Process Validation Statistics

Bass Masri

Principal Consultant

Statistical Techniques

www.statisticaltechniques.com.au

National GMP & Validation Forum

Hosted by PharmOut

Minitab

Introduction

- Minitab Statistical Software was first developed in 1972 by three professors to teach their students statistics. Minitab is still a leading provider of software and services for quality improvement.

- Statistical Techniques is a Sydney consulting business specializing in quality analysis and strategic research. ‘Statistical Techniques’ is an important section of Quality Management Systems Regulations.

Tutorial Overview

- This tutorial was developed based on the Global Harmonization Task Force Quality Management Systems Guidance on Process Validation.

- A ‘heat sealing’ process uses equipment to seal a pouch to act as a sterility barrier for a medical device. This process requires validation.

- Where the results of a process cannot be fully verified by inspection and test, the process shall be validated with high degree of assurance.

Process Validation

Defined as establishing by objective evidence that a process consistently produces a result or product meeting its predetermined requirements.

1. evidence is the documented collection of facts, data and analysis that demonstrate your process is operating at a validated state.
2. consistently produces links the statistical techniques of process stability (statistical process control) and process capability (Cpk) .
3. predetermined specifications are the specifications that, if met result in the product meeting customers needs and intended use.

Benefits and Why

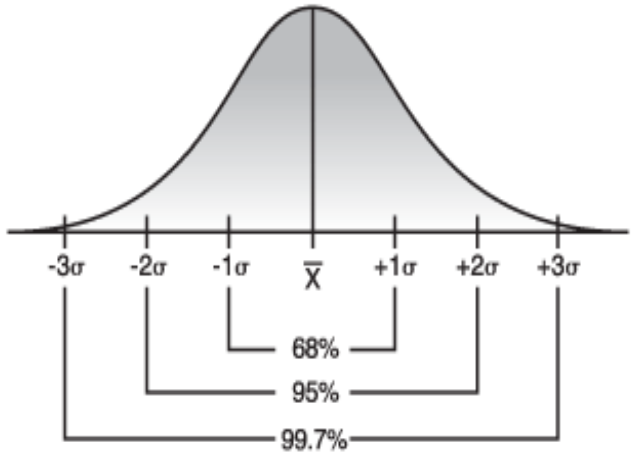
- Process validation results in a process that consistently produces a high quality product for your customers .
- Think about this in terms of your customer's satisfaction, customer experience and your brands reputation.
- Process validation and control results in benefits for your organization (cost of quality) as well as your customers.
- Scrap reduction, reduced rework, increased productivity, reduced customer complaints and reduced product liability.

