The Value of Simple Statistics in Retrospective Process Validation

Brad Roberts

SeerPharma Pty Ltd

The Guidance Document

Background – Part B. Approach to Process Validation

"For purposes of this guidance………….describes process validation activities in three stages.

Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control. "

"Manufacturers should:

Understand the sources of variation

Detect the presence and degree of variation

Understand the impact of variation on the process and ultimately on product attributes

Control the variation in a manner commensurate with the risk it represents to the process and product "

"Focusing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality."

"Manufacturers should use ongoing programs to collect and analyse product and process data to evaluate the state of control of the process. These programs may identify process or product problems or opportunities for process improvements…………"

The Guidance Document

Recommendations - D. Stage 3 — Continued Process Verification

"The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process."

"Production data should be collected to evaluate process stability and capability."

"If properly carried out, these efforts can identify variability in the process and/or signal potential process improvements."

The Value of Simple Statistics in Retrospective & Ongoing Process ~~Validation~~ Review

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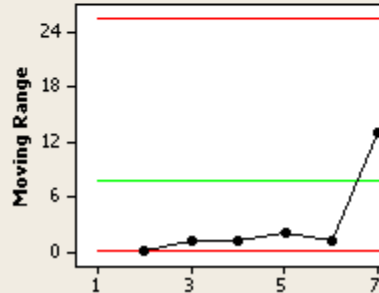# How Familiar is this Scenario?
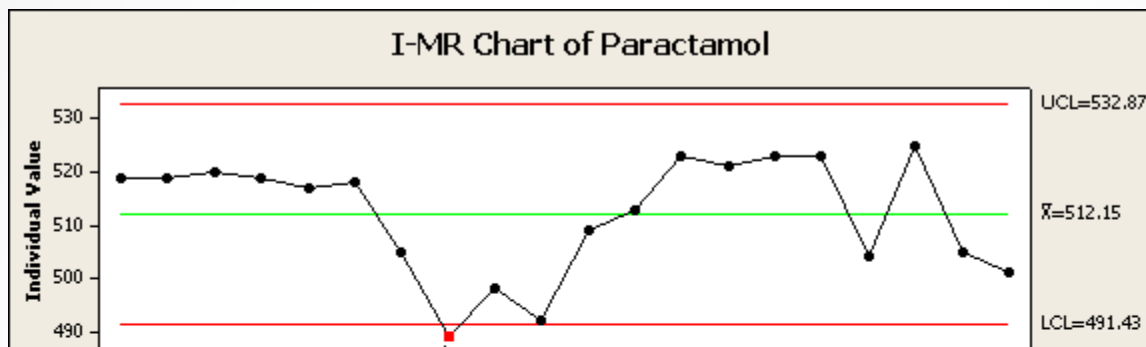
Company XYZ

QC Record Card

Product: Cough Cold Tablets

Batch Number	Description	Yield % Min 98%	Ave Tablet Weight (mg)	Disintegration (Mins)	Hardness (SCU)	Friability %	Paractamol (475-525 mg/tab)	Assay Results		
								Pseudoephedrine HCl (28.5-31.5 mg/tab)	Codeine Assay Composite (5.7-6.3 mg/tab)	Codeine Assay Content Uniformity (5.1-6.9 mg/tab)
77592	Conforms	99.1	627	4	4	1	519	29.6	6.03	Conforms
77590	Conforms	100	625	9	6	1	519	29.8	5.78	Conforms
77501	Conforms	100	628	4	8	0.6	520	29.8	6.01	Conforms
77214	Conforms	99.7	625	5	5	1	519	29.6	5.85	Conforms
77204	Conforms	99.5	624	4	6	0.8	517	30	5.73	Conforms
77588	Conforms	99.8	623	5	7	0.7	518	29.9	6.04	Conforms
77741	Conforms	99.2	625	4	5	1	505	30.8	6.15	Conforms
77696	Conforms	99.8	625	5	4	1	489	29.6	6.17	Conforms
77687	Conforms	98.2	626	5	4	1	498	30.2	6.1	Conforms
77700	Conforms	99.6	622	4	5	1	492	28.6	5.9	Conforms
77698	Conforms	99.8	623	5	4	1	509	29.6	5.87	Conforms
77670	Conforms	99.9	625	5	4	1	513	30.6	6.18	Conforms
77983	Conforms	99.9	625	4	6	0.7	523	30	5.82	Conforms
77796	Conforms	99.8	625	5	4	0.9	521	29.8	5.87	Conforms
77529	Conforms	100	624	5	5	0.9	523	29.7	5.76	Conforms
77527	Conforms	100.1	624	5	5	0.91	523	29.5	5.77	Conforms
77981	Conforms	99.9	625	4	6	0.9	504	30.4	6.03	Conforms
77743	Conforms	99.8	624	4	6	0.6	525	30.9	5.91	Conforms
78145	Conforms	99.3	628	4	5	0.8	505	29.6	5.93	Conforms
78144	Conforms	99.7	624	5	6	0.8	501	29	5.75	Conforms

Data Analysis & Review
Process Control & Capability Analysis

Data Analysis & Review

Process Capability Sixpack of Assay

I Chart
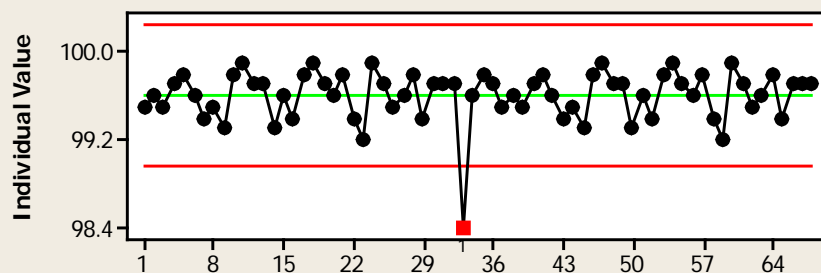
UCL = 100.245
$\bar{X}$ = 99.601
LCL = 98.958

