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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

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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.

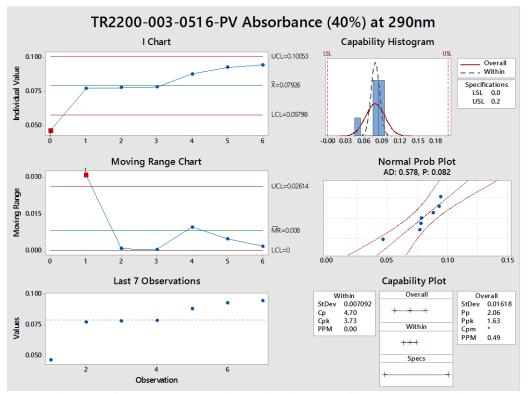
Storage

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 $40^{\circ}\text{C} + 2^{\circ}\text{C}$ 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.

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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.

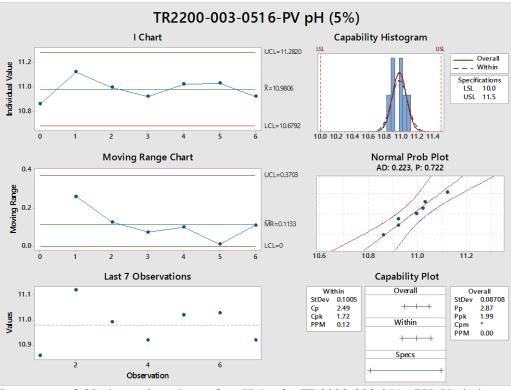
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TR2200-003-0516-PV Assay I Chart Capability Histogram UCL=100.651 ____ Overall __ - Within 100.5 Individual Value Specifications LSL 99 USL 101 X=100.03 LCL=99.409 **Moving Range Chart** Normal Prob Plot AD: 0.239, P: 0.659 8.0 UCL=0.7624 Moving Range 0.4 MR=0.2333 LCL=0 0.0 100.5 **Capability Plot** Last 7 Observations 100.5 Overall Within Overall StDev 0.2069 Cp 1.61 Cpk 1.56 PPM 1.69 0.2238 1.49 1.44 StDev Pp Ppk Cpm PPM Values Within 9.43 99.9 Specs Observation

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.

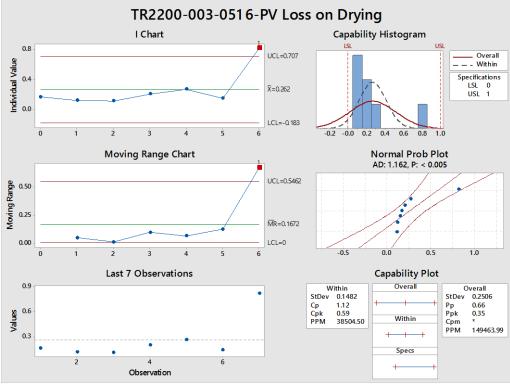
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Graph 3: TR2200-003-0516-PV pH (5%)

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.

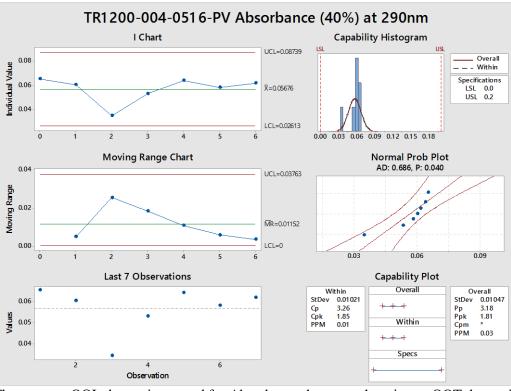
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Graph 4: TR2200-003-0516-PV Loss on Drying

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.

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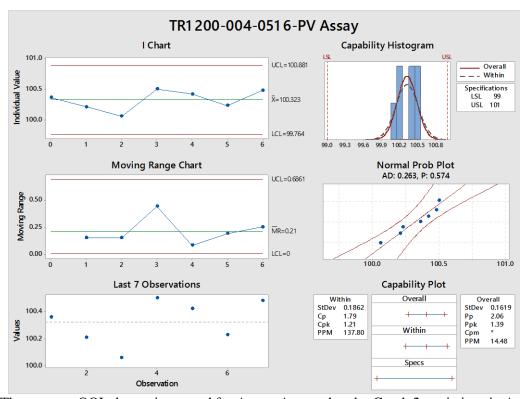


Graph 5: TR1200-004-0516-PV Absorbance (40%) at 290nm

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.

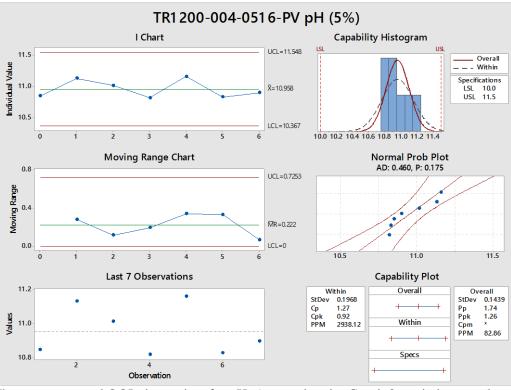
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Graph 6: TR1200-004-0516-PV Assay



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.