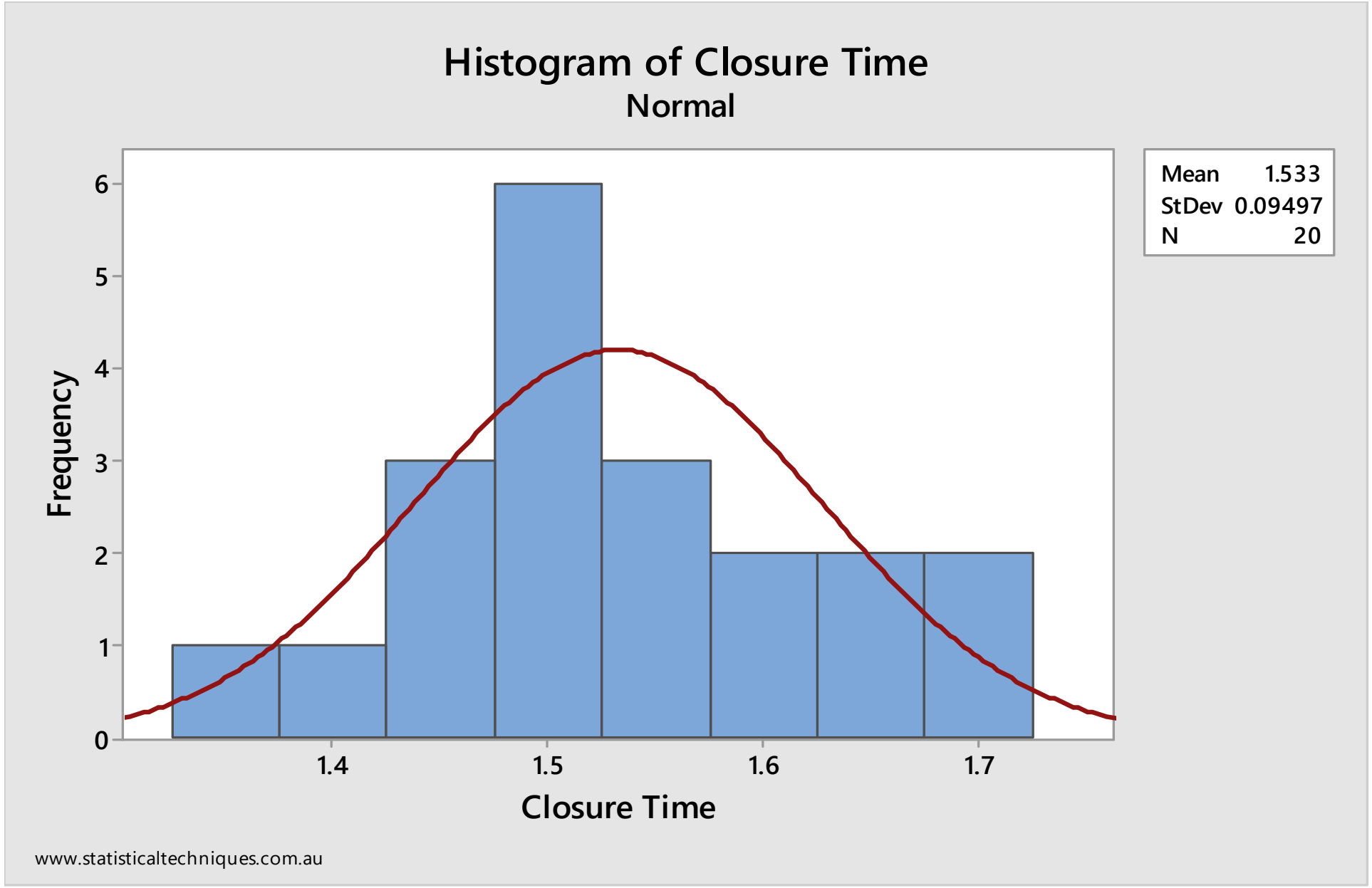
Statistical Methods

- Three process variables: time, temperature and pressure are used to illustrate statistical methods in manufacturing process validation.
    1. Histogram Distributions
    2. Statistical Process Control
    3. Process Capability
    4. Design of Experiments
    5. Measurement Systems Analysis
    6. Sampling Plans

