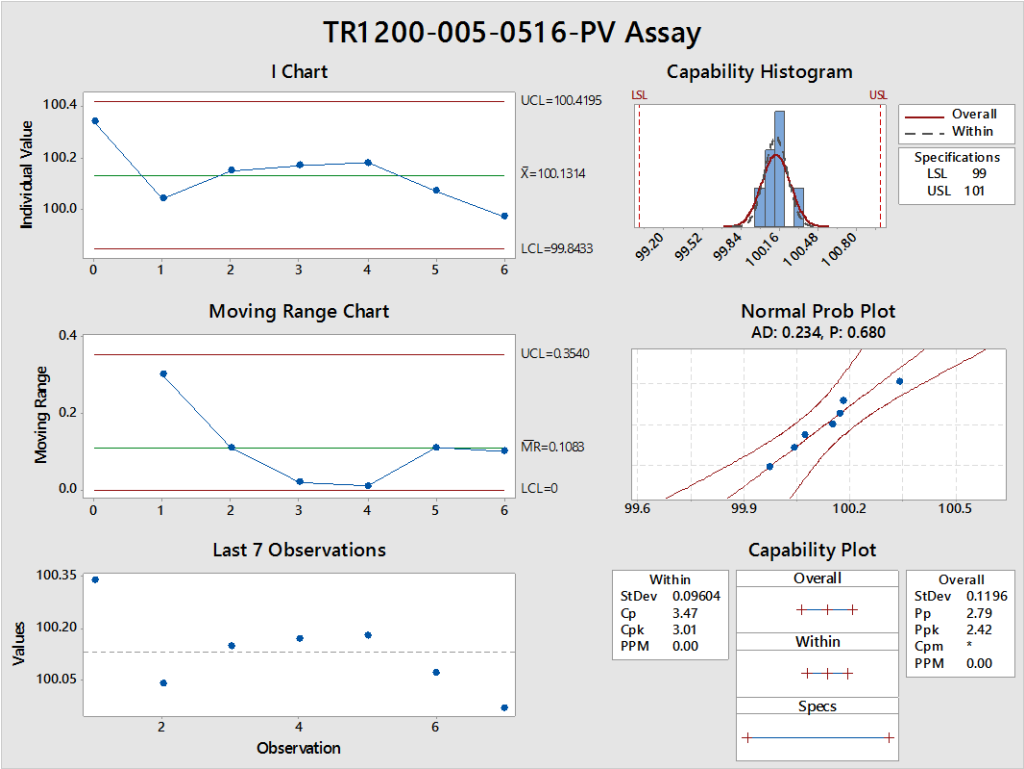
There are no OOL data points noted, however the T=6 data point is OOT. This may be attributed to the integrity of the gasket on the lid of the packaging, as explained under Graph 4. All data meet specification and are considered acceptable.

Graph 9: TR1200-005-0516-PV Absorbance (40%) at 290nm



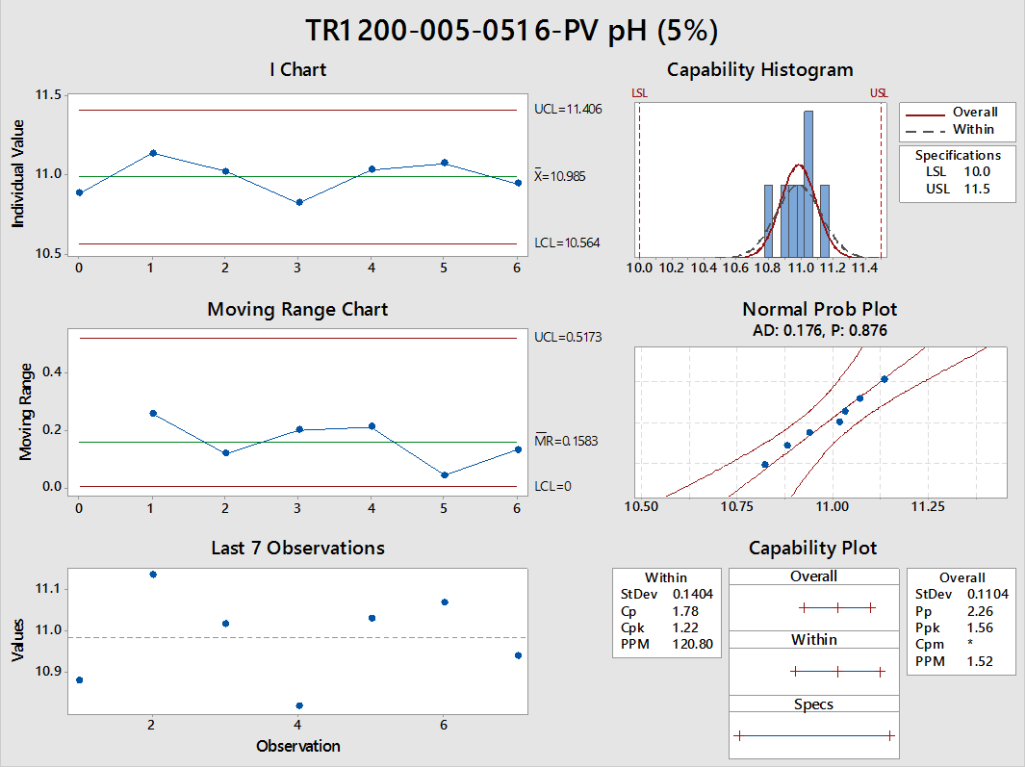
There are no OOL or OOT data points noted.

Graph 10: TR1200-005-0516-PV Assay



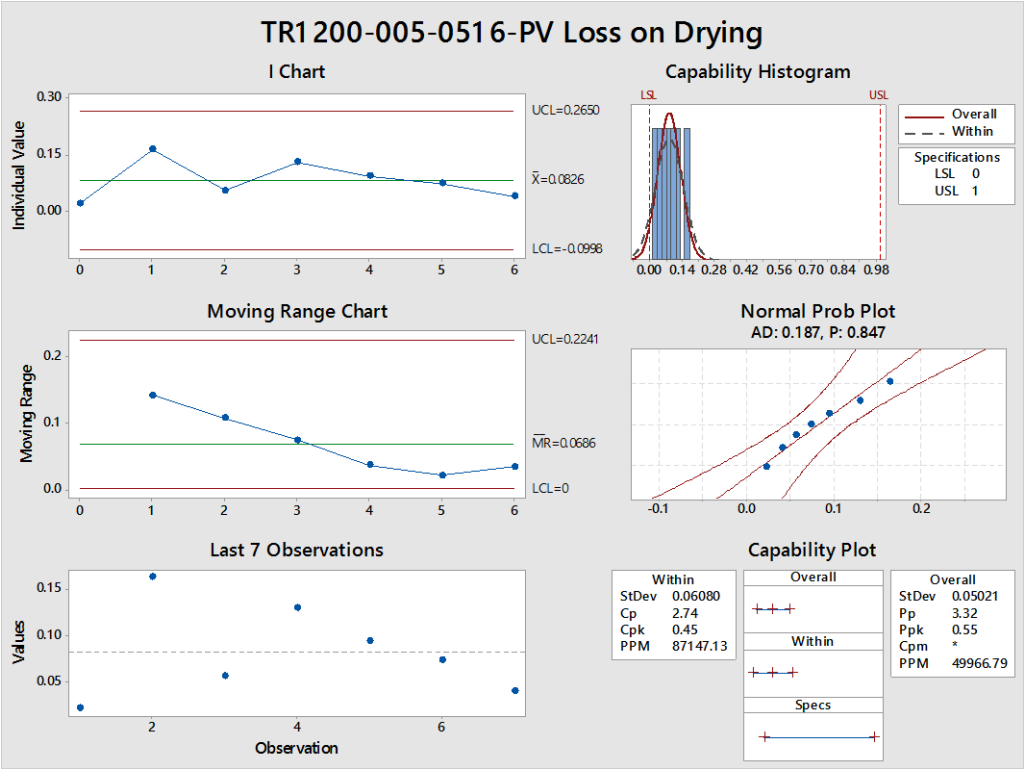
There are no OOL data points noted for Assay. As noted under Graph 2, variations in Assay may be attributed to pH calibrations and standardizations being performed on different days.

