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

Effective Date:	10-Mar-2017		: Date of Next Review
Initiated By:	Fisher, Nicole	N/A	: Supersedes
Reason for Revision:	New document.		

Approval:

Approvers

Date	Time	Group	Name
09-Mar-2017	10:45:47 AM	DOC SPEC	Storm, Jamie
09-Mar-2017	11:05:31 AM	QUALITY	Fisher, Nicole
09-Mar-2017	11:48:32 AM	QUALITY	Hamelburg, Crystal
10-Mar-2017	01:25:17 PM	SNR MGMT	Meissner, Dora

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

Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

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

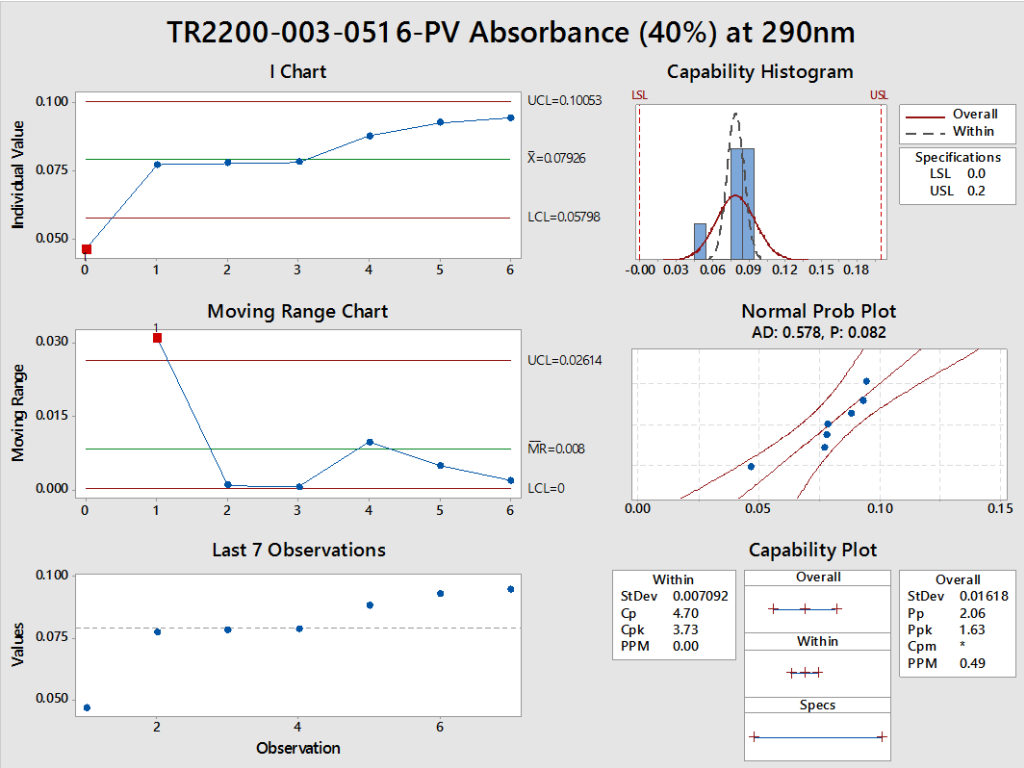
Samples initially placed on the stability program consisted of one Tris Bio Active Process Validation batch and four Tris Bio FUISA Process Validation batches. Stability samples from each of the batches were put into a round poly pail lined with two poly liners (P/P), with the outer liner being goose-neck 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:

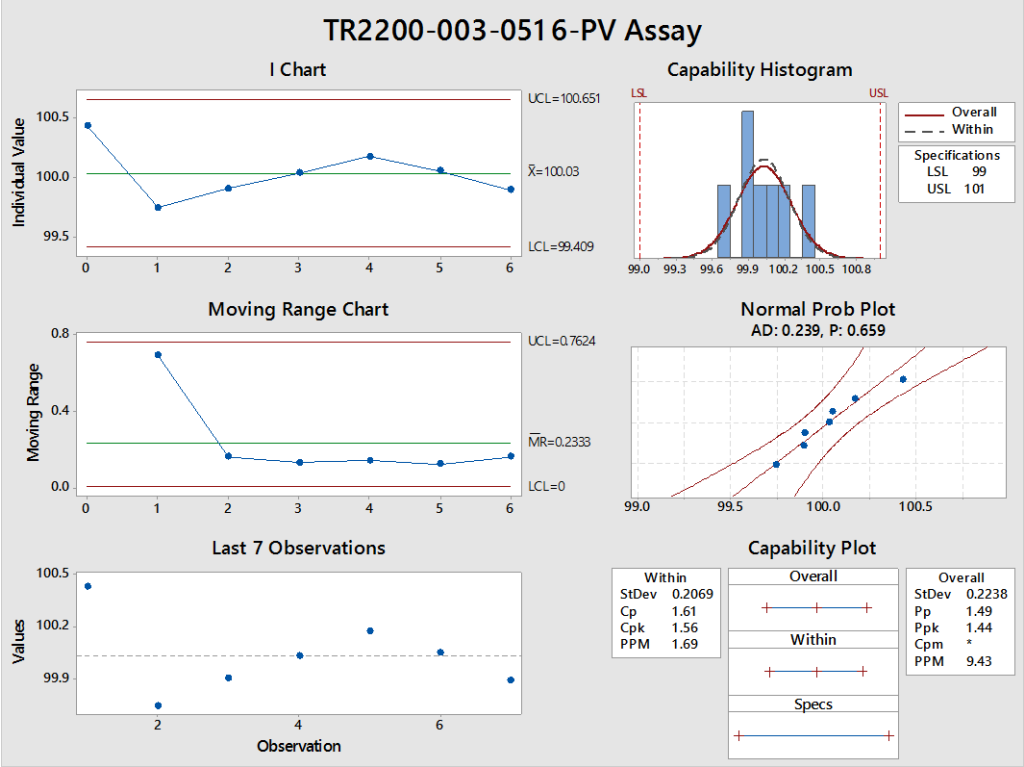
Graph 1: TR2200-003-0516-PV Absorbance (40%) at 290 nm



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.