Capability Histogram

LSL
USL
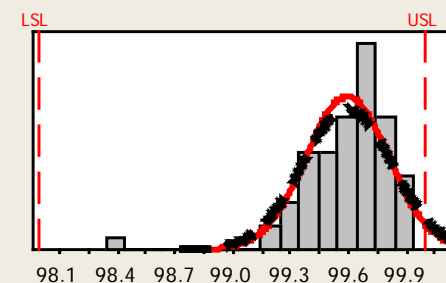
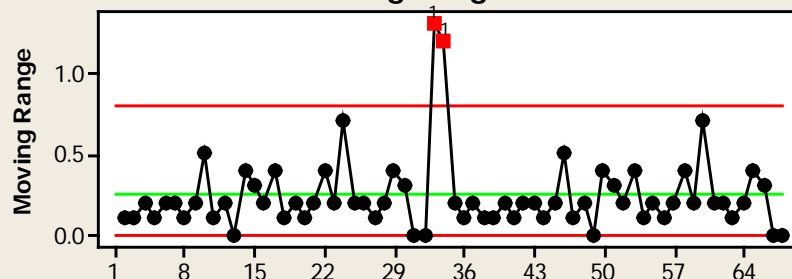| Specifications	
LSL	98
USL	100

98.1 98.4 98.7 99.0 99.3 99.6 99.9

Moving Range Chart

UCL = 0.790
$\overline{MR}$ = 0.242
LCL = 0

Normal Prob Plot

AD: 1.955, P: < 0.005

98.4   99.0   99.6   100.2

Last 25 Observations

45   50   55   60   65
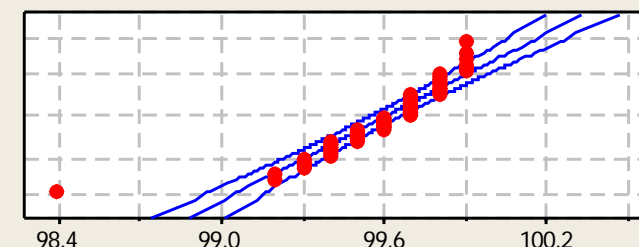
Observation
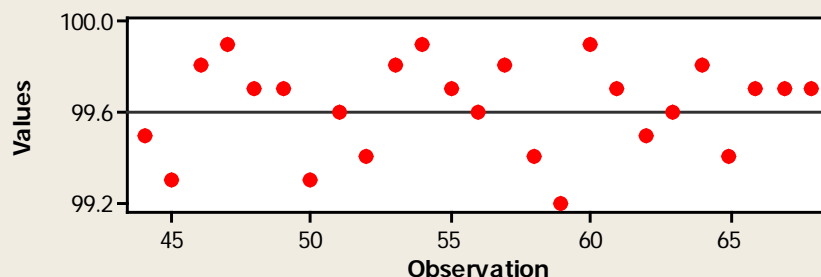
Capability Plot

Within	
StDev	0.2144
Cp	1.56
Cpk	0.62
PPM	31498.44

Within

Overall

Specs

Overall	
StDev	0.2340
Pp	1.42
Ppk	0.57
Cpm	*
PPM	44299.15

Post Validation Review/Ongoing Product Review

Aciclovir Cold Sore Cream

Assay Results			
Specification - 0.950% - 1.050%			
Batch Number	Duplicate 1	Duplicate 2	
1	0.999	1.001	
2	1	1.01	
3	0.99	0.98	
4	0.982	0.973	
5	0.966	0.974	
6	0.982	0.973	
7	0.977	0.973	
8	0.976	0.979	
9	0.975	0.973	
10	0.976	0.971	
11	0.972	0.972	
12	0.967	0.97	
13	0.966	0.965	

File   Edit   View   Window   Layouts   Help

Histo / B-W

Histogram

Specs   Distrib

1.065
1.055
1.045   Usl:
1.035   1.050
1.025
1.015
1.005
0.995   +3 sigma:
0.985   Target: 0.9930
0.975   1.000
0.965   Mean:
0.955   0.9789
0.945   Lsl:
0.935   0.950   -3 sigma:
                               0.9648