Graph 11: TR1200-005-0516-PV pH (5%)



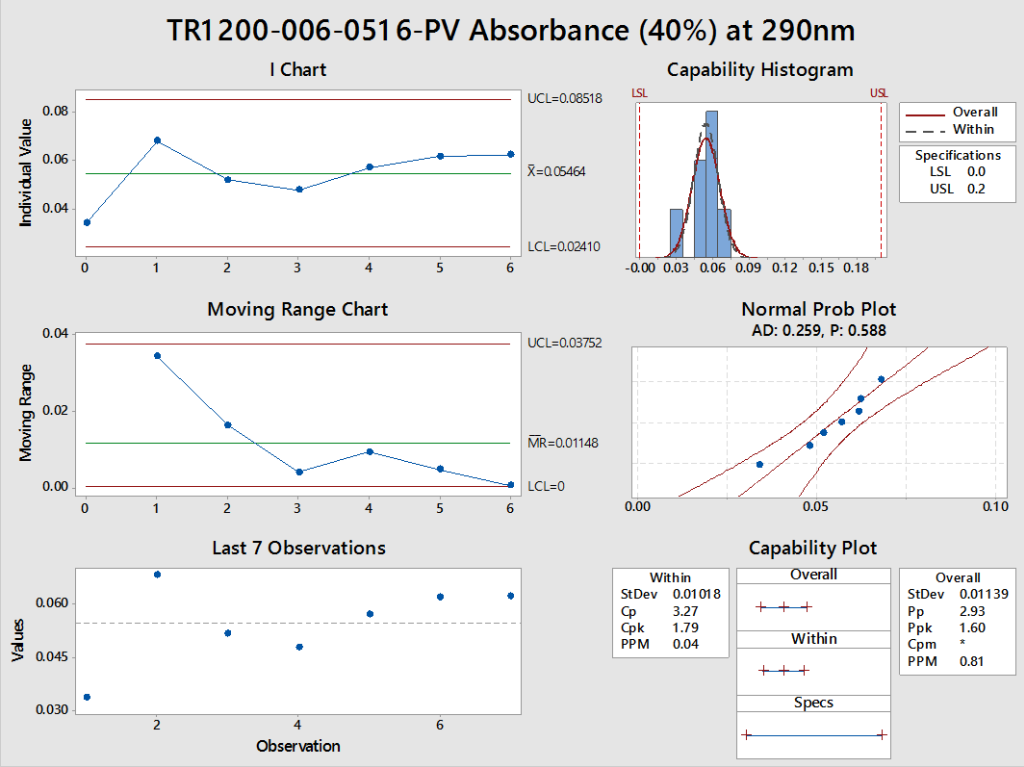
There are no OOL data points noted for pH. As noted under Graph 3, variation may be attributed to pH calibrations being performed on different days.

Graph 12: TR1200-005-0516-PV Loss on Drying



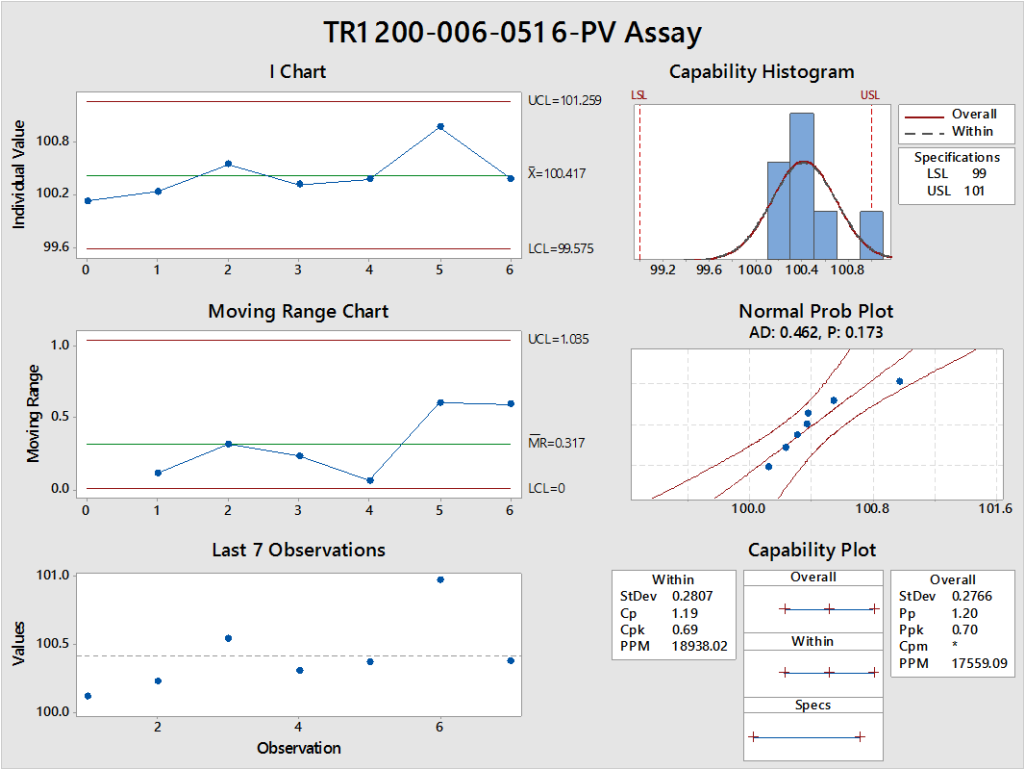
There are no OOL data points noted for Loss on Drying.

Graph 13: TR1200-006-0516-PV Absorbance (40%) at 290nm



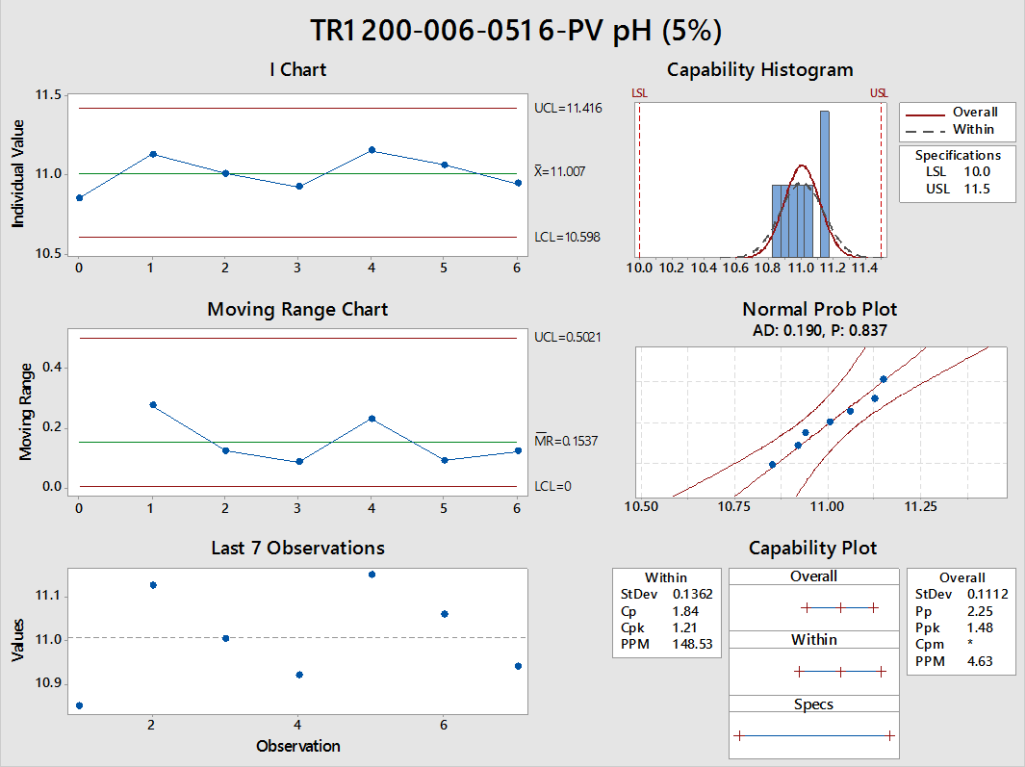
There are no OOL data points noted for Absorbance, however there is one OOT data point at T=1. This is likely due to analyst preparation of the sample or cuvettes. All data are within specification and considered acceptable.