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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.

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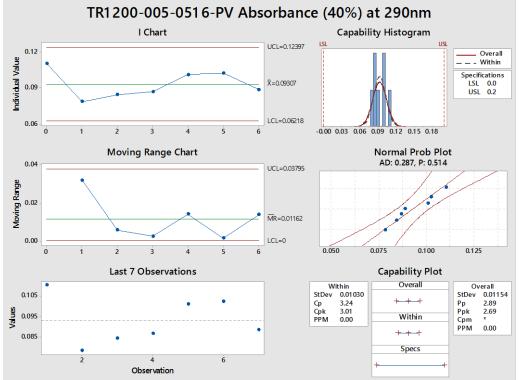
TR1 200-004-051 6-PV Loss on Drying I Chart Capability Histogram UCL=0.1806 Overall Individual Value _ _ Within Specifications LSL 0 USL 1 X=0.0716 LCL=-0.0374 -0.00 0.15 0.30 0.45 0.60 0.75 0.90 **Moving Range Chart** Normal Prob Plot AD: 0.410, P: 0.243 UCL=0.1340 Moving Range 0.05 ___ MR=0.041 LCL=0 0.00 0.2 **Capability Plot** Last 7 Observations Within Overall 0.15 StDev Cp Cpk PPM 0.03635 4.59 0.66 24426.45 StDev 0.04434 3.76 Pp Ppk Cpm PPM Values 0.10 0.54 53194.08 0.05 Specs Observation

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.

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



There are no OOL or OOT data points noted.

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TR1200-005-0516-PV Assay I Chart Capability Histogram Overall Individual Value _ _ Within 100.2 Specifications X=100.1314 LSL 99 USL 101 100.0 10016 LCL=99.8433 Normal Prob Plot AD: 0.234, P: 0.680 **Moving Range Chart** 0.4 UCL=0.3540 Moving Range 0.2 MR=0.1083 0.0 100.2 100.5 **Capability Plot** Last 7 Observations 100.35 Overall Within Overall StDev Cp Cpk PPM 0.09604 3.47 3.01 0.00 StDev Pp Ppk Cpm PPM 0.1196 2.79 2.42 Within 0.00 +++ 100.05 Specs Observation

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.

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TR1 200-005-051 6-PV pH (5%) I Chart Capability Histogram UCL=11.406 Overall Individual Value _ _ Within Specifications LSL 10.0 USL 11.5 Ā=10.985 LCL=10.564 10.5 10.0 10.2 10.4 10.6 10.8 11.0 11.2 **Moving Range Chart** Normal Prob Plot AD: 0.176, P: 0.876 UCL=0.5173 Moving Range MR=0.1583 0.0 10.50 11.00 11.25 Last 7 Observations **Capability Plot** Overall Overall StDev 0.11 Within 11.1 StDev 0.1404 Cp 1.78 Cpk 1.22 PPM 120.80 0.1104 2.26 1.56 Pp Ppk Cpm PPM Values Within 1.52 10.9 Specs Observation

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.

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TR1 200-005-051 6-PV Loss on Drying I Chart Capability Histogram 0.30 UCL=0.2650 Individual Value 0.15 Specifications LSL 0 USL 1 X=0.0826 0.00 LCL=-0.0998 0.00 0.14 0.28 0.42 0.56 0.70 0.84 0.98 **Moving Range Chart** Normal Prob Plot AD: 0.187, P: 0.847 UCL=0.2241 0.2 Moving Range MR=0.0686 LCL=0 0.0 -0.1 0.0 0.2 **Capability Plot** Last 7 Observations Within
ev 0.06080
2.74
0.45
1 87147.13 Overall StDev 0.050 Pp 3.32 Ppk 0.55 Cpm * PPM 4996 Overall 0.15 StDev Cp Cpk PPM 0.05021 3.32 0.55 Values 49966.79 0.05 Specs 4 Observation

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

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

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TR1200-006-0516-PV Absorbance (40%) at 290nm I Chart Capability Histogram Overall Individual Value _ _ Within 0.06 Specifications LSL 0.0 USL 0.2 X=0.05464 LCL=0.02410 -0.00 0.03 0.06 0.09 0.12 0.15 0.18 **Moving Range Chart** Normal Prob Plot AD: 0.259, P: 0.588 0.04 UCL=0.03752 Moving Range 0.02 MR=0.01148 0.00 0.05 0.00 Last 7 Observations **Capability Plot** Within Overall StDev Cp Cpk PPM 0.01018 3.27 1.79 0.04 0.01139 2.93 StDev 0.060 Pp Ppk Cpm PPM Values 1.60 Within 0.045 0.81 Specs Observation

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.