0   (each point = 1 sample)   80
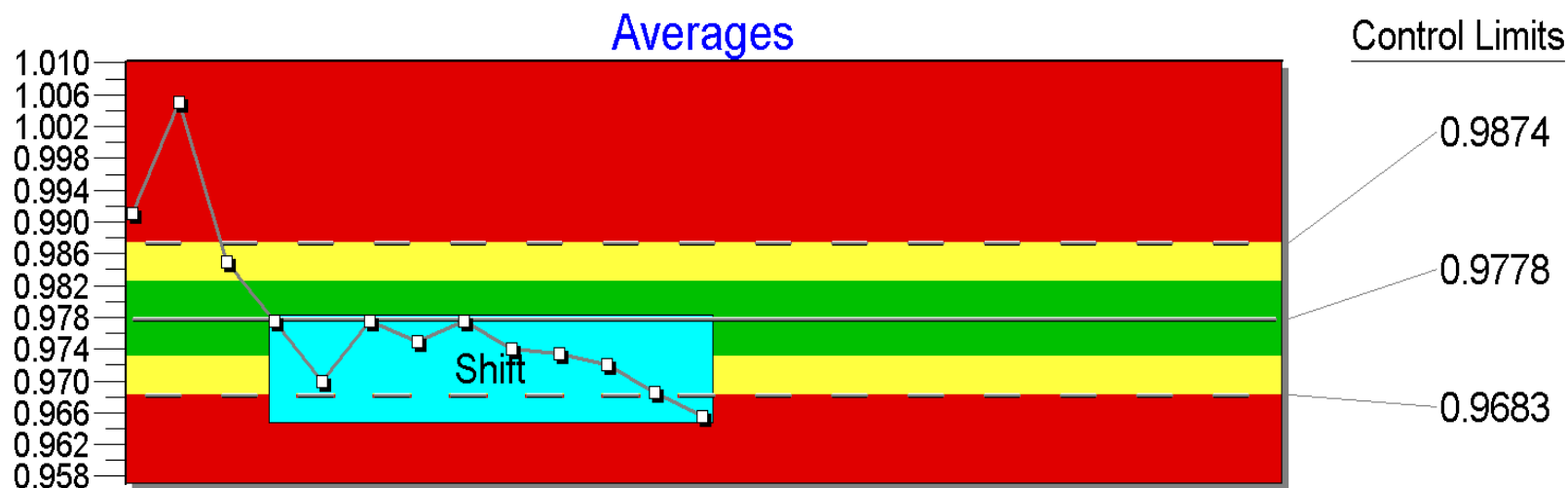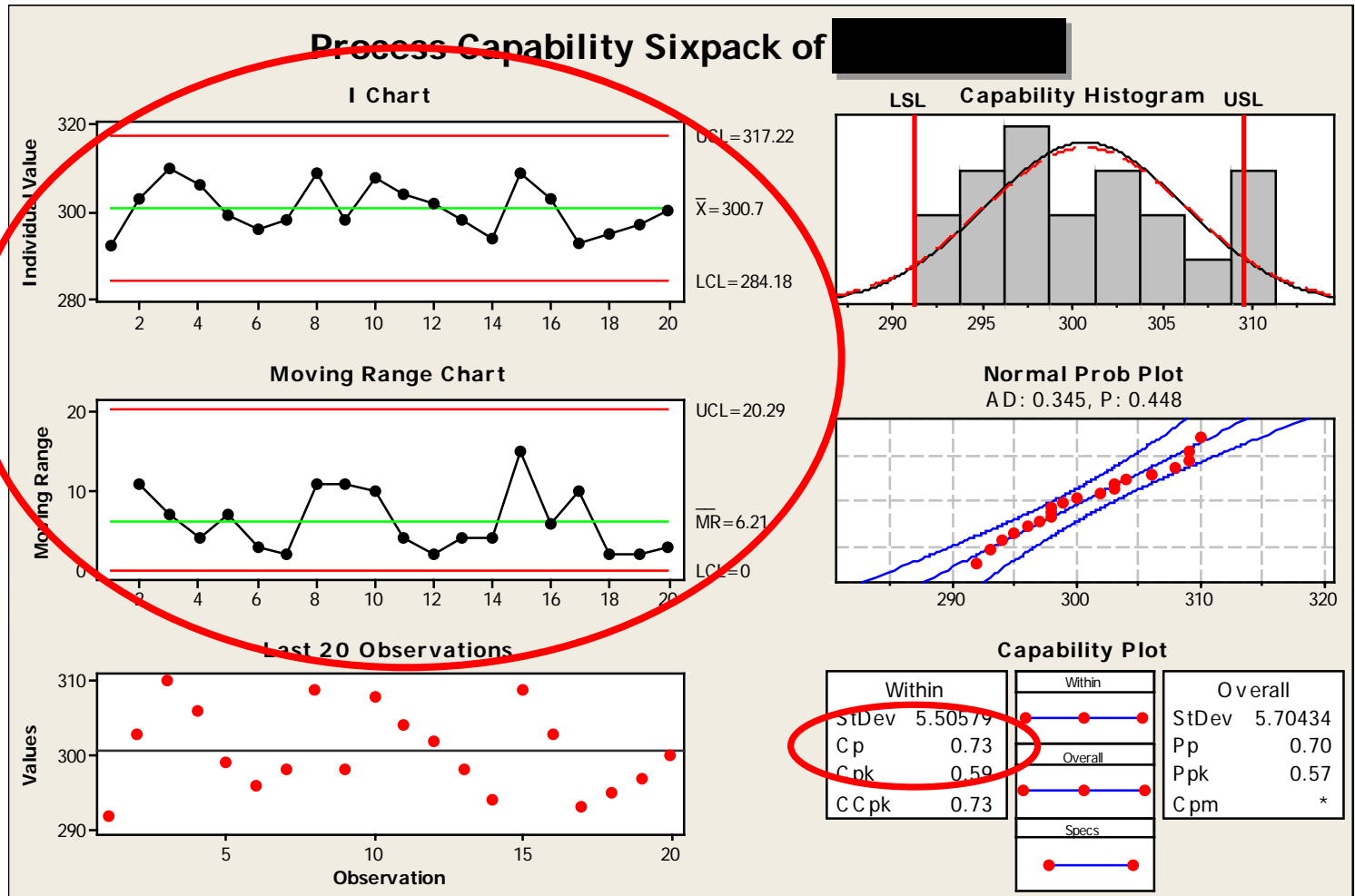
Customer: Std Dev = 0.0047
Part Number: Cold Sore Cream   SD type = R/d2
Characteristic: Assay ---- QC   Cp = 3.542
Subgroups: 13: 1 - 13 (Most recent 25 SGs)   Cpk = 2.046

For Help, press F1   P1 HW:___   Subgroup #___   NUM

10:18 AM
2/05/2011

CASE STUDIES

Process in Statistical Control, But Not Capable
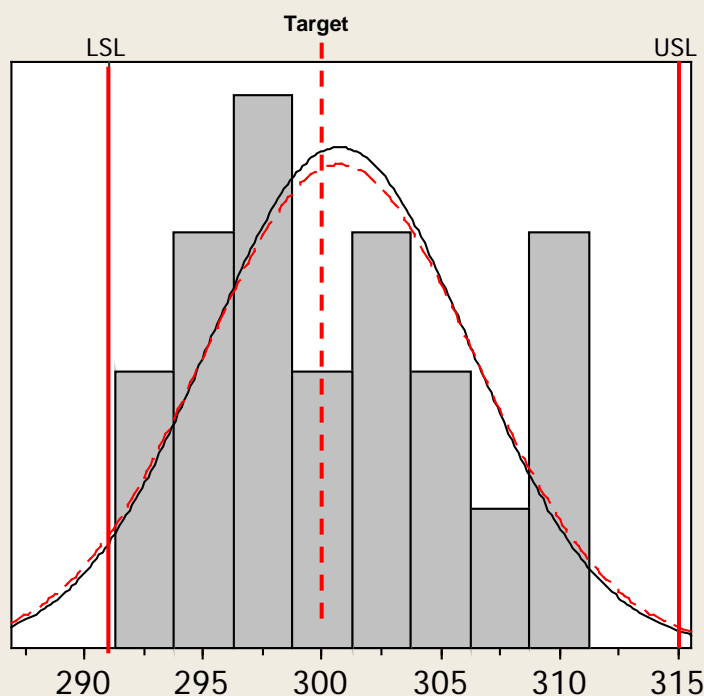
Process in Statistical Control, But Not Capable
Release Specifications