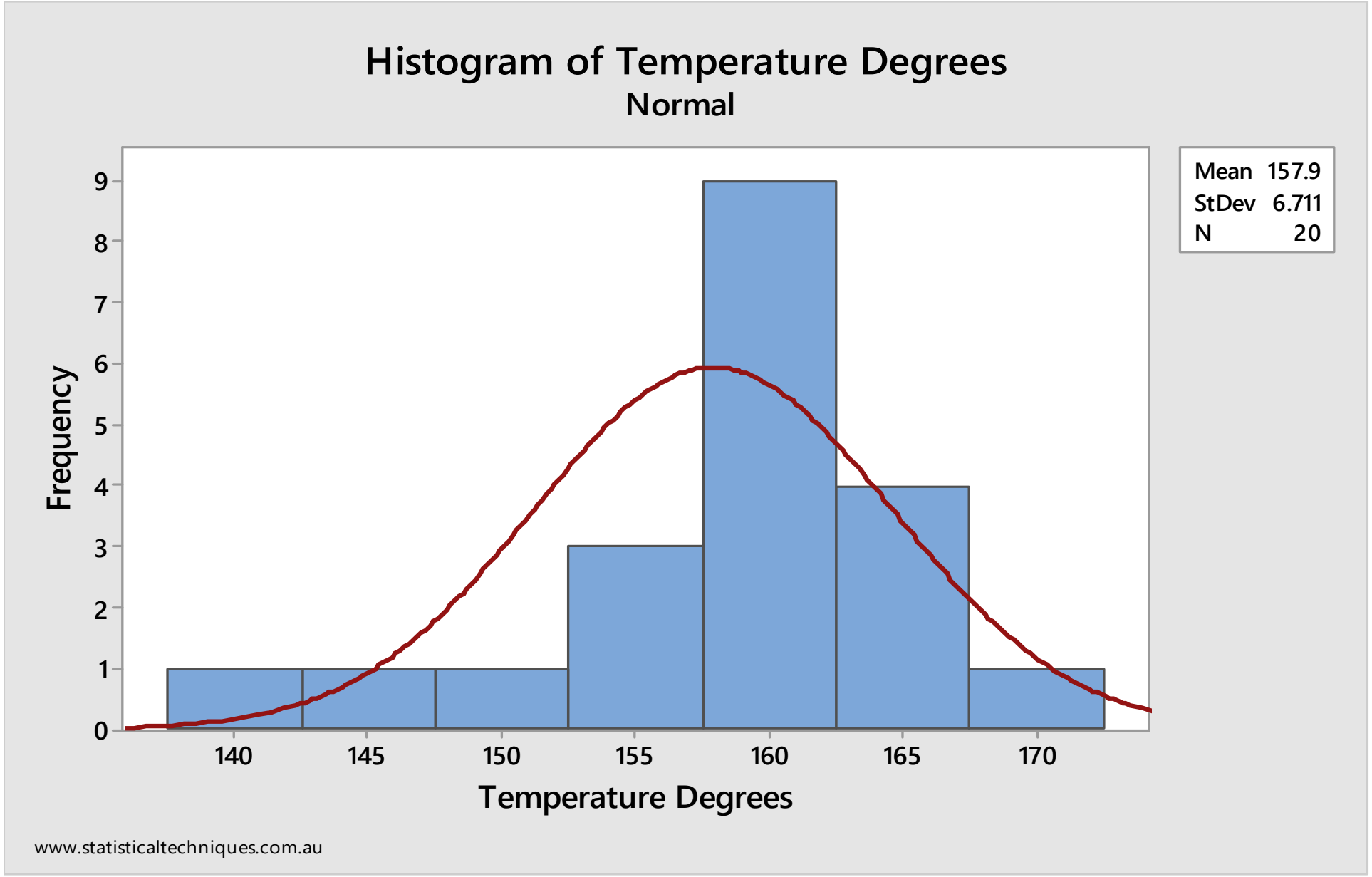
Method 1 – Statistical Distribution

Characterise the ‘distribution’ of process parameters closure time, temperature and pressure using a Histogram - Normal overlay.