Graph 14: TR1200-006-0516-PV Assay



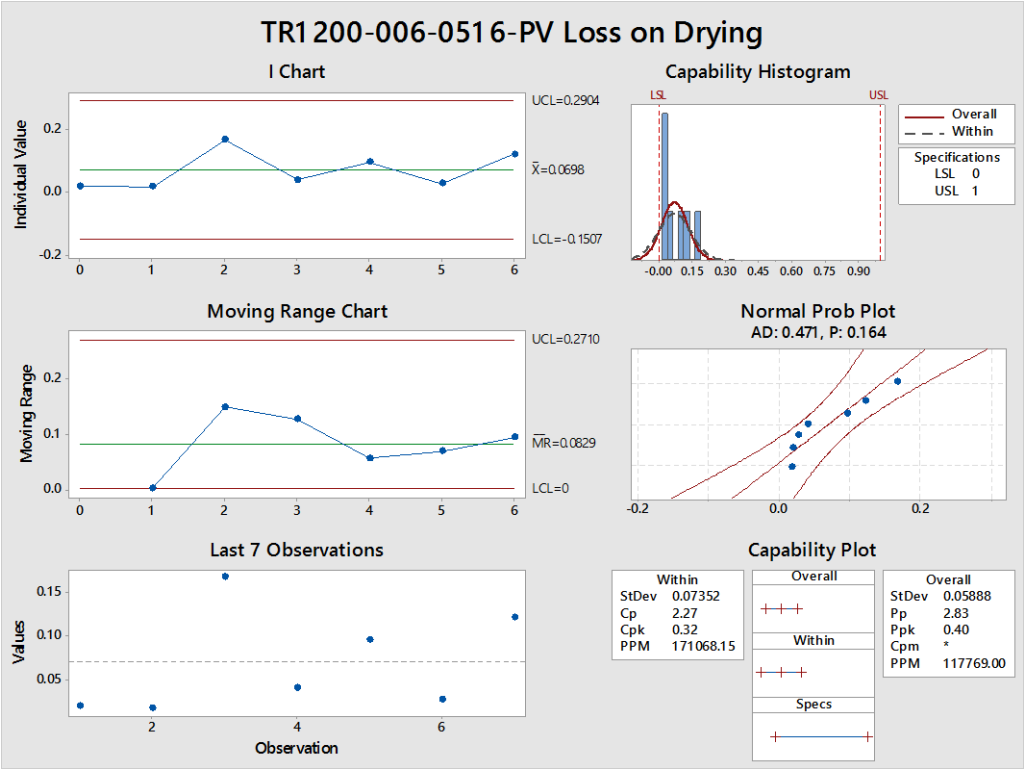
There are no OOL data points noted for Assay. As noted under Graph 2, variations in Assay may be attributed to pH calibrations being performed on different days.

Graph 15: TR1200-006-0516-PV pH (5%)



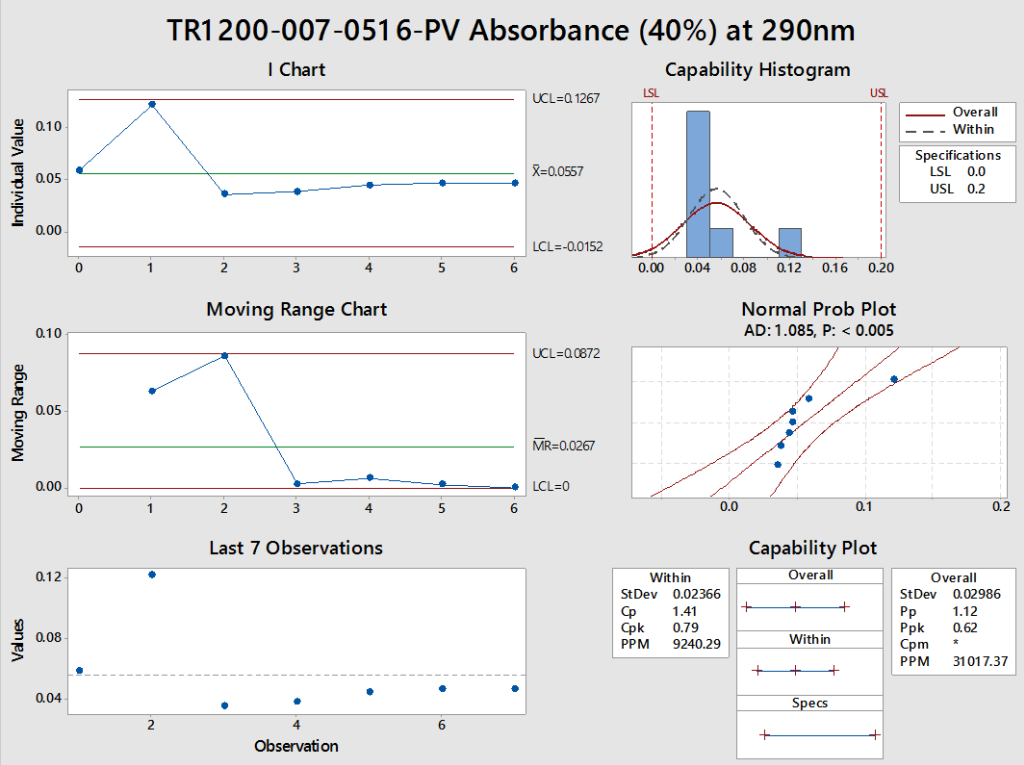
There are no OOL data points noted for pH. As noted under Graph 3, variations may be attributed to pH calibrations being performed on different days.