Process Capability of ▓▓▓▓▓▓▓

Process Data
LSL   291.00000
Target   *
USL   315.00000
Sample Mean   300.70000
Sample N   20
StDev(Within)   5.50579
StDev(Overall)   5.70434

Within
Overall

Potential (Within) Capability
Cp   0.73
CPL   0.59
CPU   0.87
Cpk   0.59
CCpk   0.73

Overall Capability
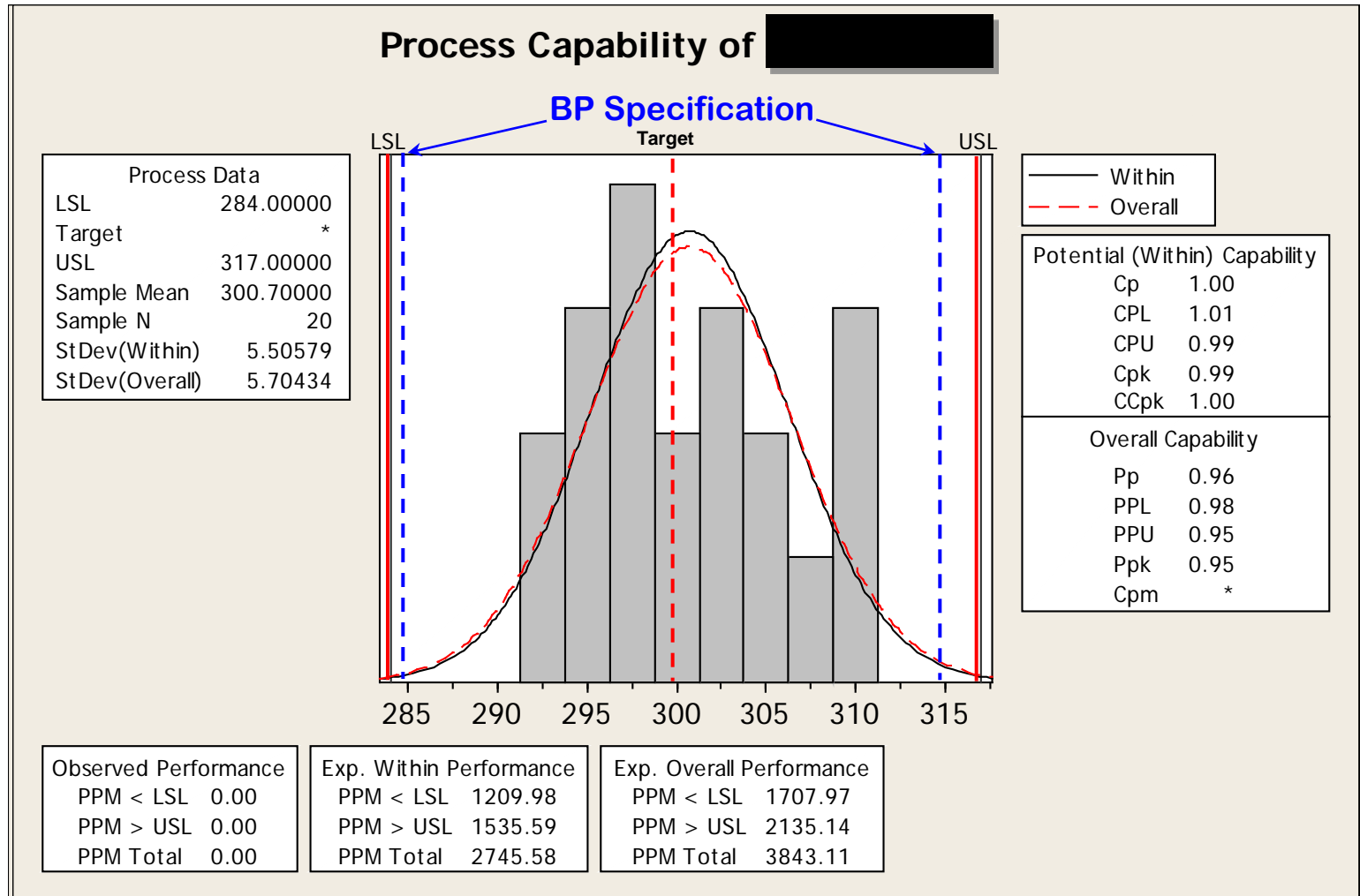Pp   0.70
PPL   0.57
PPU   0.84
Ppk   0.57
Cpm   *

Observed Performance	Exp. Within Performance	Exp. Overall Performance
PPM < LSL 0.00	PPM < LSL 39052.98	PPM < LSL 44522.23
PPM > USL 0.00	PPM > USL 4698.43	PPM > USL 6090.39
PPM Total 0.00	PPM Total 43751.41	PPM Total 50612.62

CONFIDENCE
IN
COMPLIANCE

Process in Statistical Control, But Not Capable
What Specification is the Current Process Capable of Meeting?