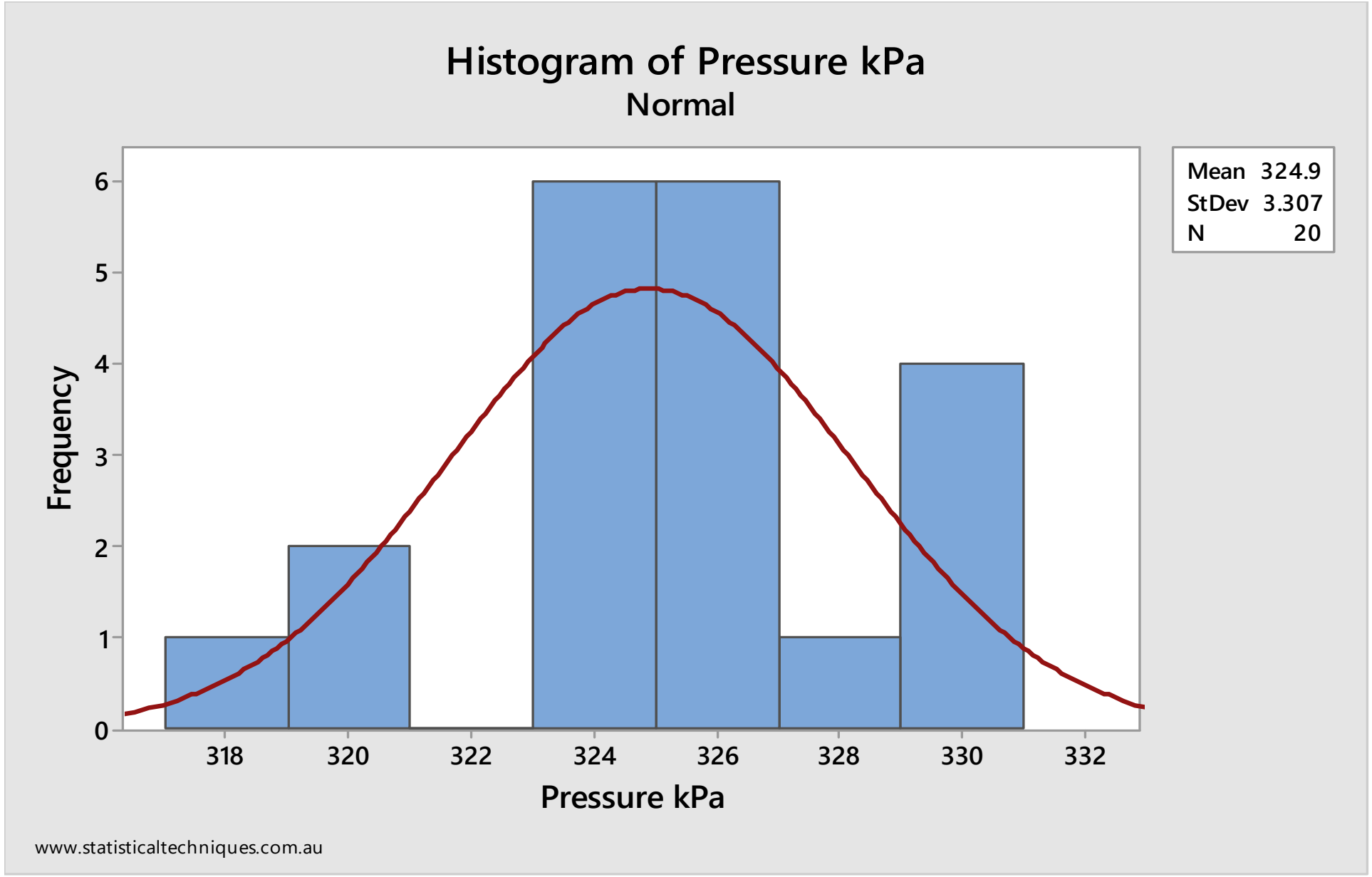




www.statisticaltechniques.com.au



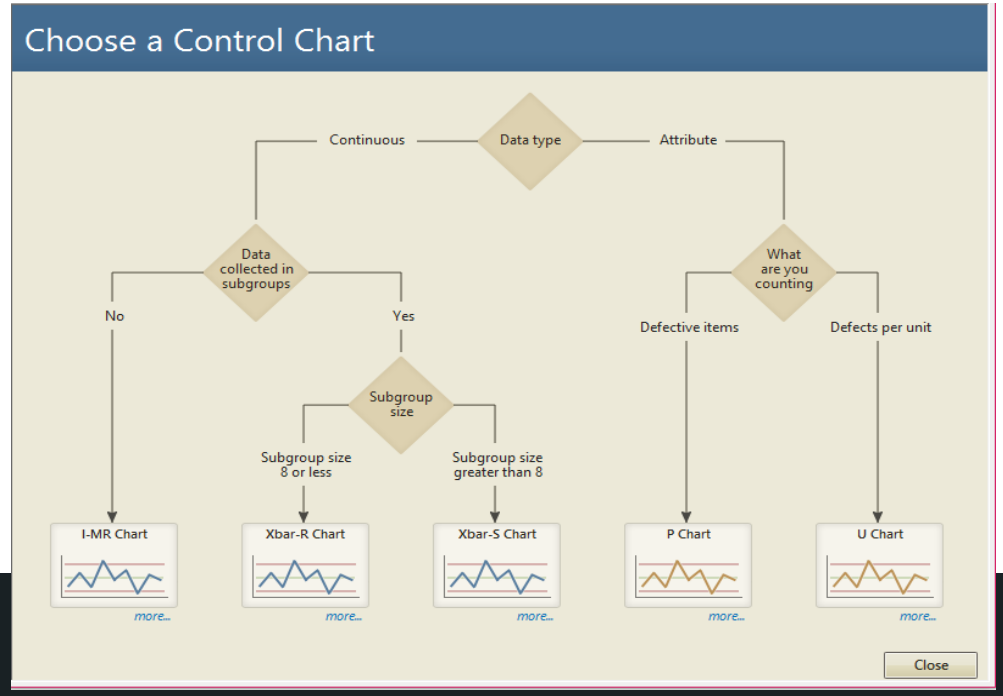
www.statisticaltechniques.com.au

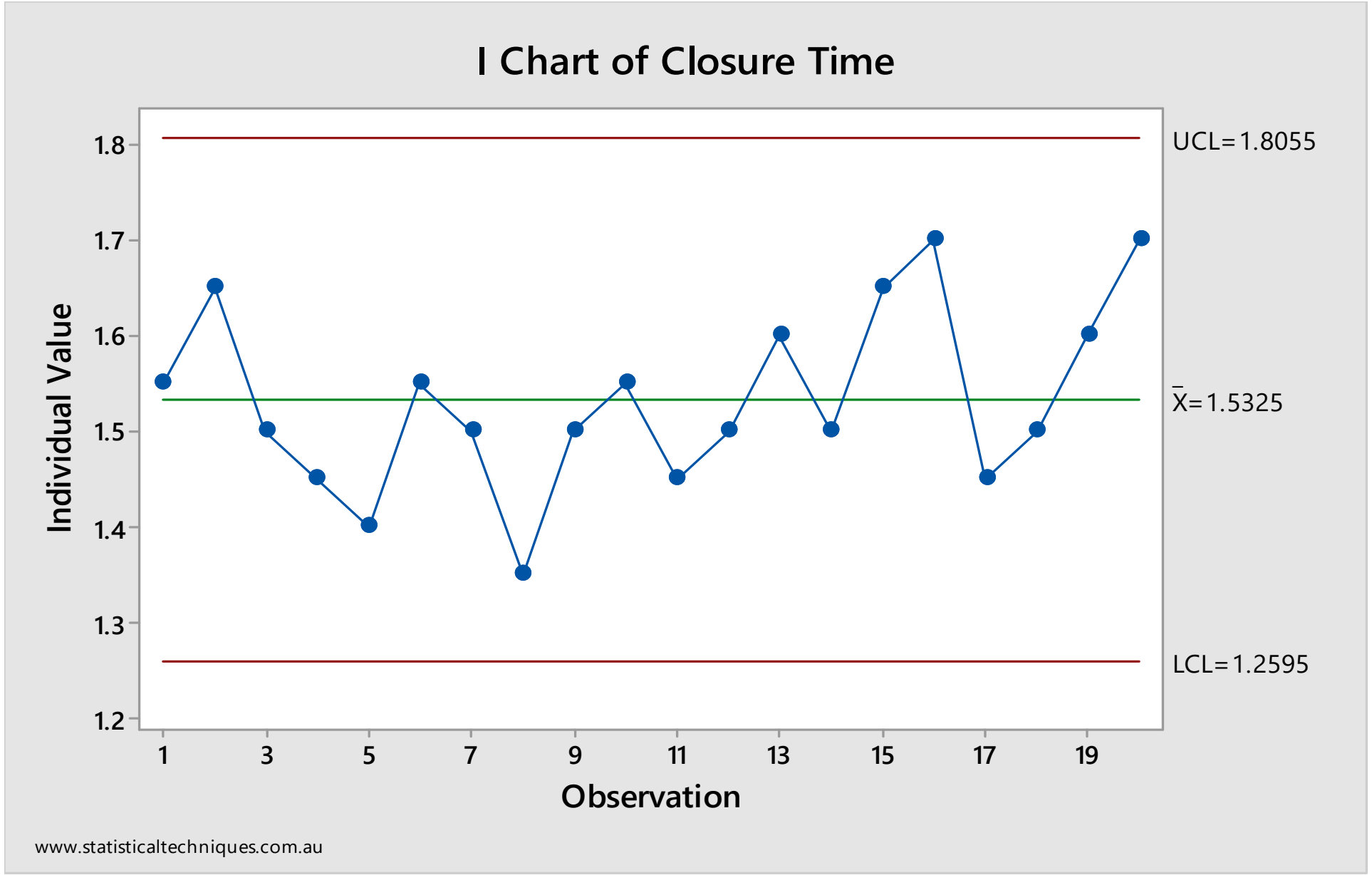