Graph 16: TR1200-006-0516-PV Loss on Drying



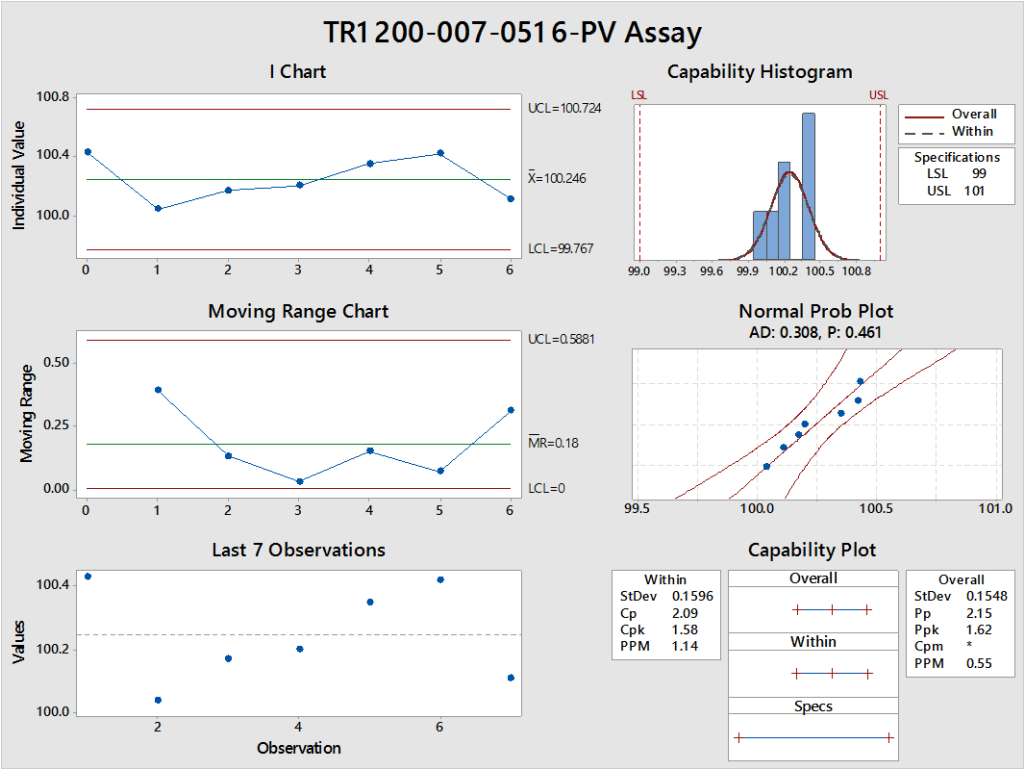
There are no OOL data points noted for Loss on Drying.

Graph 17: TR1200-007-0516-PV Absorbance (40%) at 290nm



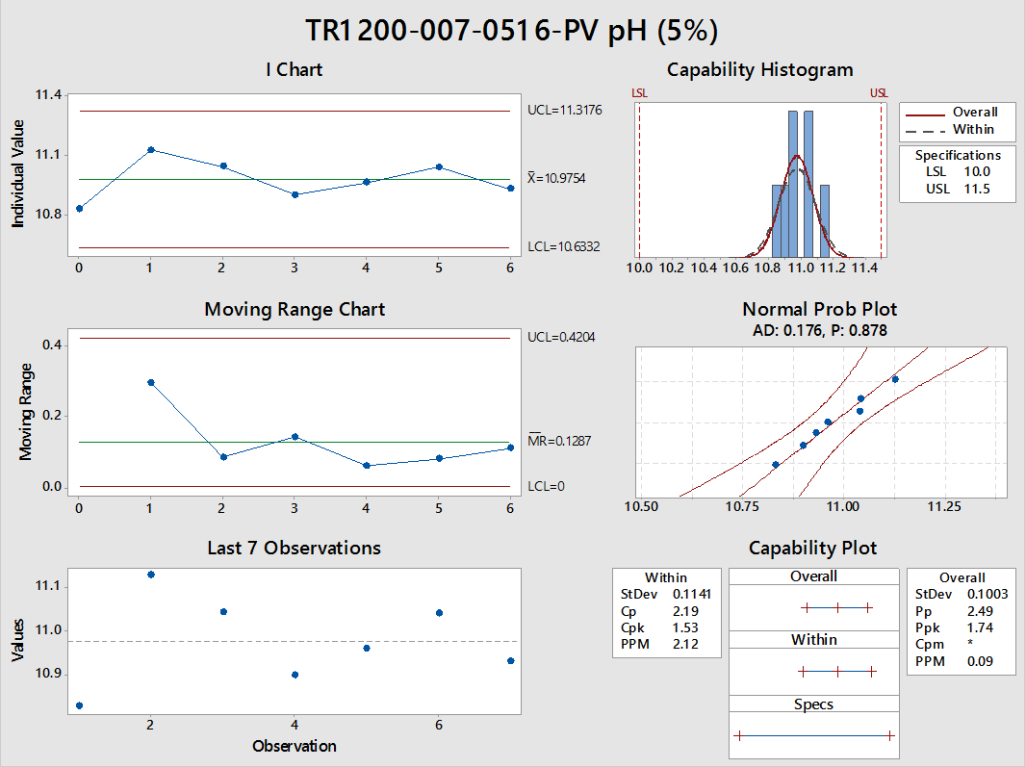
There are no OOL data points noted for Absorbance, however there is one OOT data point at T=1. This is likely due to analyst preparation of the sample or cuvettes. All data are within specification and considered acceptable.

Graph 18: TR1200-007-0516-PV Assay



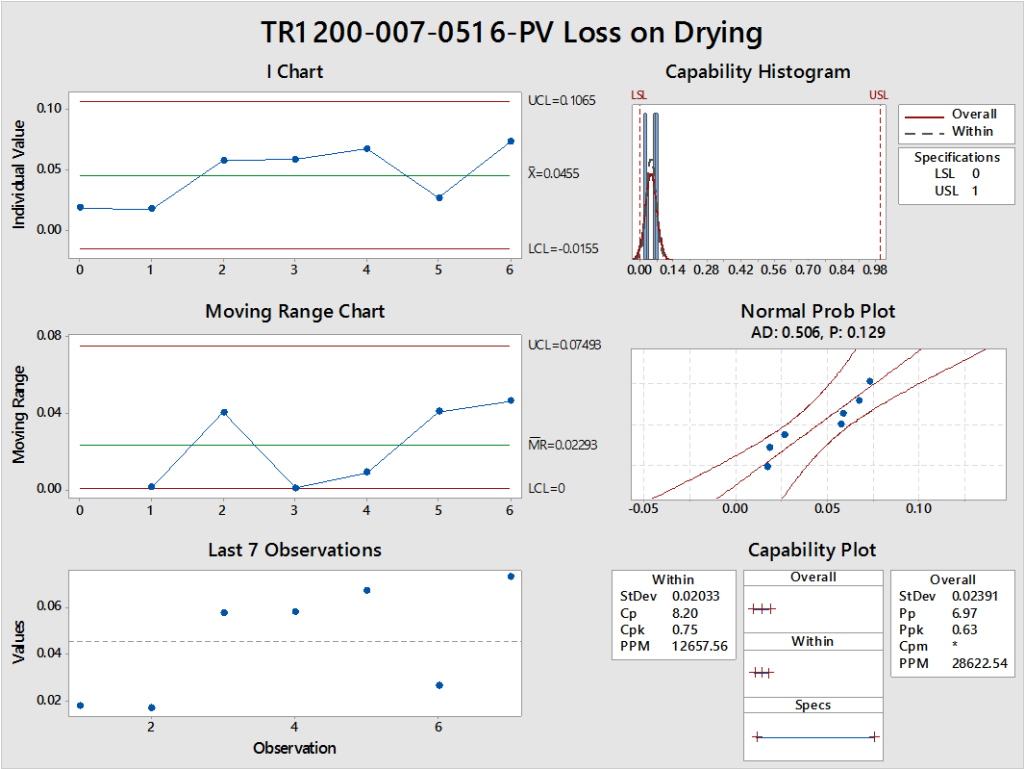
There are no OOL data points noted for Assay. As noted under Graph 2, variations in Assay may be attributed to pH calibrations and standardizations being performed on different days.

Graph 19: TR1200-007-0516-PV pH (5%)



There are no OOL data points noted for pH. As noted under Graph 3, variations may be attributed to pH calibrations being performed on different days.

Graph 20: TR1200-007-0516-PV Loss on Drying



There are no OOL or OOT data points noted for Loss on Drying.