Process Capability of ▮▮▮▮▮▮

BP Specification

Process Data	
LSL	284.00000
Target	*
USL	317.00000
Sample Mean	300.70000
Sample N	20
StDev(Within)	5.50579
StDev(Overall)	5.70434

— Within
- - - Overall

Potential (Within) Capability	
Cp	1.00
CPL	1.01
CPU	0.99
Cpk	0.99
CCpk	1.00

Overall Capability	
Pp	0.96
PPL	0.98
PPU	0.95
Ppk	0.95
Cpm	*

Observed Performance	Exp. Within Performance	Exp. Overall Performance
PPM < LSL 0.00	PPM < LSL 1209.98	PPM < LSL 1707.97
PPM > USL 0.00	PPM > USL 1535.59	PPM > USL 2135.14
PPM Total 0.00	PPM Total 2745.58	PPM Total 3843.11

Pitfalls in Setting Incorrect Specification Ranges
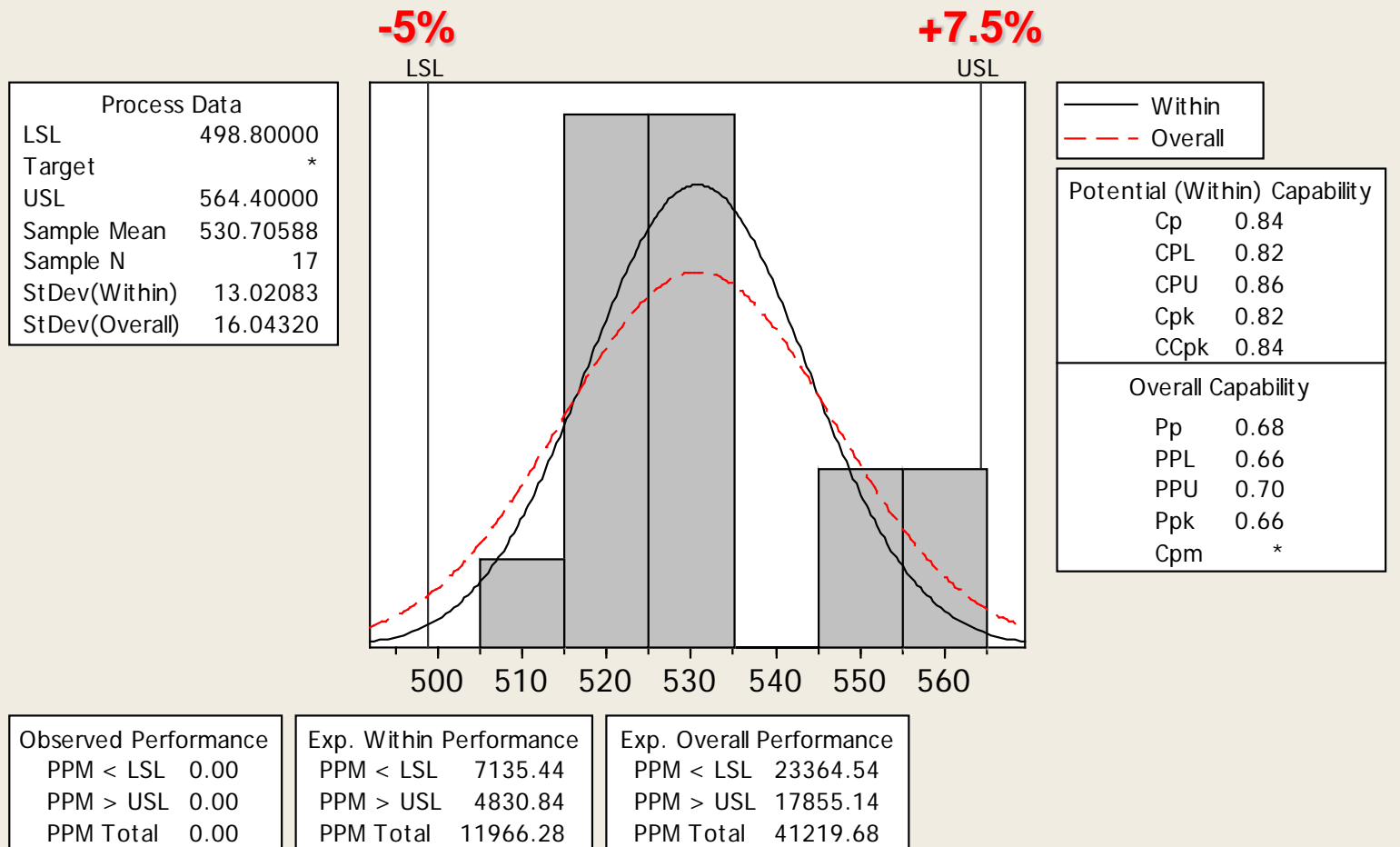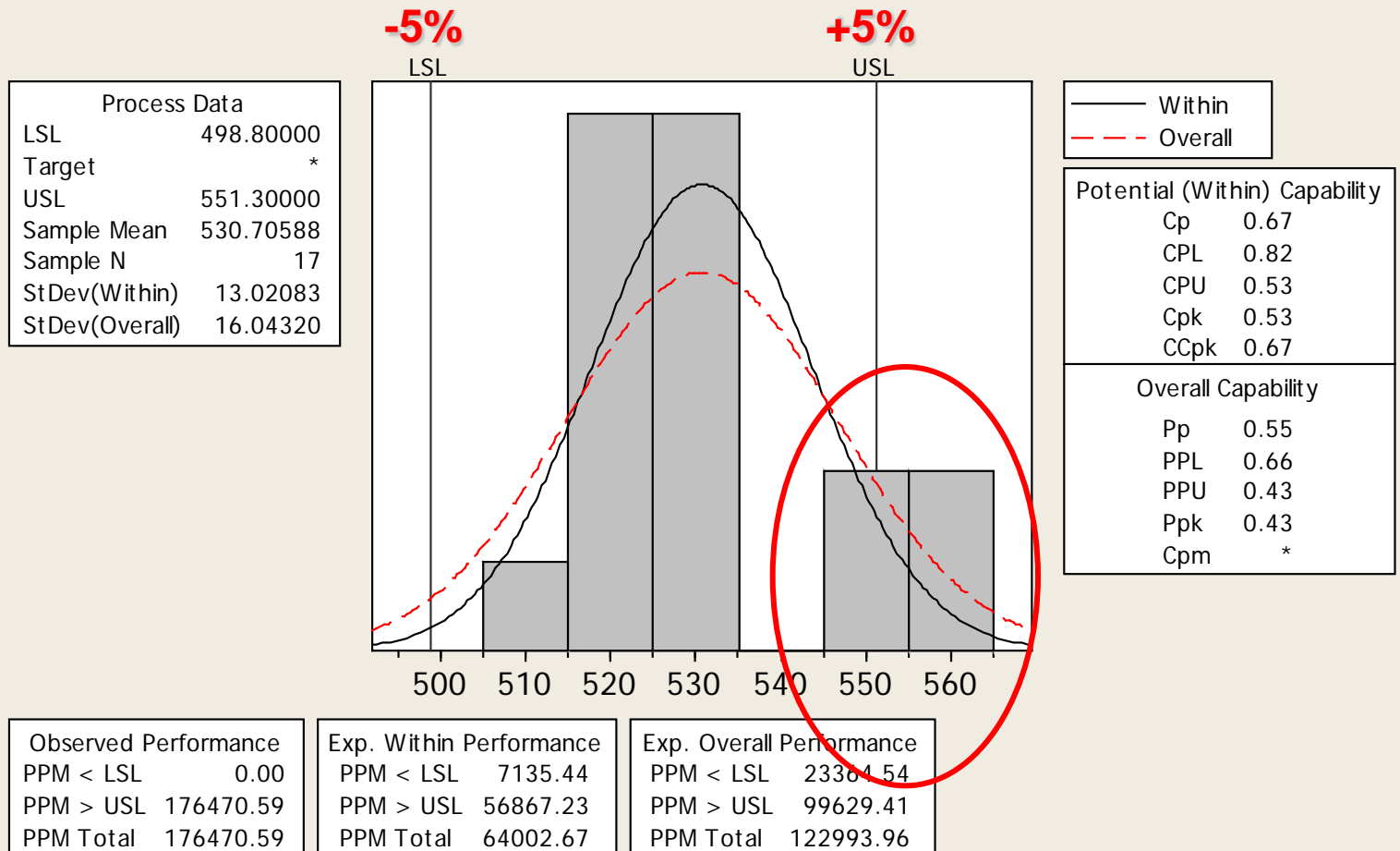