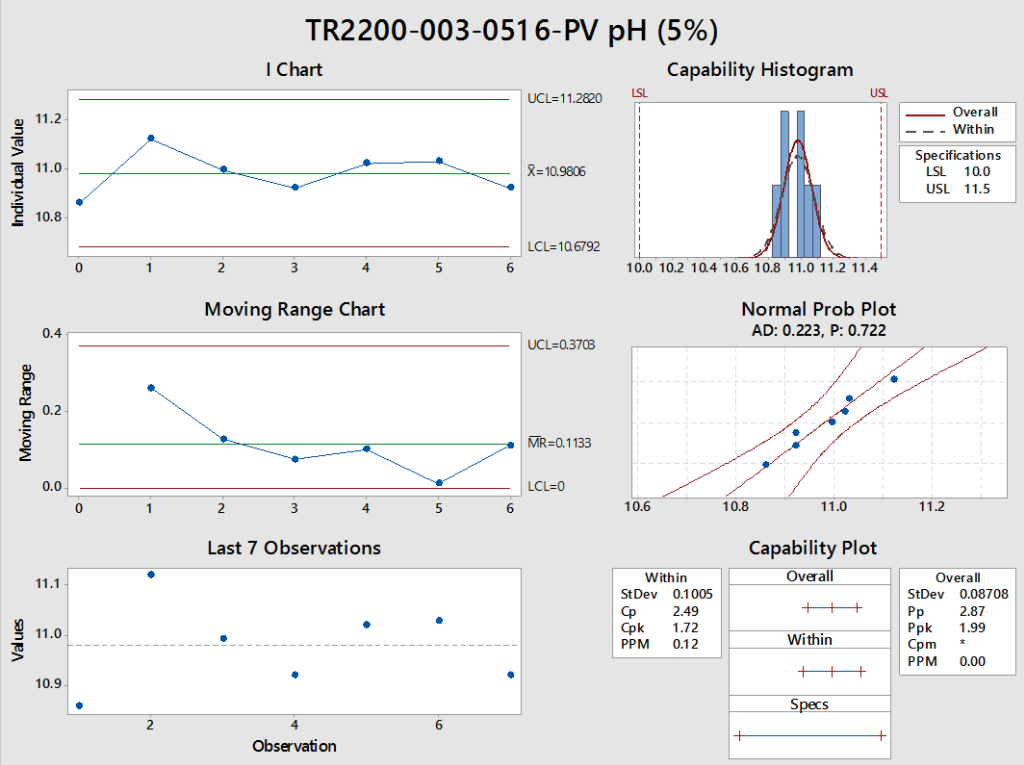
Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

Graph 2: TR2200-003-0516-PV Assay



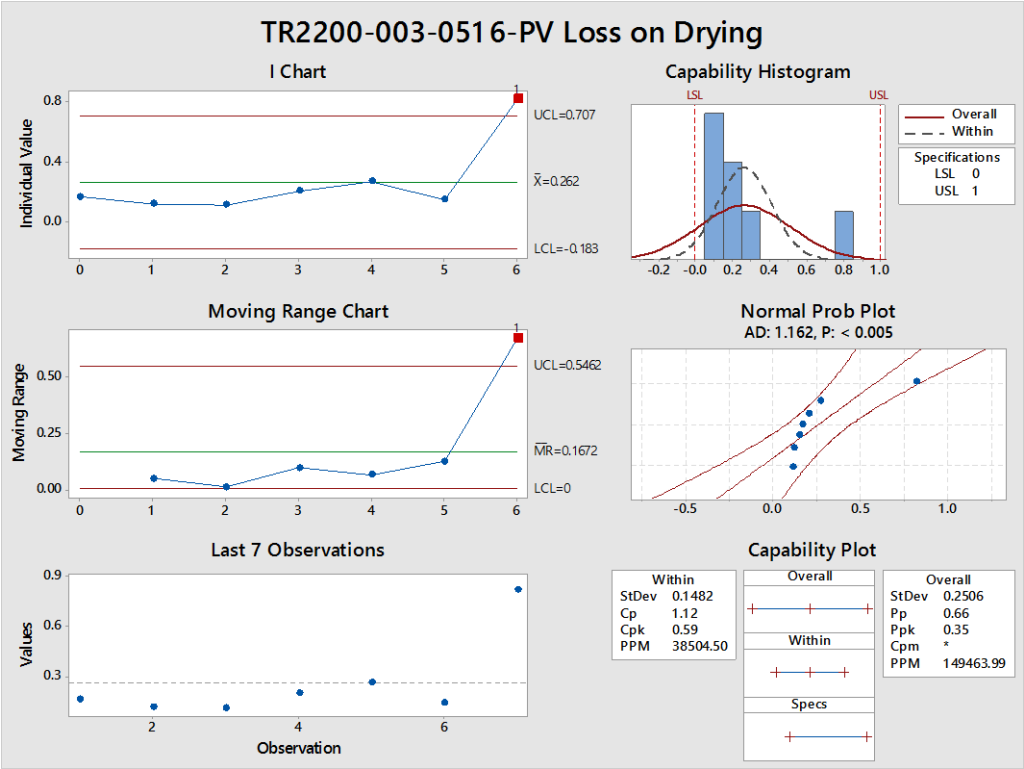
No OOL data points are shown for TR2200-003-0516-PV for Assay analysis. Variation may be attributed to the nature of the assay being performed under different pH calibrations and being standardized on different days.

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



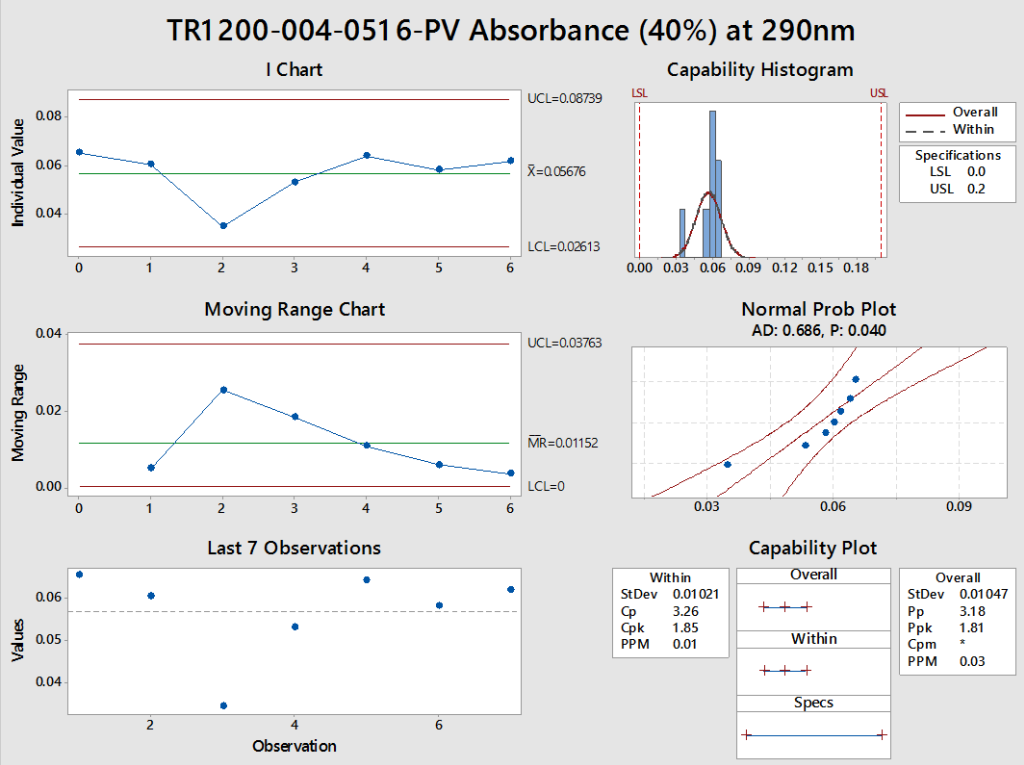
There are no OOL data points shown for pH 5% for TR2200-003-0516-PV. Variation may be attributed to pH calibrations being performed on different days. The higher pH of the T=1 sample would cause the Assay value to be lower since the titration uses hydrochloric acid. A more acidic sample would require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