Conclusion:

All data met the specifications set forth in the Stability Program. All lots have Cp values greater than the calculated Cpk, indicating a stable process. A proposed two year retest date will be assigned to all Tris Bio FUISA and Tris Bio Active lots manufactured at BioSpectra in the Bangor, PA facility.

Statement of Commitment

- BioSpectra is responsible for the following regarding API Stability Data in this report:
  - All ongoing stability data points obtained from this program will be submitted to the DMF on an annual basis.
  - 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.
  - 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.
  - 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.
  - In the event that any out of specification results are confirmed, all authorized users of the material will be notified.

TRIS BIO FUISA AND BIO ACTIVE
LONG TERM STABILITY REPORT
2016 VALIDATION

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the stability of Tris Bio FUISA Grade and Bio Active Grade manufactured in API Suite 3, Room E04 of BioSpectra's Bangor, PA facility. Samples were initially placed on the Stability Testing Program in May 2016 consisting of one Tris Bio Active Process Validation batch and four Tris Bio FUISA Process Validation batches. 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, notated as T_0, T_3, T_6, T_9, T_{12}, T_{18}, T_{24}, and T_{36}. Analysis has been conducted for a total of thirty six months in order to assure that the manufactured product remains stable under the specified conditions and for the specified interval of time.

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 Testing Program. The data was also analyzed utilizing I Charts with an explanation of the trend. All quantitative data was analyzed using these methods. The data can be found in the Tris Real Time Stability Program binders as well as attached to this report.

This Stability Study assesses the stability of one Tris Bio Active Grade lot and four lots of Tris Bio FUISA Grade up to the T_{36} pull date. This material was placed on stability on 05/23/16 and the T_{36} sample was taken on 5/26/19. The study included the following analysis: Absorbance (40%) @ 290 nm, Assay, Identification (IR), pH (5%), and Loss on Drying as determined by the stability indicating report. BDI18-09 was initiated for Absorbance (40%), Identification (IR) and pH (5%) not being performed at T=12. All remaining Identification (IR) results met requirements and were not analyzed as they are qualitative.

2. DEFINITIONS:

2.1. $\overline{X}$: The mean for I Charts
2.2. CL: Control Limit
2.3. UCL: Upper control limit, 3 sigma above the CL
2.4. LCL: Lower control limit, 3 sigma below the CL
2.5. No Shelf Life Determined: The material meets specifications and there is no calculated point at which the material is expected to fail.
2.6. OOL: Point(s) that fall outside the UCL or LCL

2.7. OOT: Out Of Trend, this means that the material still meets control limits but was not in trend with the rest of the material.

2.8. OOS: Out of Specification, for the purpose of this stability analysis, OOS will mean that there is a point(s) that fall outside of the UCL or LCL.

3. SAMPLE DESIGNATION:

Samples placed on the Stability Testing Program consisted of one Tris Bio Active Process Validation batch and four Tris Bio FUISA Process Validation batches. Stability samples from each of the batches were packaged into a small liner (Polyethylene), placed into another liner (Polyethylene) and into a round poly pail (HDPE) with the outer liner being goose-neck tied closed. These batches were placed on stability in the Zone M Warehouse located in the BioSpectra Bangor, PA facility, the samples have been moved in accordance with BCC18-40 and starting 6/22/18 the samples are on stability in room L05 located in the BioSpectra Bangor, PA facility. The type of packaging utilized in the Stability Study was based on BioSpectra packaging.

4. STORAGE:

Storage conditions have been continuously measured and recorded using MadgeTech data loggers with regulated conditions for temperature (15-30°C) and humidity (monitor) except for any of the time periods listed below.

5. INVESTIGATIONS:

5.1. BLI16-16: LOD Analysis for TR1200-005-0516-PV T=3 was questionably high in comparison to the five other Tris stability lots that were being tested. The sample was retested by two Analysts to ensure passing results. All results met specification of 1.0% maximum. An extra stability sample was taken and tested, yielding a result of 0.6279%, which also met specification. These analyses confirmed the initial result was accurate.

5.2. BDI16-08: On 1/14/16 MadgeTech Data Logger SN: Z01616 initiated an alarm for “No Readings”. Upon inspection it was found that the wireless connection was not communicating with the MadgeTech Software and the Data Logger was not visible to the software. The Data Logger was inspected and the wireless connection was re-established at this time. On 1/18/16, the Data Logger triggered another alarm for “No Readings”. No other alarms were issued during this period and therefore no impact to the products stored in the warehouse. On 1/18/16 the Data Logger SN: Z01616 was replaced with Data Logger SN: P59293. Upon further investigation it was found that the battery in Data Logger SN: Z01616 was depleting and didn’t

have enough power to support the Data Logger at this time. Due to the low power of the battery, the data logger was not visible when using the MadgeTech software and did not visibly show a low battery warning. Quarter 1 2016 Warehouse Temperature and Humidity Monitoring assessment between 1/06/2016 and 04/01/2016 had seven other data loggers recording, which ranged in temperatures between 14.73°C and 25.82°C with Relative Humidity between 7.1%RH and 73.4%RH. Furthermore, the mean kinetic temperature did not exceed 25°C. Therefore, there was no impact to the quality of the materials stored in the Bangor Zone M Warehouse Real Time Stability as a result of this discrepancy.

5.3. BDI16-42: The recorded Warehouse temperature exceeded 30°C on 07/23/16. The alarm rule is set to send notification if the Data Logger is reporting a temperature exceeding 30°C. On 7/23/16 an alarm rule "Above 28°C" was triggered at 7:30 p.m. The alarm was triggered due to the temperature on the Data Logger SN: Z00300 reaching 30.04°C at 6:40 p.m. and 31.13°C at 7:30 p.m. The Data Logger SN: Z00300 is located in the Quality Control Quarantine near a window. The Data Logger was relocated and moved closer to the wall to minimize temperature fluctuations caused by direct sunlight. Furthermore, an additional data logger was placed half way to the QC Quarantine cage. Upon analysis of Q3 2016 on 12/23/16 it was found that the Mean Kinetic Temperature did exceed 25°C but did not exceed 28°C. However, there is no impact to the material as seen in T=3 Stability Testing performed on 8/23/16 for all Tris Stability lots, as all analyses met specification.

5.4. BDI16-48: No data logger was present in the Zone M Warehouse to monitor the temperature and humidity of the Real-Time Stability and Finished Good retains on the following dates: 06/10/16 through 07/14/16 and from 08/03/16 through 09/13/16, due to reconstruction of the Warehouse and storage racking system. All Tris stability samples located in the Zone M Real-Time Stability QC Storage area were pulled utilizing the "extra" sample and tested on 10/10/16 for Absorbance (40%), Identification (IR), and Loss on Drying. There is no impact to the product, as all results were within specification and a data logger was placed in the Real-Time Stability storage area located in the Zone M Warehouse on 9/13/16 to begin recording temperature and humidity at 10-minute intervals.