Process Capability Sixpack of Ascorbic Acid

Pitfalls in Setting Incorrect Specification Ranges
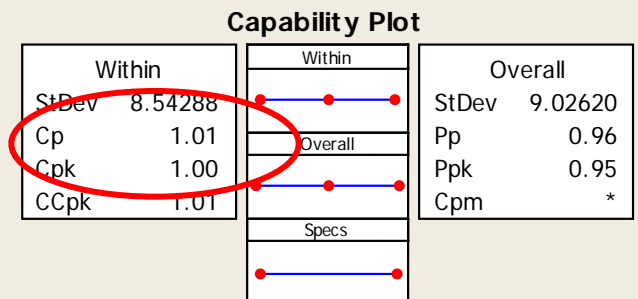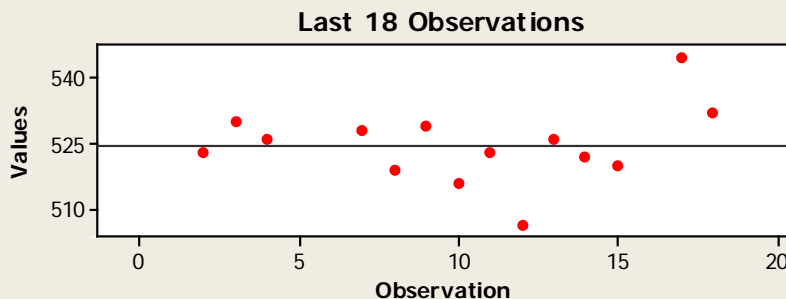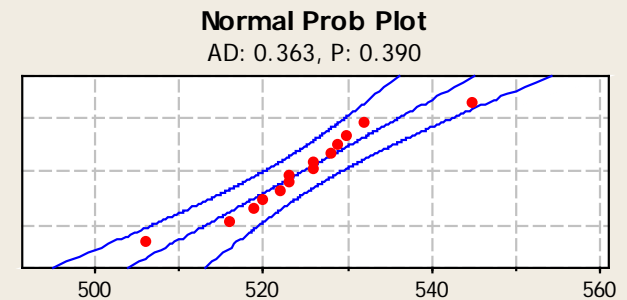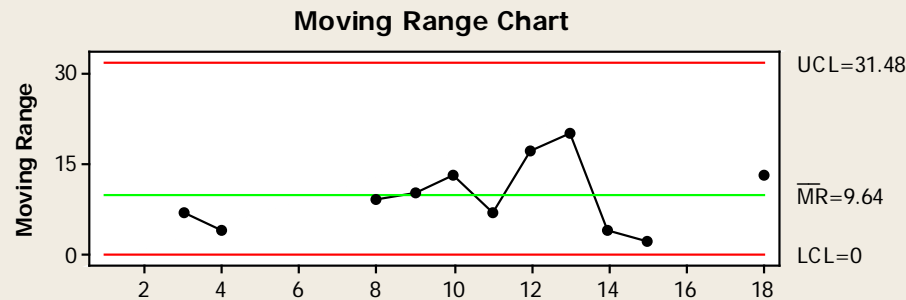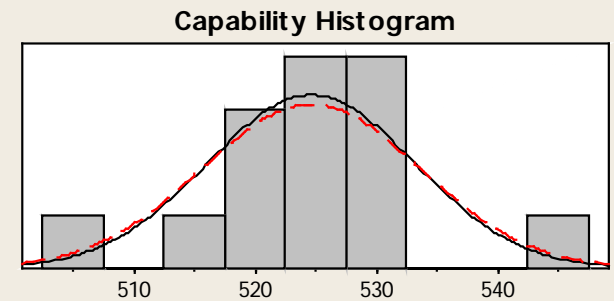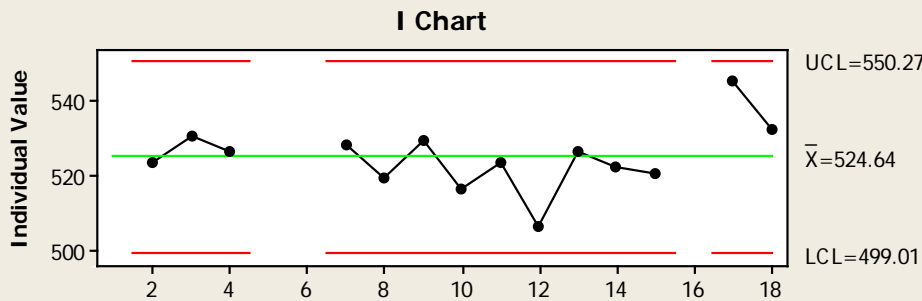