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



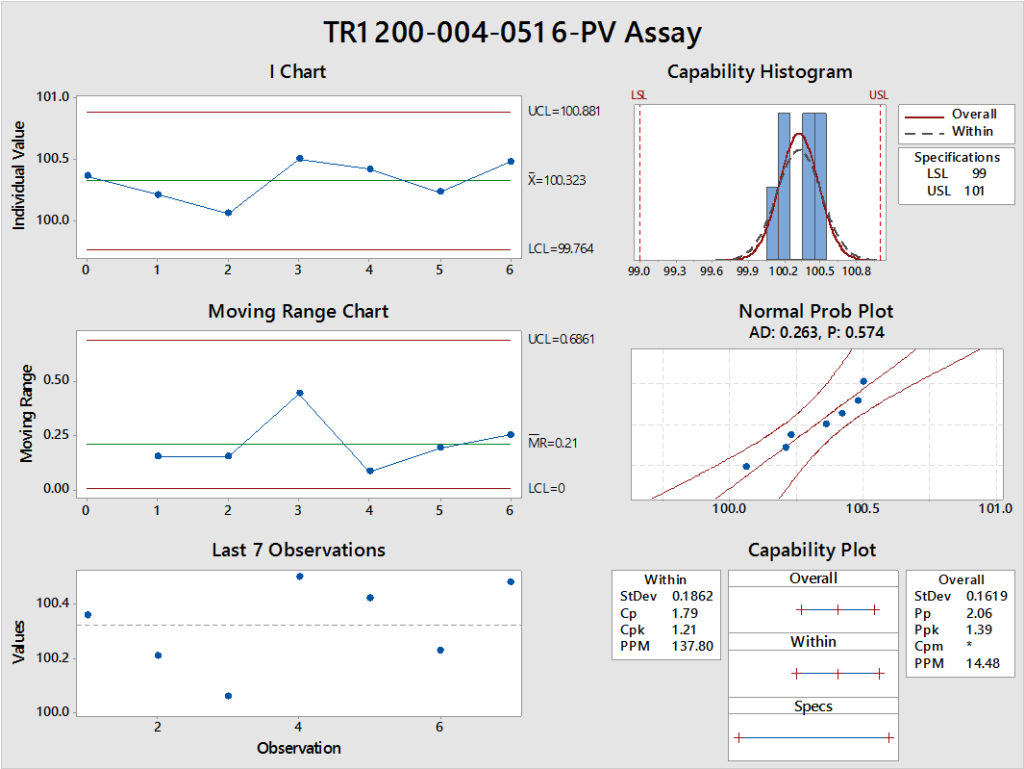
There is one OOL data point noted for the Loss on Drying for the T=6 sample. The neoprene gasket on the T=6 pail was kinked in multiple areas. This allowed for moisture to enter the pail thus increasing the Loss on Drying. SCR17-04 and SCR17-06 were initiated to evaluate the application of pail lids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

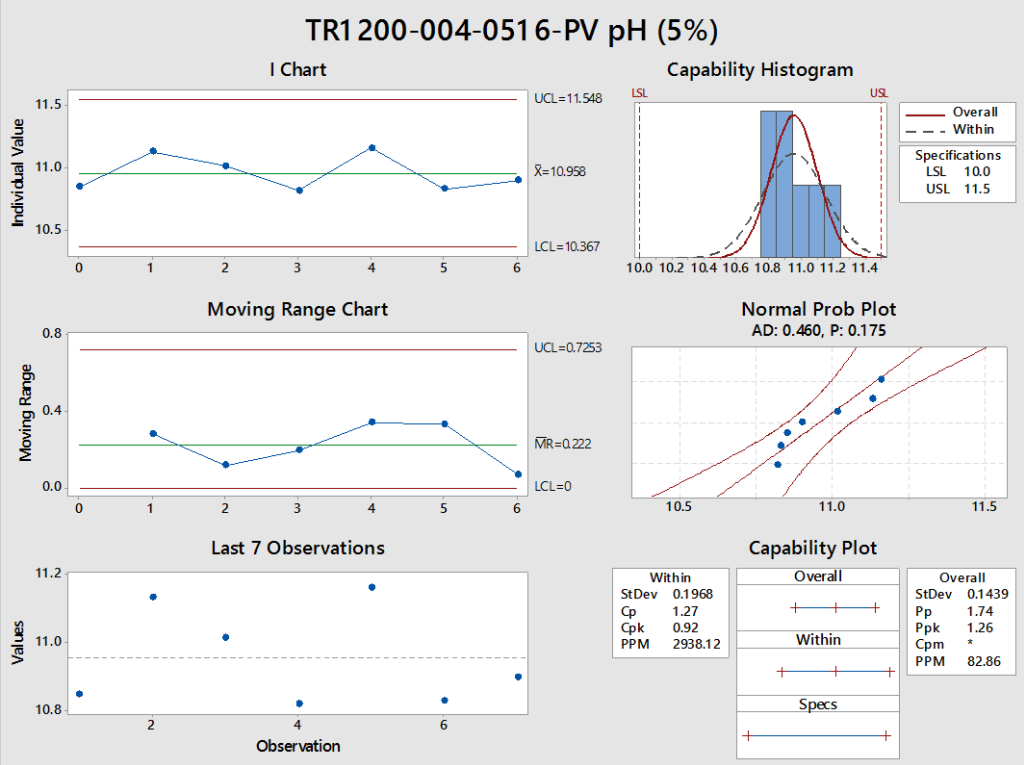
Graph 6: TR1200-004-0516-PV Assay



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.

Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

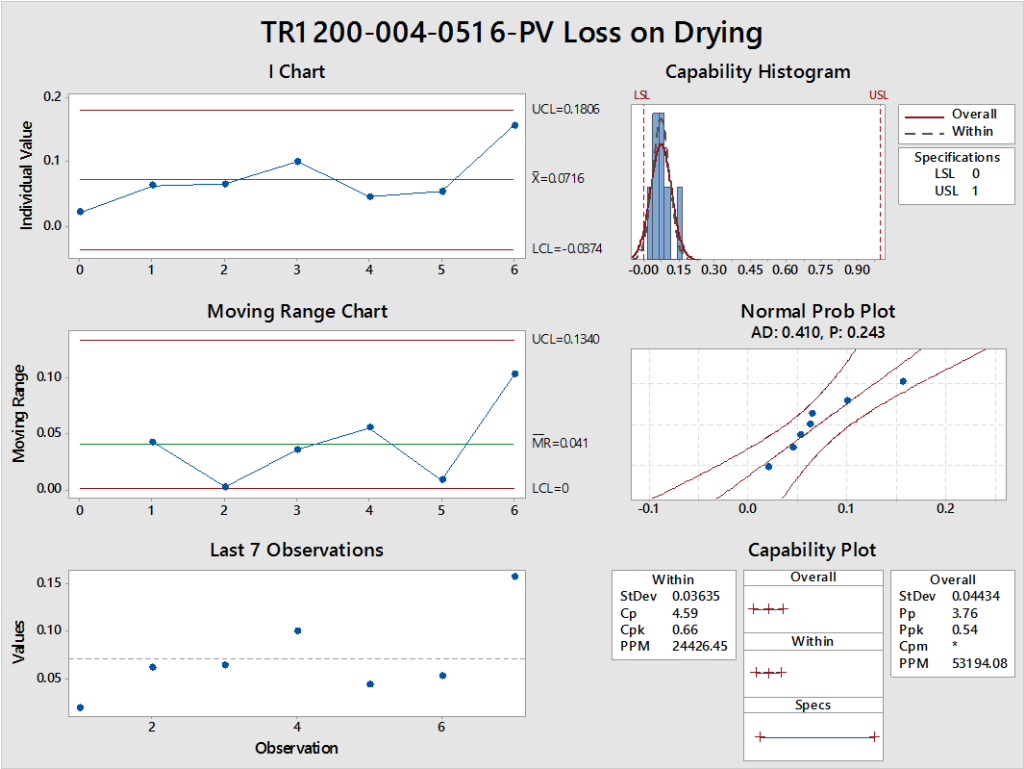
Graph 7: TR1200-004-0516-PV pH (5%)



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.

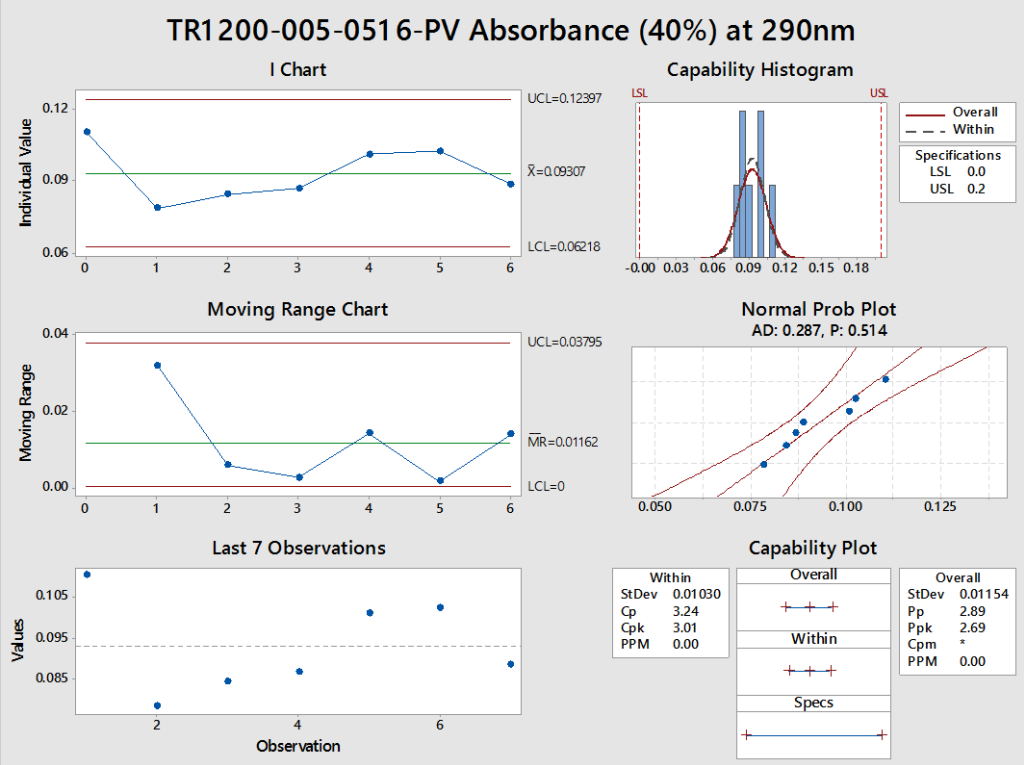
Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

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.

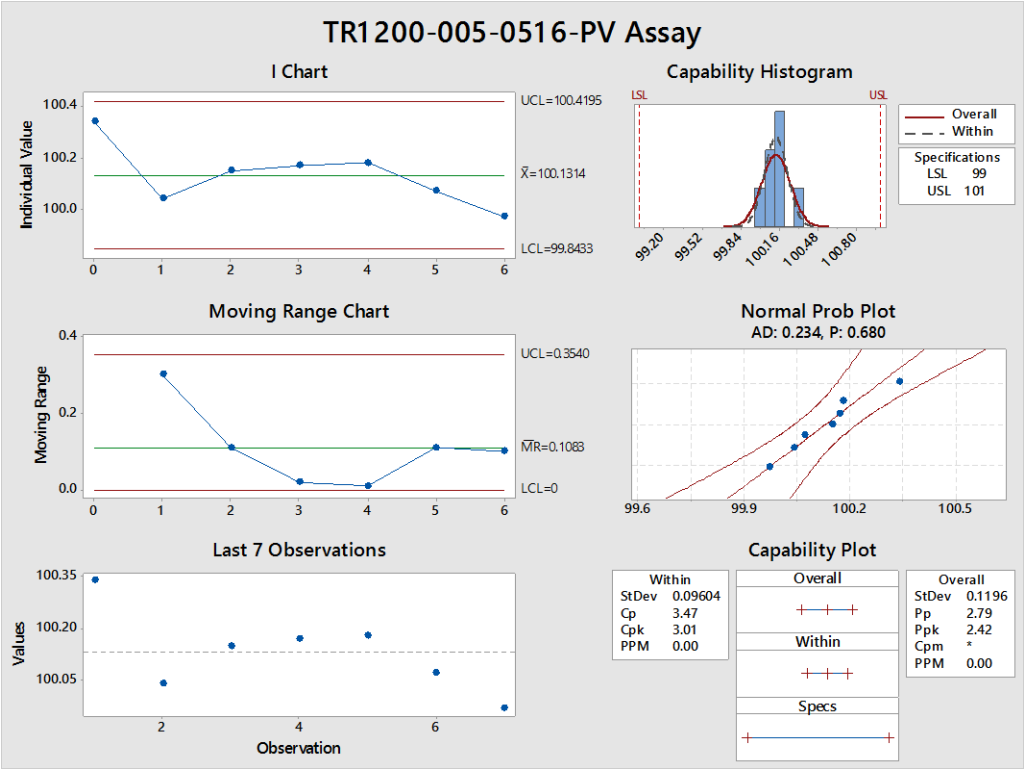
Graph 9: TR1200-005-0516-PV Absorbance (40%) at 290nm



There are no OOL or OOT data points noted.

Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

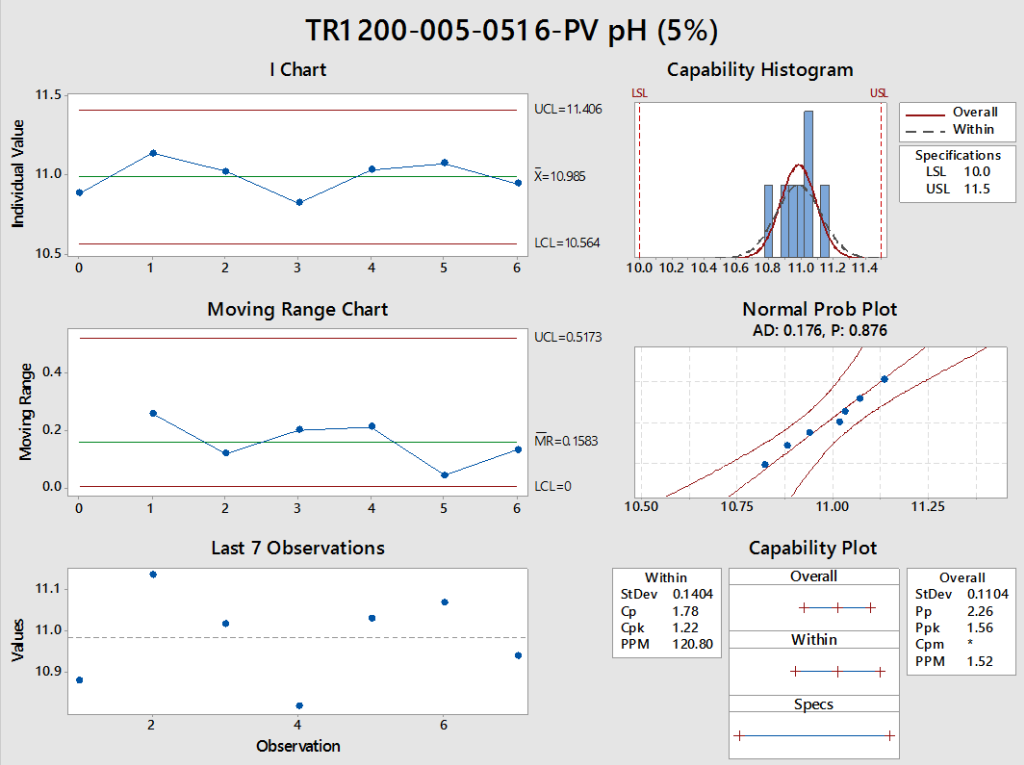
Graph 10: TR1200-005-0516-PV Assay



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.

Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

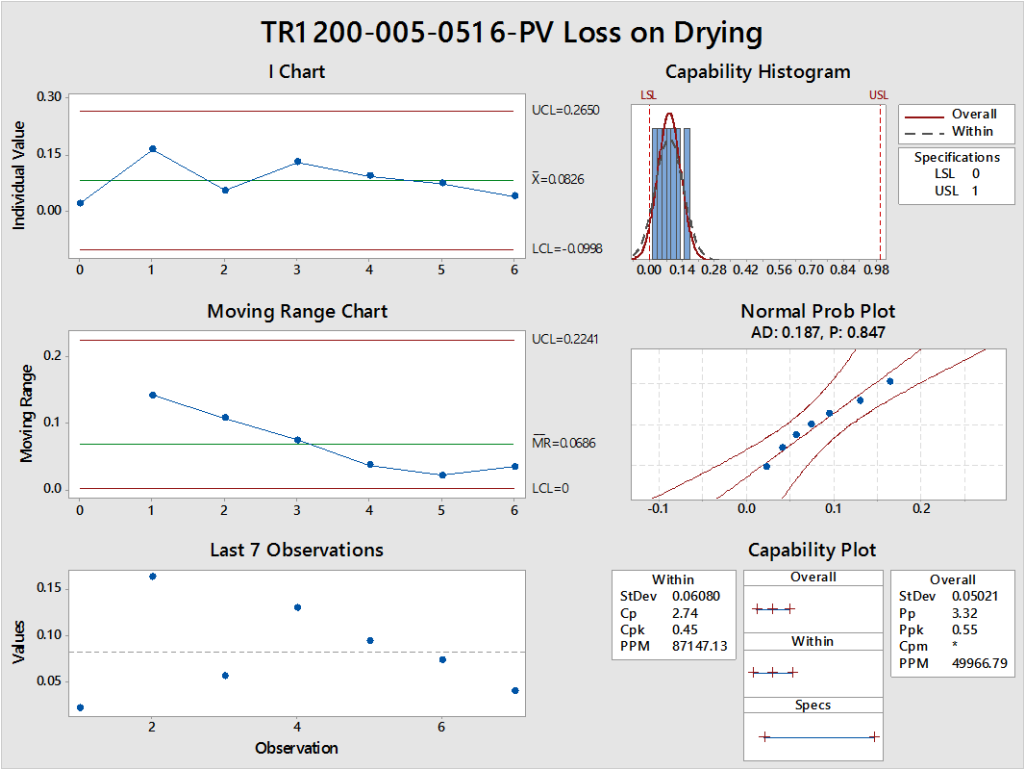
Graph 11: TR1200-005-0516-PV pH (5%)



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.

Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

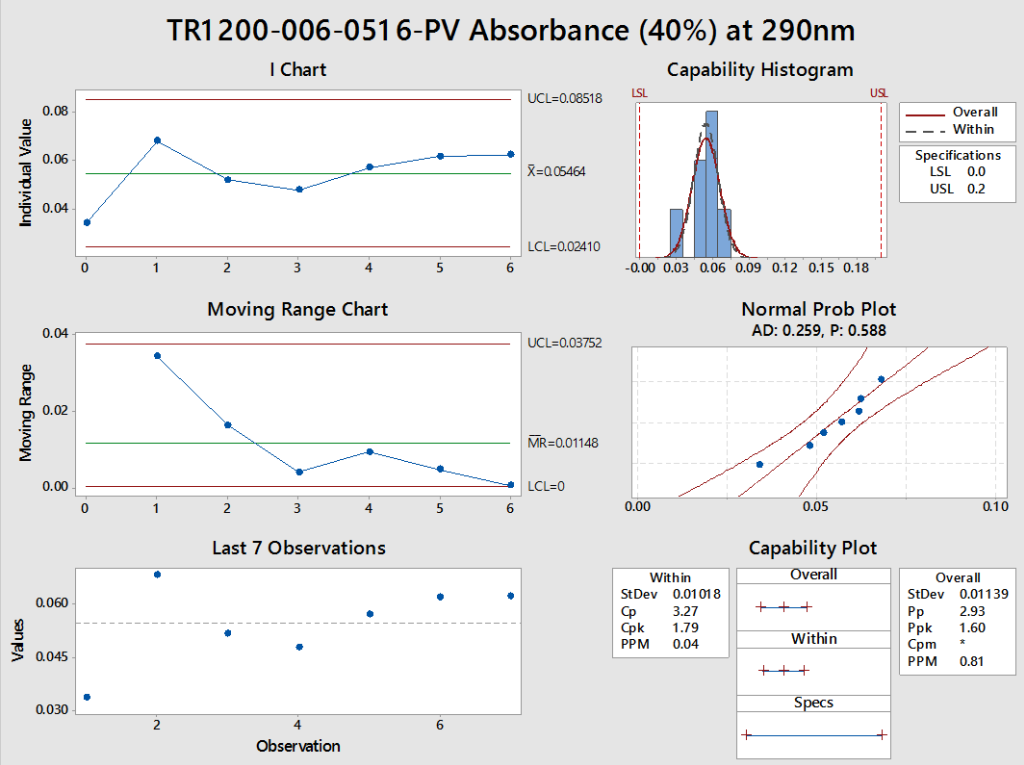
Graph 12: TR1200-005-0516-PV Loss on Drying



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

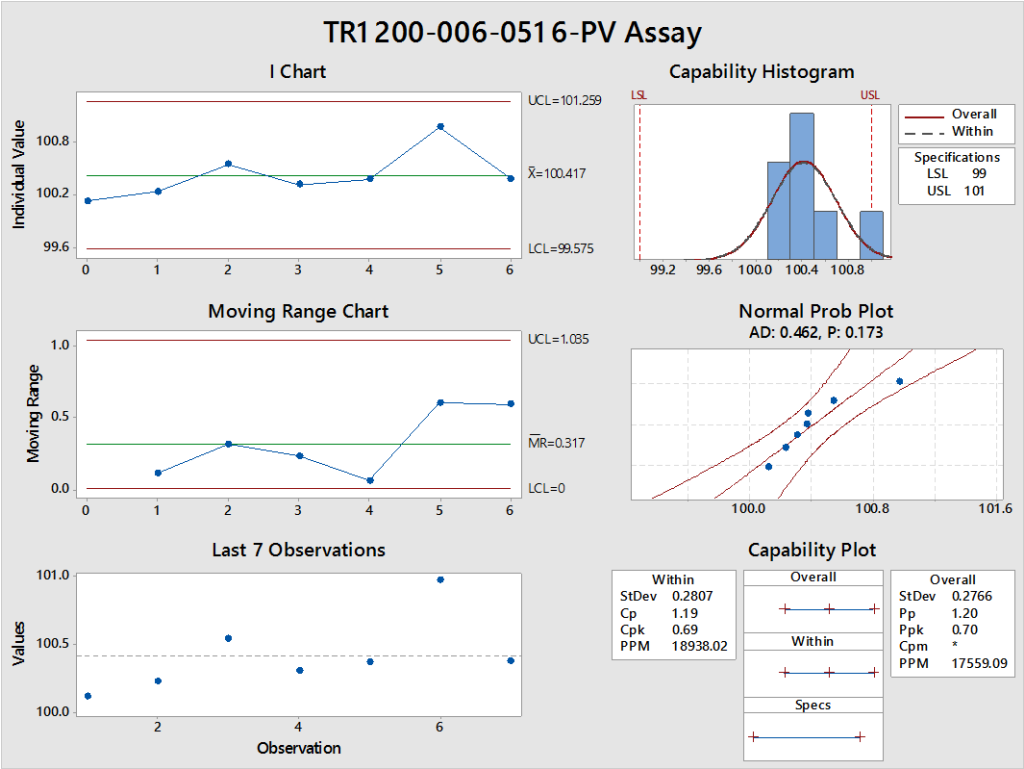
Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

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.

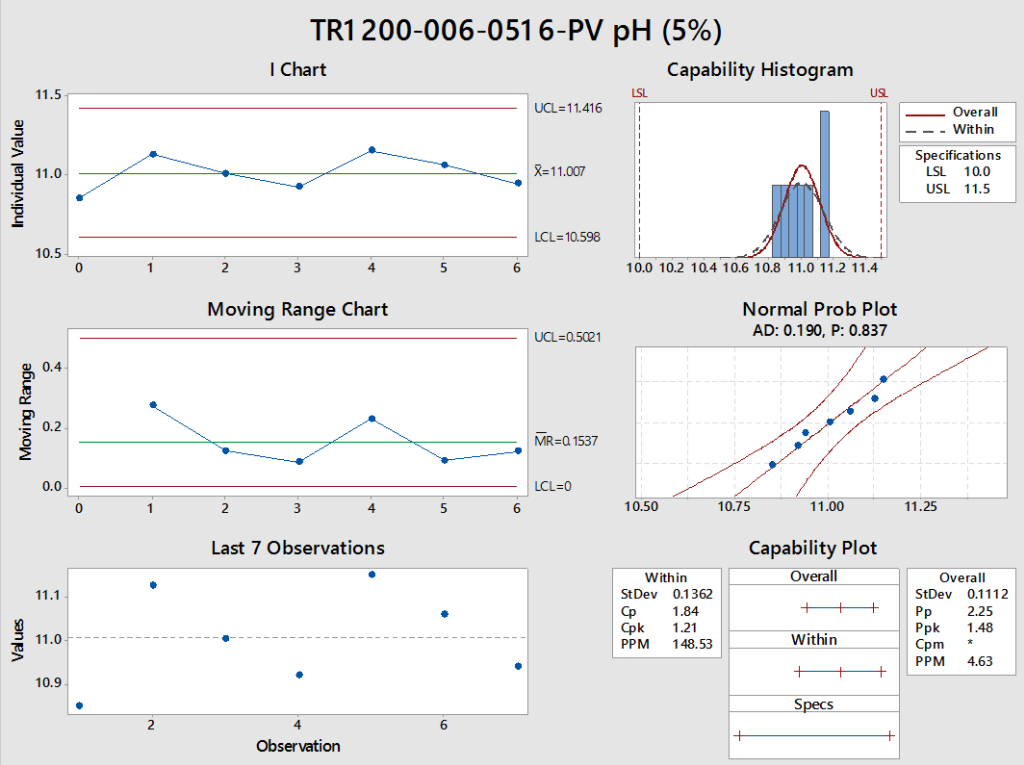
Graph 14: TR1200-006-0516-PV Assay



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.