5.5. BDI18-09: Absorbance (40%), Identification (IR) and pH (5%) were not performed at T=12. The Stability Summary Sheet utilized for Bio Excipient Grade was accidentally printed for the Tris Bio FUISA Grade and Bio Active Grade lots. The summary sheet printed does not list the

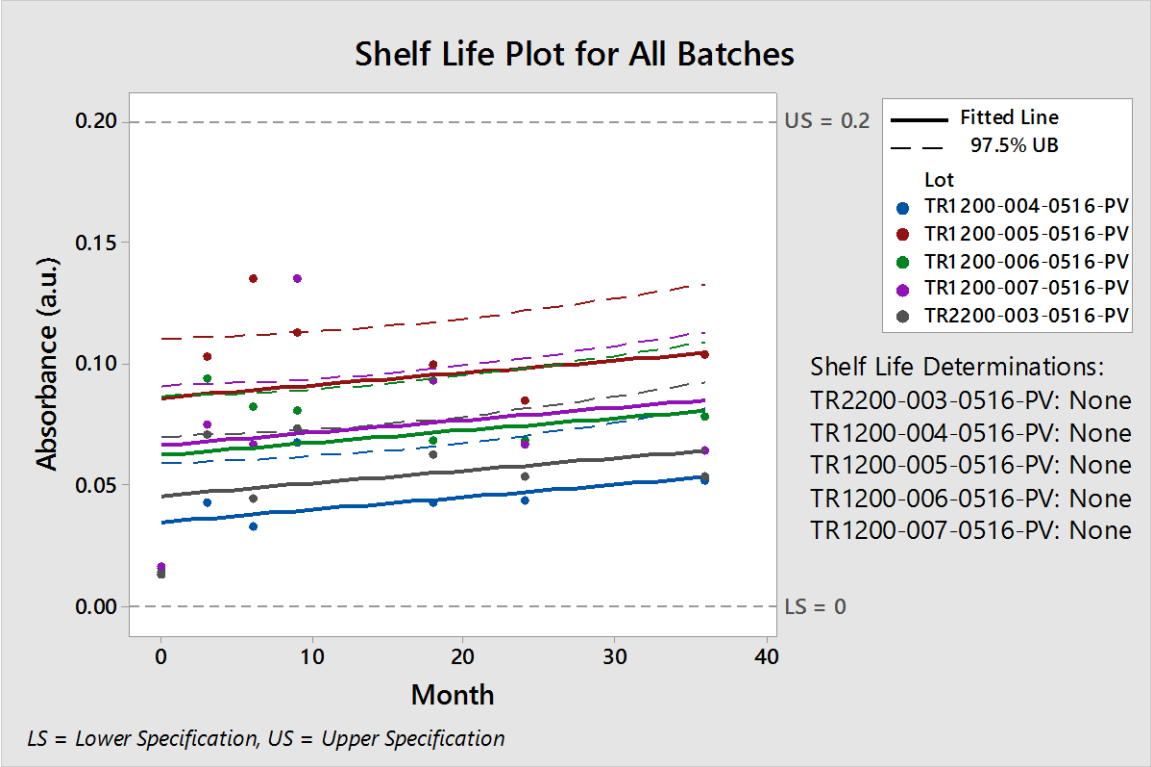
product grade and does not require Absorbance (40%), Identification (IR) and pH (5%). The summary sheets for both grades will be merged to include testing for both codes on one summary sheet. Additionally, the DCN of the summary sheets will be added to the Stability Pull Lists.

5.6. BDI18-20: The recorded Warehouse temperature was below 15°C on multiple dates ranging from 12/28/17 through 3/4/18, additionally a power outage occurred on 3/4/18. MadgeTech alarm notifications were not received for these OOS deviations. Alarms were not received due to the way alarms were established. Upon analysis of Q4 2017 on 12/18/17 to Q1 2018 on 3/6/18 it was found that the Mean Kinetic Temperature was 18.87°C, the minimum temperature was 12.20°C and the maximum temperature was 23.7°C. However, there is no impact to the material as seen in T=24 Stability Testing performed on 5/21/18 for all Tris Stability lots, as all analyses met specification and were within trend for T=0 to T=18 results.

5.7. BDI18-52: Between dates 7/3/18 and 8/7/18, the temperature in the Zone M Warehouse reached temperatures above 30°C. The Zone M Warehouse is not climate controlled; therefore, the temperature was unable to be adjusted to the specified temperature. However, there is no impact to the material as there were no products located in the Zone M Warehouse with storage temperature requirements.

6. LOT EVALUATION:

GRAPH 1: ABSORBANCE (40%) AT 290 NM

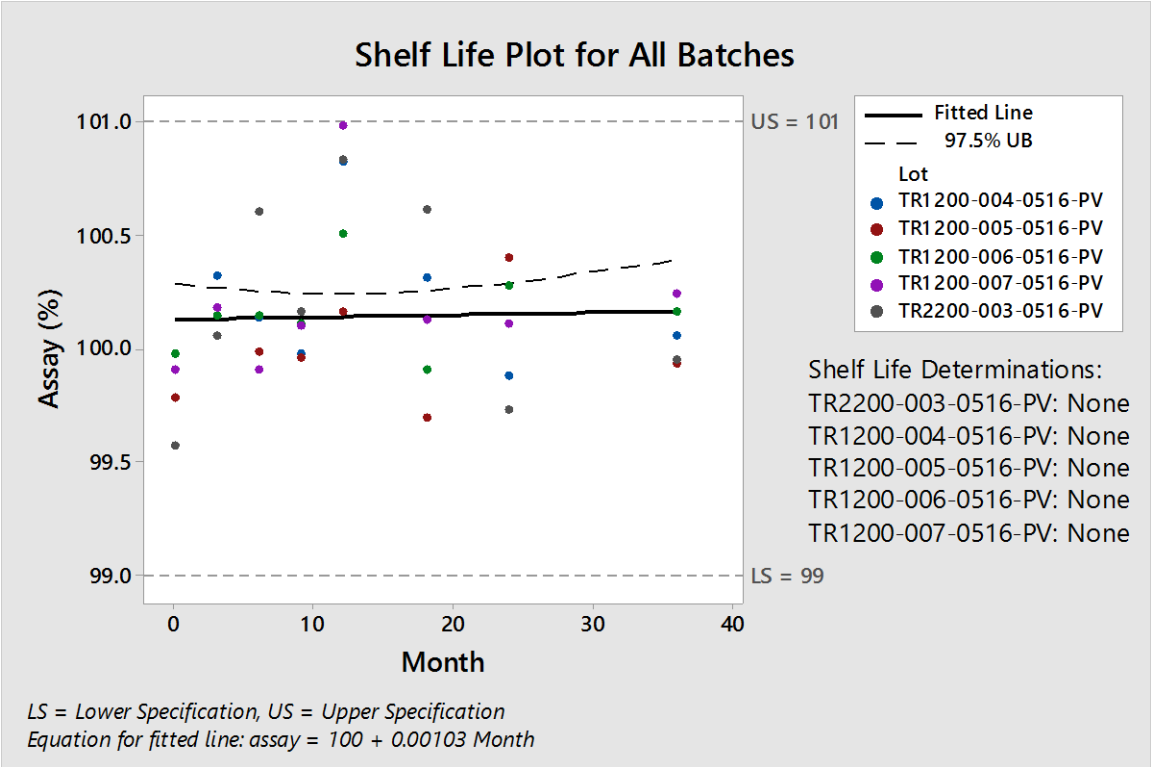


Results for 40% absorbance @ 290nm showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligable degradation of the product shown from these analyses in the 36 month analysis timeframe.