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TR1 200-006-051 6-PV Assay I Chart Capability Histogram UCL=101.259 ____ Overall __ - Within Individual Value Specifications LSL 99 USL 101 X=100.417 100.2 LCL=99.575 100.0 100.4 100.8 99.6 Normal Prob Plot AD: 0.462, P: 0.173 Moving Range Chart UCL=1.035 Moving Range MR=0.317 LCL=0 100.0 101.6 5 Last 7 Observations **Capability Plot** 101.0 Within StDev 0.2807 Cp 1.19 Cpk 0.69 PPM 18938.02 Overall 0.2766 1.20 0.70 StDev Pp Ppk Cpm PPM Values 100.5 17559.09 Specs Observation

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.

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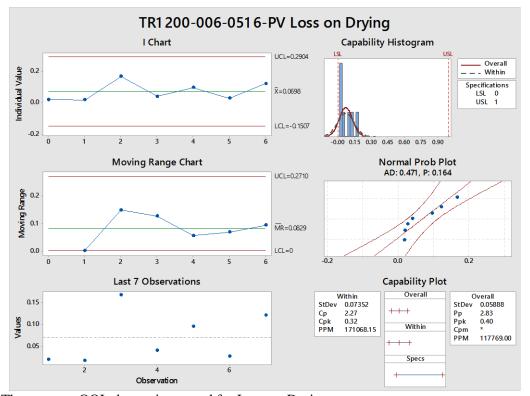
TR1200-006-0516-PV pH (5%) I Chart Capability Histogram UCL=11.416 Overall _ _ Within Individual Value Specifications LSL 10.0 USL 11.5 X=11.007 LCL=10.598 10.5 10.0 10.2 10.4 10.6 10.8 11.0 11.2 11.4 **Moving Range Chart** Normal Prob Plot AD: 0.190, P: 0.837 UCL=0.5021 Moving Range MR=0.1537 0.0 LCL=0 10.50 10.75 11.25 Last 7 Observations **Capability Plot** Within StDev 0.1362 Cp 1.84 Cpk 1.21 PPM 148.53 Overall StDev 0.11 Pp 2.25 Ppk 1.48 Cpm * PPM 4.63 Overall 0.1112 2.25 1.48 11.1 Values Within 4.63 10.9 Specs Observation

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.

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



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

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TR1200-007-0516-PV Absorbance (40%) at 290nm I Chart Capability Histogram UCL=0.1267 Overall Individual Value 0.10 _ _ Within Specifications LSL 0.0 USL 0.2 X=0.0557 0.05 0.00 LCL=-0.0152 **Moving Range Chart** Normal Prob Plot AD: 1.085, P: < 0.005 0.10 UCL=0.0872 Moving Range 0.05 MR=0.0267 0.00 0.0 **Capability Plot** Last 7 Observations 0.12 Within Overall StDev Cp Cpk PPM 0.02986 1.12 0.62 0.02366 1.41 0.79 StDev Pp Ppk Cpm PPM Values 0.08 9240.29 31017.37 0.04 Specs Observation

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.

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TR1 200-007-051 6-PV Assay I Chart Capability Histogram 100.8 UCL=100.724 ___ Overall _ - Within Individual Value Specifications LSL 99 USL 101 Ā=100.246 100.0 LCL=99.767 Moving Range Chart **Normal Prob Plot** AD: 0.308, P: 0.461 UCL=0.5881 Moving Range 0.50 MR=0.18 LCL=0 0.00 100.0 101.0 **Capability Plot** Last 7 Observations Within StDev 0.1596 Cp 2.09 Cpk 1.58 PPM 1.14 Overall Overall StDev 0.15 0.1548 2.15 1.62 Pp Ppk Cpm PPM Values Within 100.2 0.55 Specs Observation

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.

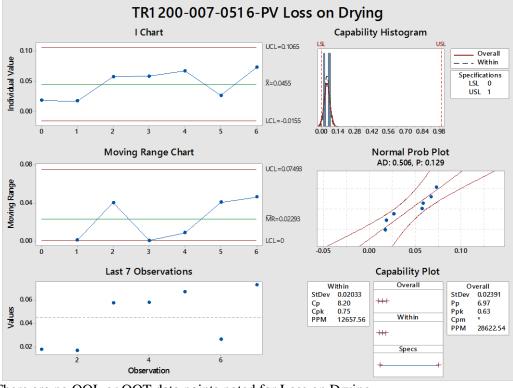
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TR1 200-007-051 6-PV pH (5%) Capability Histogram I Chart UCL=11.3176 Overall Individual Value _ _ Within 11.1 Specifications LSL 10.0 USL 11.5 X=10.9754 10.8 LCL=10.6332 10.0 10.2 10.4 10.6 10.8 11.0 11.2 11.4 **Moving Range Chart** Normal Prob Plot AD: 0.176, P: 0.878 UCL=0.4204 0.4 Moving Range 0.2 MR=0.1287 0.0 LCL=0 10.50 11.00 11.25 **Capability Plot** Last 7 Observations Within StDev 0.1141 Cp 2.19 Cpk 1.53 PPM 2.12 Overall Overall StDev 0.10 11.1 0.1003 2.49 1.74 Pp Ppk Cpm PPM Values Within 0.09 10.9 Specs Observation

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.

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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

- o 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.

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