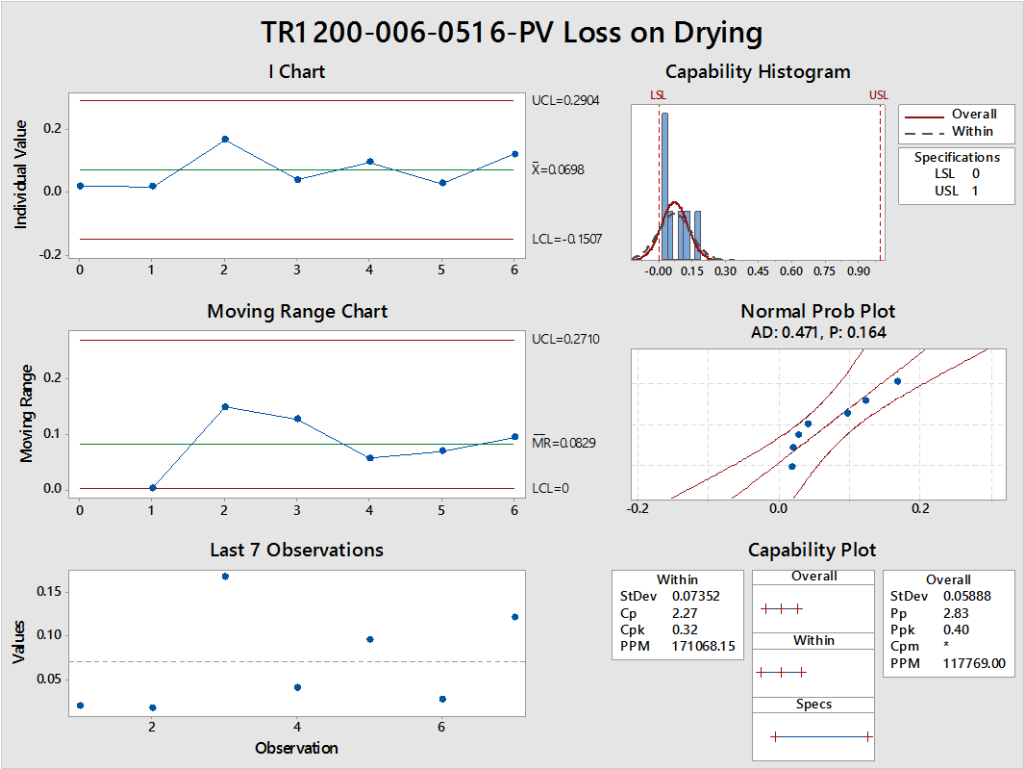
Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

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.

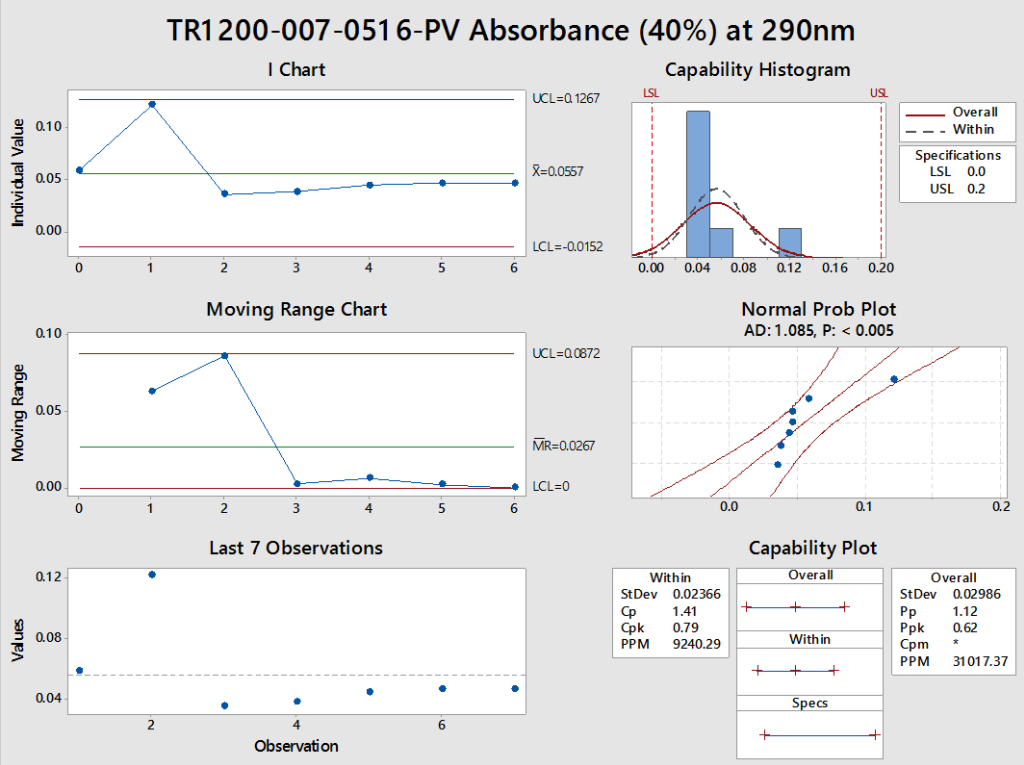
Graph 16: TR1200-006-0516-PV Loss on Drying



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

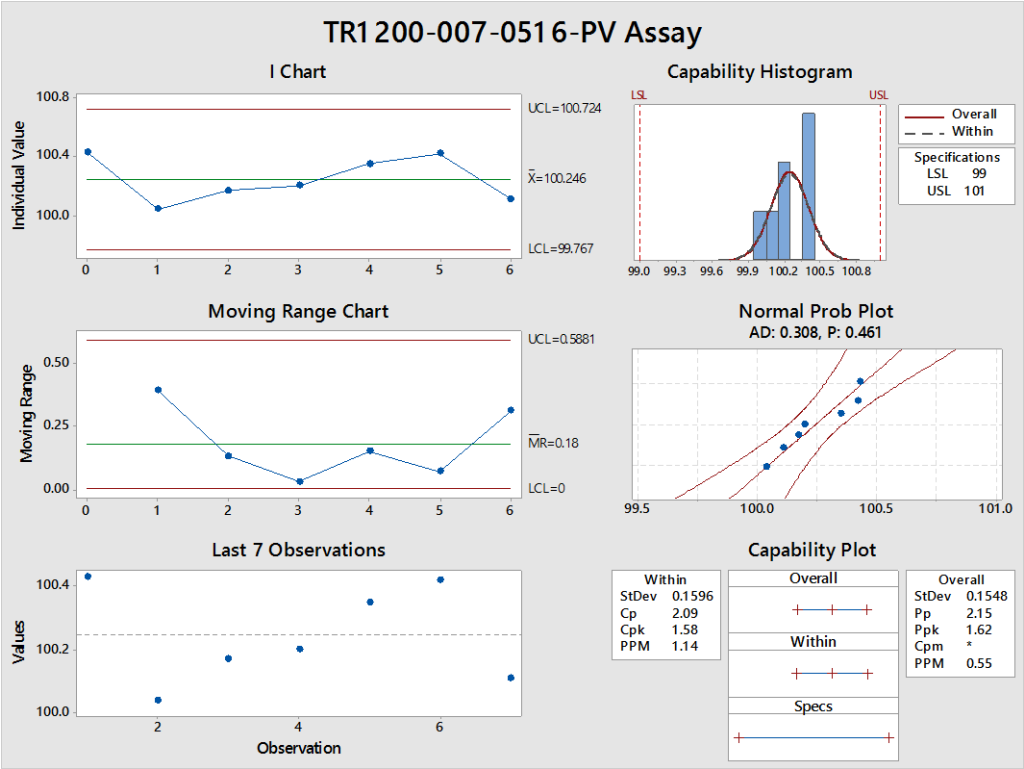
Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