Process Capability of Ascorbic Acid

Pitfalls in Setting Incorrect Specification Ranges

Process Capability of Ascorbic Acid

Pitfalls in Setting Incorrect Specification Ranges
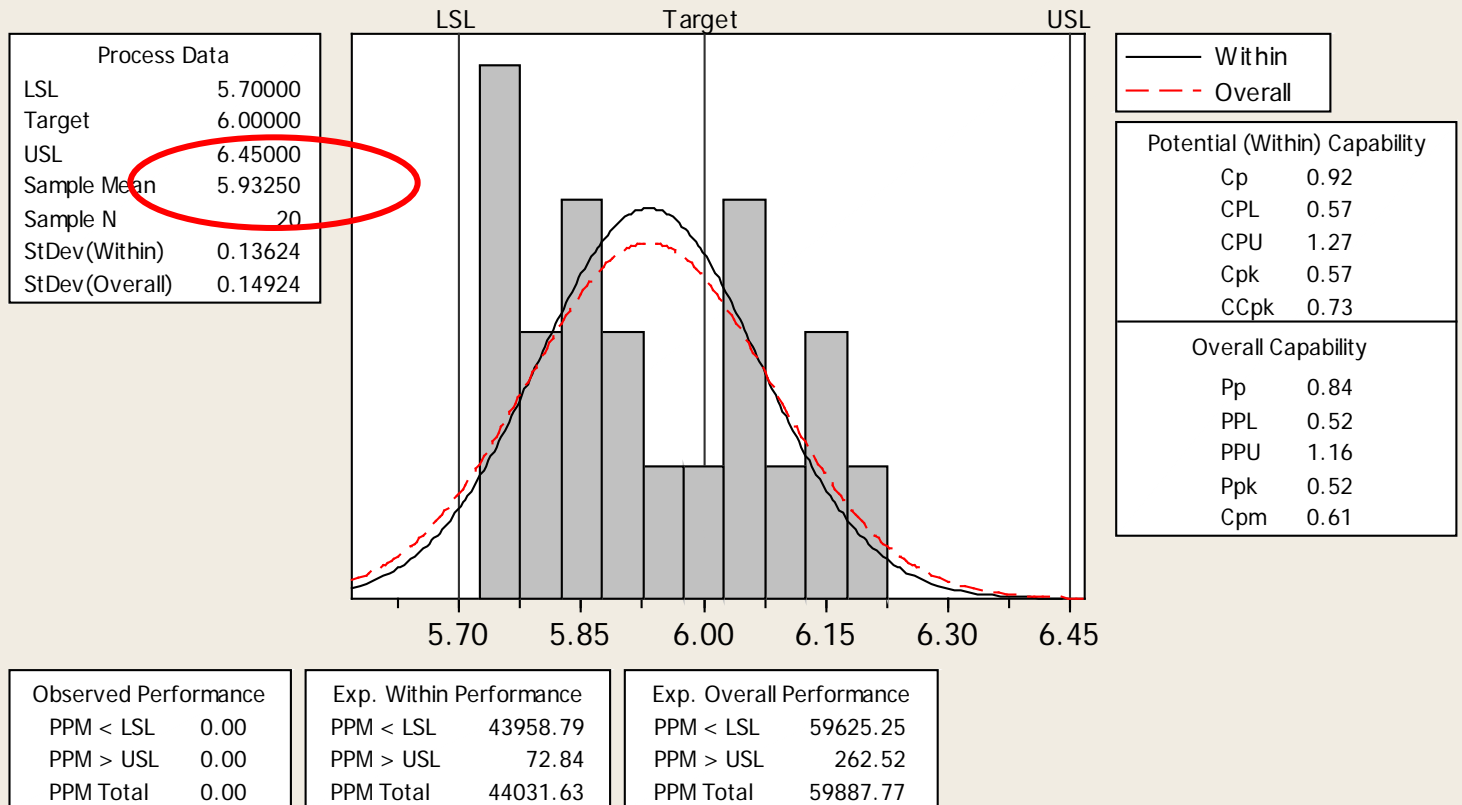