TABLE 1: ABSORBANCE (40%) AT 290 NM

Absorbance (40%)- 0.2 a.u. max @ 290nm								
Lot	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
TR2200-003-0516-PV	0.0131	0.0704	0.0443	0.0728	BDI18-09	0.0624	0.0537	0.0533
TR1200-004-0516-PV	0.0127	0.0424	0.0323	0.0677	BDI18-09	0.0425	0.0437	0.0520
TR1200-005-0516-PV	0.0135	0.1032	0.1355	0.1124	BDI18-09	0.0999	0.0847	0.1036
TR1200-006-0516-PV	0.0149	0.0939	0.0823	0.0806	BDI18-09	0.0685	0.0682	0.0781
TR1200-007-0516-PV	0.0162	0.0745	0.0669	0.1348	BDI18-09	0.0926	0.0664	0.0644

GRAPH 2: ASSAY (%)

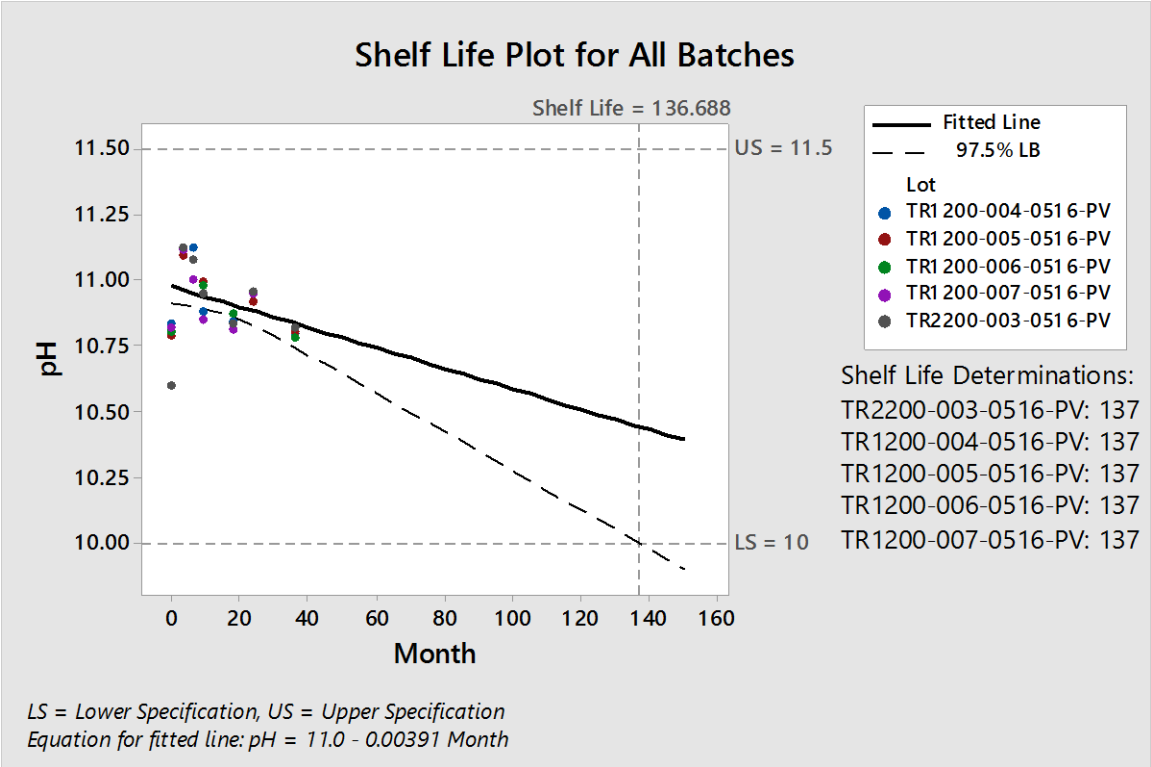


Results for Assay % showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligable degradation of the product shown from these analyses in the 36 month analysis timeframe.

TABLE 2: ASSAY (%)

Assay (Dried)- 99.0-101.0%								
Lot	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
TR2200-003-0516-PV	99.57%	100.05%	100.60%	100.16%	100.83%	100.61%	99.73%	99.95%
TR1200-004-0516-PV	99.90%	100.32%	100.13%	99.97%	100.82%	100.31%	99.88%	100.05%
TR1200-005-0516-PV	99.78%	100.18%	99.98%	99.96%	100.16%	99.69%	100.40%	99.93%
TR1200-006-0516-PV	99.97%	100.14%	100.14%	100.11%	100.50%	99.90%	100.27%	100.16%
TR1200-007-0516-PV	99.90%	100.18%	99.90%	100.10%	100.98%	100.12%	100.11%	100.24%

GRAPH 3: PH (5%)

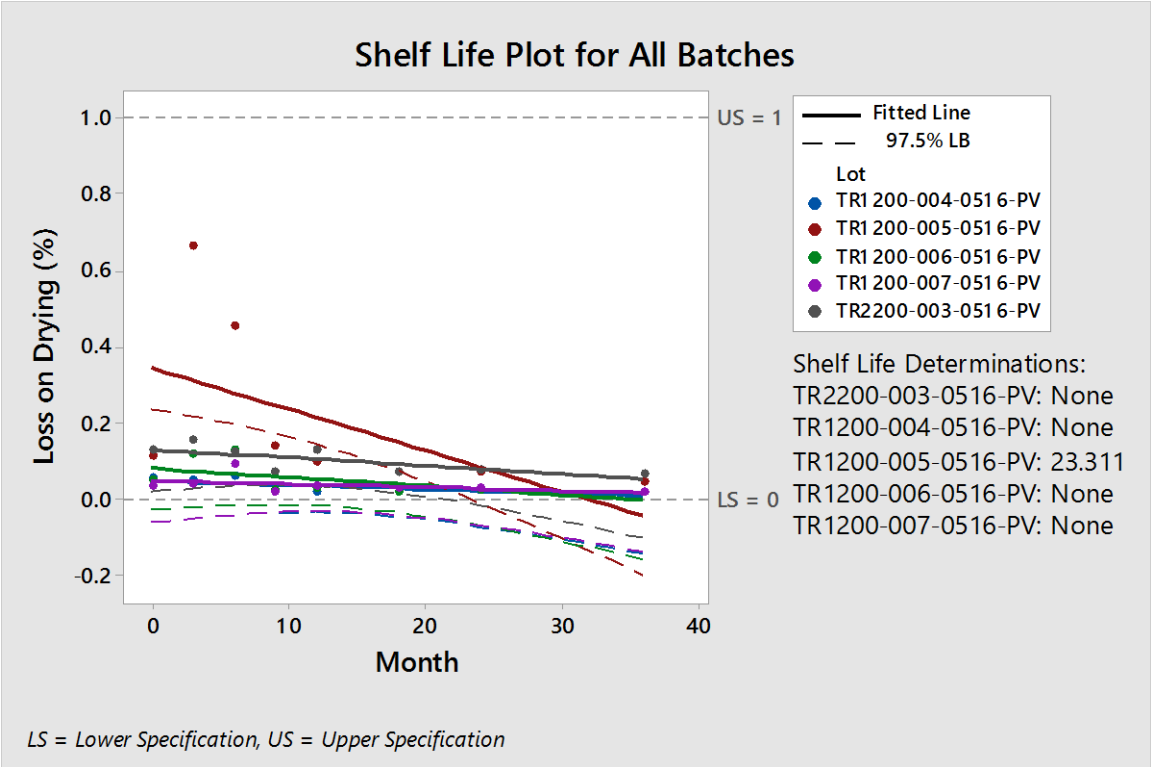


Results for pH (5%) showed a 136.688 or 137 month shelf life for all batches, which is well above the 24 month recommended retest date. This is observed as there is negligable degradation of the product shown from these analyses in the 36 month analysis timeframe.