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.

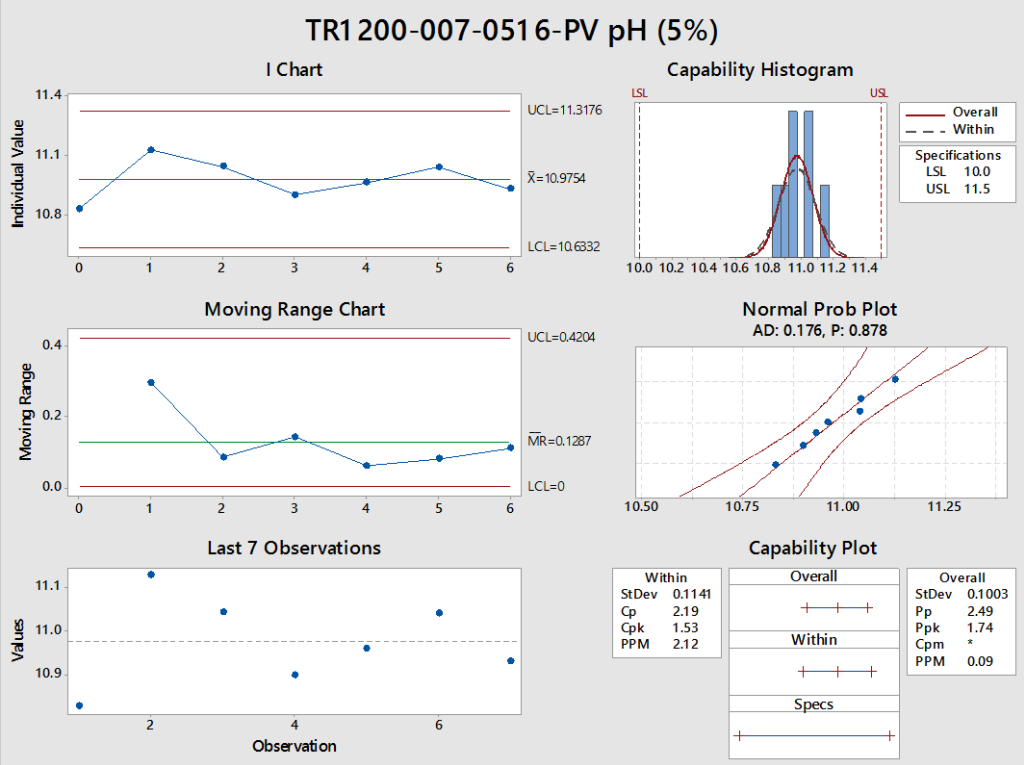
Graph 18: TR1200-007-0516-PV Assay



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.

Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

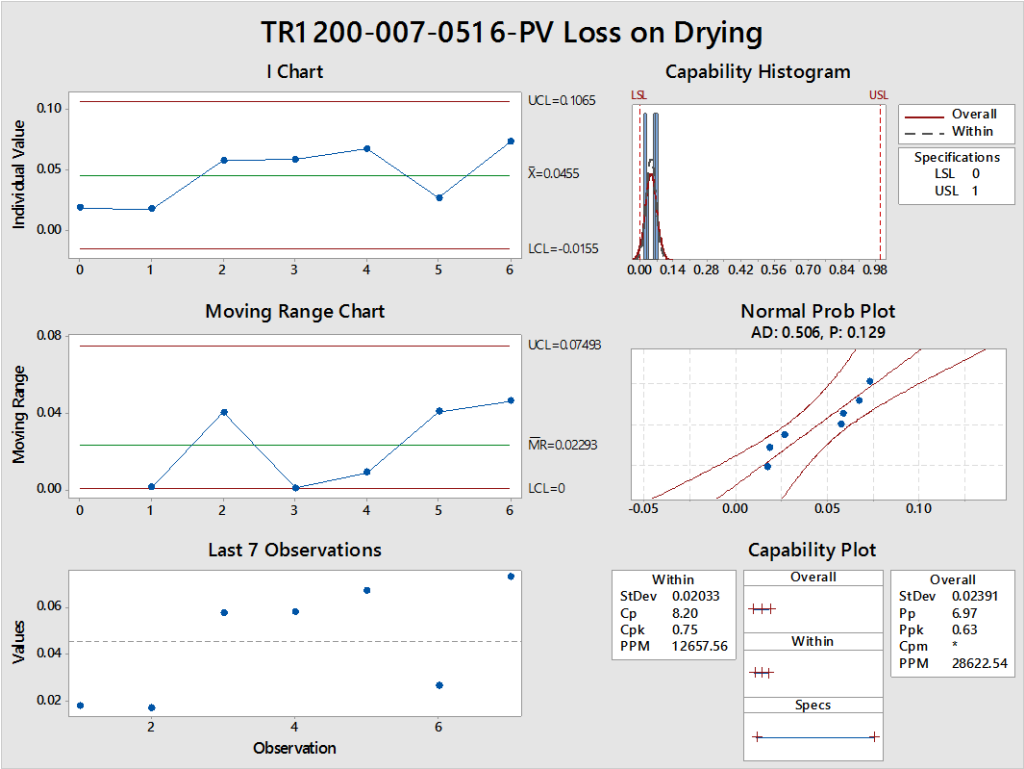
Graph 19: TR1200-007-0516-PV pH (5%)



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.

Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		

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.

Printed On:	07-Oct-2020 08:41:30 AM	Hamelburg, Crystal	: Printed By
Print Expiration:	This uncontrolled copy expires 24 hours from date of printing, or upon revision, whichever comes first.		
Notice:	The information contained herein is the property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.		