Process Capability Sixpack of Ascorbic Acid

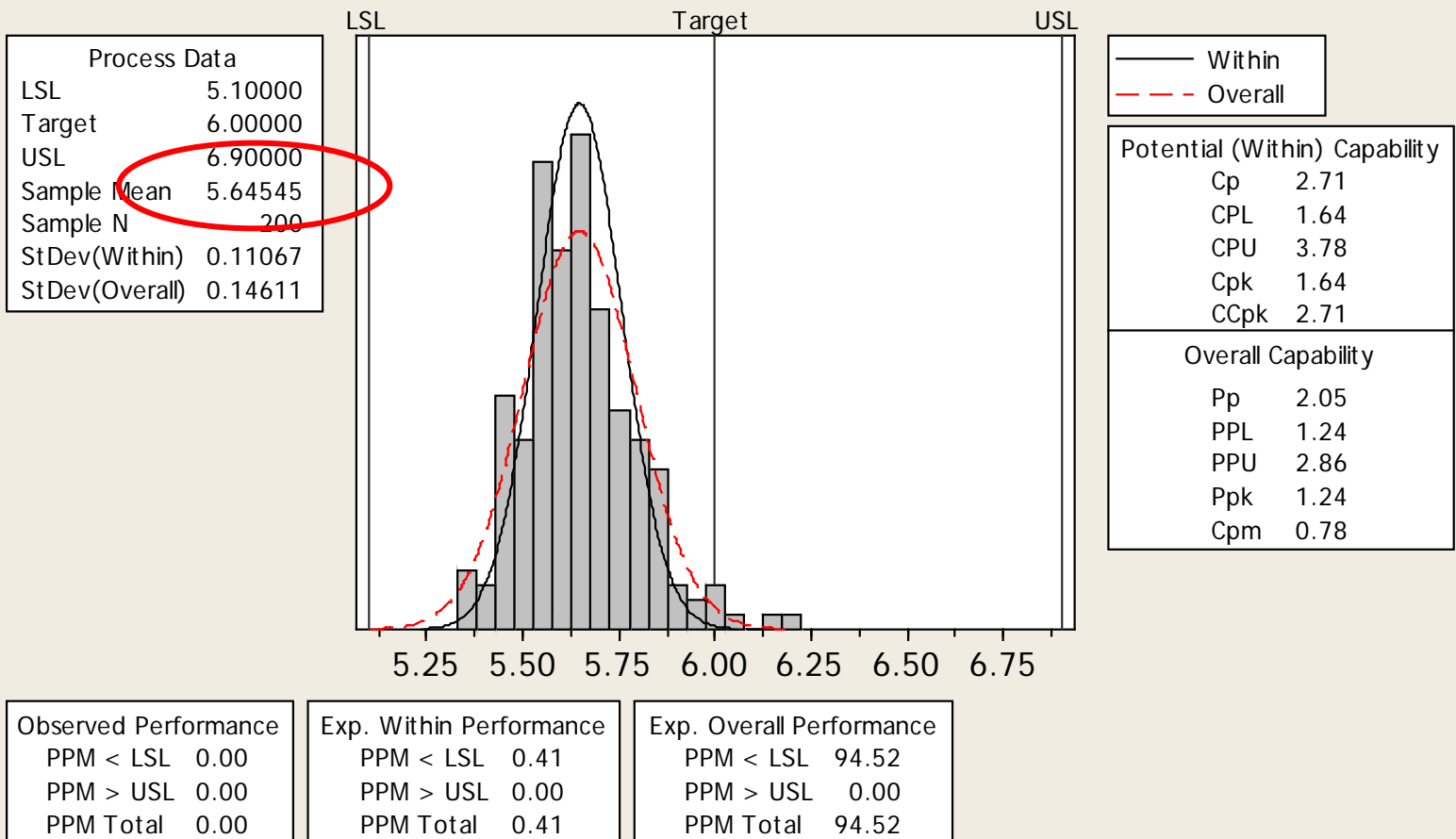# Inconsistencies Between Composite Assay And Content Uniformity Results

Process Capability of ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ Tablets

Last 20 Batches Manufactured

Process Data
LSL	5.70000
Target	6.00000
USL	6.45000
Sample Mean	5.93250
Sample N	20
StDev(Within)	0.13624
StDev(Overall)	0.14924

Potential (Within) Capability
Cp	0.92
CPL	0.57
CPU	1.27
Cpk	0.57
CCpk	0.73

Overall Capability
Pp	0.84
PPL	0.52
PPU	1.16
Ppk	0.52
Cpm	0.61

Observed Performance	Exp. Within Performance	Exp. Overall Performance
PPM < LSL 0.00	PPM < LSL 43958.79	PPM < LSL 59625.25
PPM > USL 0.00	PPM > USL 72.84	PPM > USL 262.52
PPM Total 0.00	PPM Total 44031.63	PPM Total 59887.77

Inconsistencies Between Composite Assay And Content Uniformity Results
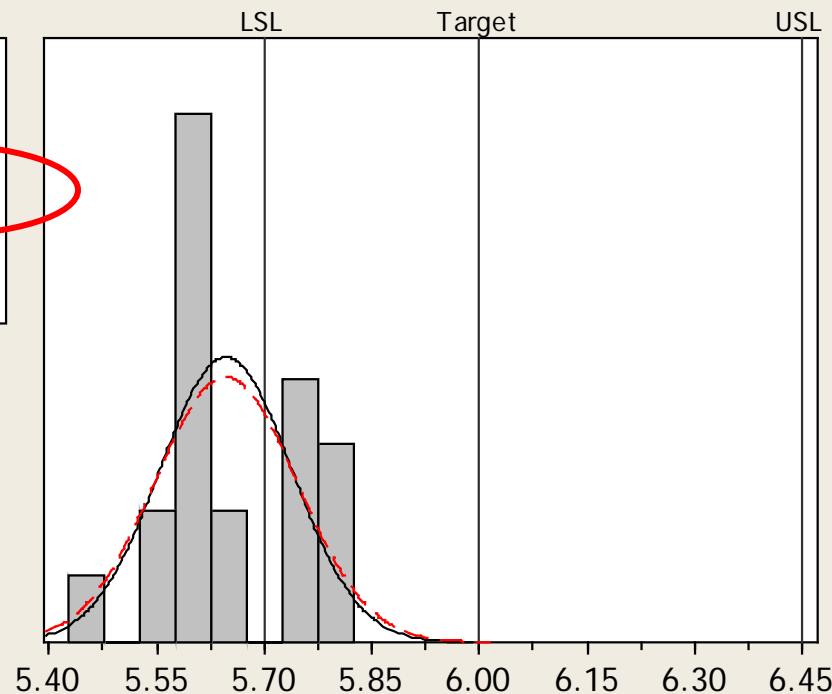

Process Capability of Content Uniformity

Inconsistencies Between Composite Assay And Content Uniformity Results

Process Capability of Average of Individual ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ Tablets

Last 20 Batches Manufactured

Process Data	
LSL	5.70000
Target	6.00000
USL	6.45000
Sample Mean	5.64545
Sample N	20
StDev(Within)	0.09229
StDev(Overall)	0.09921

Potential (Within) Capability	
Cp	1.35
CPL	-0.20
CPU	2.91
Cpk	-0.20
CCpk	1.08

Overall Capability	
Pp	1.26
PPL	-0.18
PPU	2.70
Ppk	-0.18
Cpm	0.27

Observed Performance		Exp. Within Performance		Exp. Overall Performance	
PPM < LSL	650000.00	PPM < LSL	722759.71	PPM < LSL	708777.41
PPM > USL	0.00	PPM > USL	0.00	PPM > USL	0.00
PPM Total	650000.00	PPM Total	722759.71	PPM Total	708777.41

Inconsistencies Between Composite Assay And Content Uniformity Results

Plot of Codiene Phosphate Assays in Cold & Flu Tablets

Inconsistencies Between Composite Assay And Content Uniformity Results