TABLE 3: PH (5%)

pH (5% Solution)- 10.0-11.5								
Lot	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
TR2200-003-0516-PV	10.599 @ 23.78°C	11.125 @ 22.72°C	11.08 @ 21.3°C	10.95 @ 22.6°C	BDI18-09	10.83 @ 23.9°C	10.954 @ 19.24°C	10.815 @ 2319°C
TR1200-004-0516-PV	10.831 @ 23.64°C	11.124 @ 22.66°C	11.12 @ 21.5°C	10.88 @ 22.2°C	BDI18-09	10.84 @ 24.0°C	10.953 @ 19.26°C	10.794 @ 23.49°C
TR1200-005-0516-PV	10.786 @ 23.49°C	11.092 @ 22.57°C	11.08 @ 21.4°C	10.99 @ 22.2°C	BDI18-09	10.83 @ 24.0°C	10.920 @ 19.19°C	10.803 @ 23.04°C
TR1200-006-0516-PV	10.803 @ 23.31°C	11.115 @ 22.47°C	11.08 @ 21.1°C	10.98 @ 22.3°C	BDI18-09	10.87 @ 24.0°C	10.954 @ 19.26°C	10.781 @ 23.02°C
TR1200-007-0516-PV	10.819 @ 22.96°C	11.116 @ 22.43°C	11.00 @ 21.6°C	10.85 @ 22.3°C	BDI18-09	10.81 @ 24.0°C	10.949 @ 19.24°C	10.818 @ 23.43°C

GRAPH 4: LOSS ON DRYING (%)



The only Shelf Life determined for Loss on Drying % was 23.311 months for TR1200-005-0516-PV. This Shelf Life was predicted due to the Loss on Drying % being close to the Lower Specification of 0%. The Lower Specification (LS) was set as an arbitrary specification for this analysis at 0% as it is not possible to achieve an LOD of <0%. An LOD that approaches zero is not a concern as there is only a maximum specification of 1.0%.

TABLE 4: LOSS ON DRYING (%)

Loss on Drying- 1.0% max								
Lot	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
TR2200-003-0516-PV	0.1257%	0.1528%	0.1195%	0.0680%	0.1277%	0.0718%	0.0735%	0.0632%
TR1200-004-0516-PV	0.0524%	0.0486%	0.0578%	0.0234%	<0.0176%	<0.0150%	<0.0271%	0.0183%
TR1200-005-0516-PV	0.1114%	0.6601%[1]	0.4507%	0.1391%	0.0958%	<0.0150%	0.0680%	0.0409%
TR1200-006-0516-PV	0.0465%	0.1182%	0.1282%	<0.0196%	<0.0258%	<0.0150%	<0.0235%	0.0150%
TR1200-007-0516-PV	0.0316%	0.0397%	0.0886%	<0.0183%	0.0335%	0.0258%	<0.0275%	0.0178%

TABLE 5: TABULATED SUMMARY OF 2016 STABILITY LOTS

Lot	Analysis	Spec.	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
TR2200-003-0516-PV	Absorbance (40%)	0.2 a.u. max @ 290nm	0.0131	0.0704	0.0443	0.0728	BDI18-09	0.0624	0.0537	0.0533
	Assay (Dried)	99.0-101.0%	99.57%	100.05%	100.60%	100.16%	100.83%	100.61%	99.73%	99.95%
	pH (5% Solution)	10.0-11.5	10.599 @ 23.78°C	11.125 @ 22.72°C	11.08 @ 21.3°C	10.95 @ 22.6°C	BDI18-09	10.83 @ 23.9°C	10.954 @ 19.24°C	10.815 @ 2319°C
	Loss on Drying	1.0% max	0.1257%	0.1528%	0.1195%	0.0680%	0.1277%	0.0718%	0.0735%	0.0632%
TR1200-004-0516-PV	Absorbance (40%)	0.2 a.u. max @ 290nm	0.0127	0.0424	0.0323	0.0677	BDI18-09	0.0425	0.0437	0.0520
	Assay (Dried)	99.0-101.0%	99.90%	100.32%	100.13%	99.97%	100.82%	100.31%	99.88%	100.05%
	pH (5% Solution)	10.0-11.5	10.831 @ 23.64°C	11.124 @ 22.66°C	11.12 @ 21.5°C	10.88 @ 22.2°C	BDI18-09	10.84 @ 24.0°C	10.953 @ 19.26°C	10.794 @ 23.49°C
	Loss on Drying	1.0% max	0.0524%	0.0486%	0.0578%	0.0234%	<0.0176%	<0.0150%	<0.0271 %	0.0183%
TR1200-005-0516-PV	Absorbance (40%)	0.2 a.u. max @ 290nm	0.0135	0.1032	0.1355	0.1124	BDI18-09	0.0999	0.0847	0.1036
	Assay (Dried)	99.0-101.0%	99.78%	100.18%	99.98%	99.96%	100.16%	99.69%	100.40%	99.93%
	pH (5% Solution)	10.0-11.5	10.786 @ 23.49°C	11.092 @ 22.57°C	11.08 @ 21.4°C	10.99 @ 22.2°C	BDI18-09	10.83 @ 24.0°C	10.920 @ 19.19°C	10.803 @ 23.04°C
	Loss on Drying	1.0% max	0.1114%	0.6601%	0.4507%	0.1391%	0.0958%	<0.0150%	0.0680%	0.0409%
TR1200-006-0516-PV	Absorbance (40%)	0.2 a.u. max @ 290nm	0.0149	0.0939	0.0823	0.0806	BDI18-09	0.0685	0.0682	0.0781
	Assay (Dried)	99.0-101.0%	99.97%	100.14%	100.14%	100.11%	100.50%	99.90%	100.27%	100.16%
	pH (5% Solution)	10.0-11.5	10.803 @ 23.31°C	11.115 @ 22.47°C	11.08 @ 21.1°C	10.98 @ 22.3°C	BDI18-09	10.87 @ 24.0°C	10.954 @ 19.26°C	10.781 @ 23.02°C
	Loss on Drying	1.0% max	0.0465%	0.1182%	0.1282%	<0.0196 %	<0.0258%	<0.0150%	<0.0235 %	0.0150%
TR1200-007-0516-PV	Absorbance (40%)	0.2 a.u. max @ 290nm	0.0162	0.0745	0.0669	0.1348	BDI18-09	0.0926	0.0664	0.0644
	Assay (Dried)	99.0-101.0%	99.90%	100.18%	99.90%	100.10%	100.98%	100.12%	100.11%	100.24%
	pH (5% Solution)	10.0-11.5	10.819 @ 22.96°C	11.116 @ 22.43°C	11.00 @ 21.6°C	10.85 @ 22.3°C	BDI18-09	10.81 @ 24.0°C	10.949 @ 19.24°C	10.818 @ 23.43°C
	Loss on Drying	1.0% max	0.0316%	0.0397%	0.0886%	<0.0183 %	0.0335%	0.0258%	<0.0275 %	0.0178%

7. CONCLUSION:

All data met the specifications set forth in the Stability Program. Shelf Life Determinations were only assigned based on the Loss on Drying % analysis and pH (5%) analysis. The shortest Shelf Life assigned was 23.2311 months; however, this Shelf Life is not a concern as this Shelf Life was predicted due to the Loss on Drying % being close to the Lower Specification of 0%. The Lower Specification (LS)

was set as an arbitrary specification for this analysis at 0% as it is not possible to achieve an LOD of <0%. An LOD that approaches zero is not a concern as there is only a maximum specification of 1.0%. The longest Shelf Life assigned was 136.688 months; however, this Shelf Life is not a concern as this Shelf Life is well above the 2-year recommended retest date. There was no significant change throughout the duration of the long-term stability profile, as indicated by all analyses meeting specifications.

A proposed two-year (24 month) retest date will continue to be assigned to all Tris Bio FUISA and Tris Bio Active lots manufactured at BioSpectra in the Bangor, PA facility.

8. STATEMENT OF COMMITMENT:

8.1. BioSpectra is responsible for the following regarding API Stability Data in this report:

8.1.1. All ongoing stability data points obtained from this program will be submitted to the DMF on an annual basis.

8.1.2. 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.

8.1.2.1. 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.

8.1.3. 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.

8.1.4. In the event that any out of specification results are confirmed, all authorized users of the material will be notified.