www.statisticaltechniques.com.au

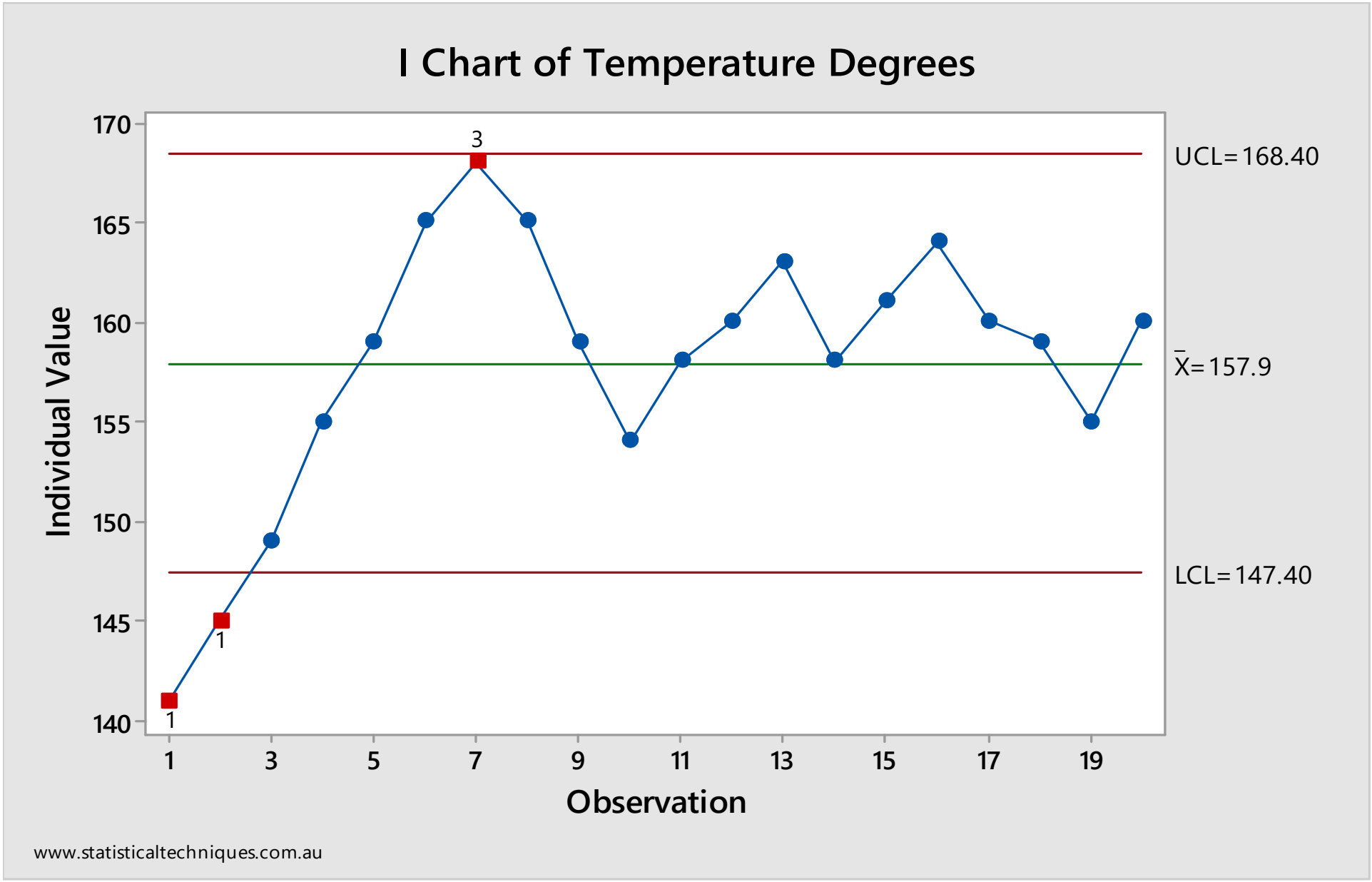
Method 2 – Statistical Process Control

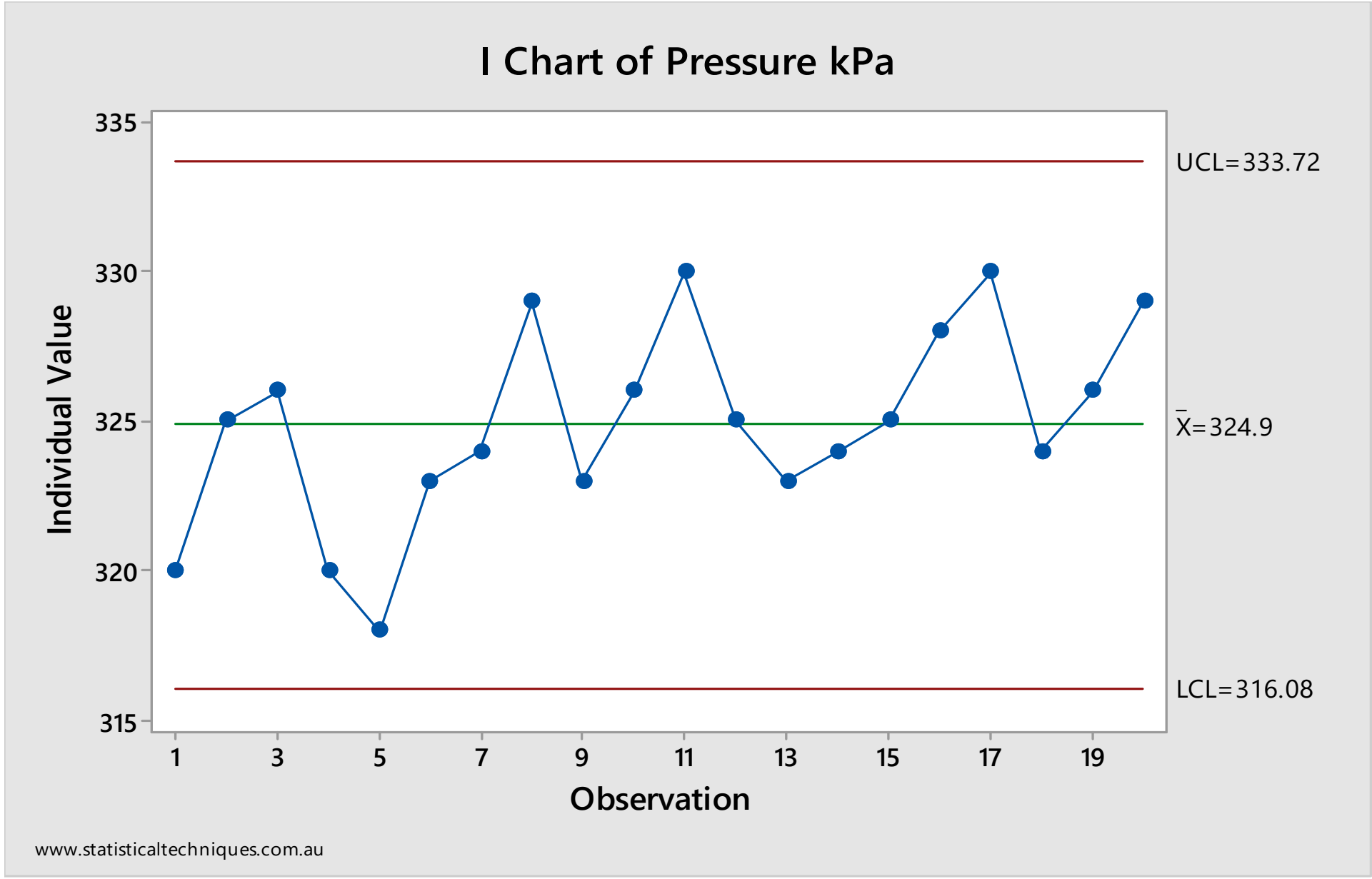
Determine whether the parameters closure time, temperature, and pressure are in ‘statistical control’ using control charts (with tests for special cause 1, 2, 3)





www.statisticaltechniques.com.au

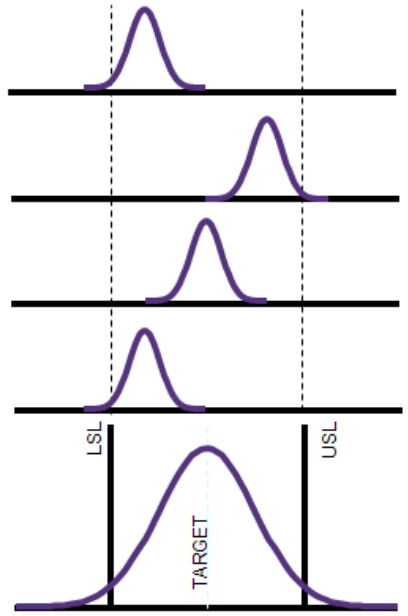

I Chart of Temperature Degrees
Individual Value
Observation
170
165
160
155
150
145
140
1
3
5
7
9
11
13
15
17
19
3
1
1
UCL=168.40
X̄=157.9
LCL=147.40
www.statisticaltechniques.com.au



www.statisticaltechniques.com.au

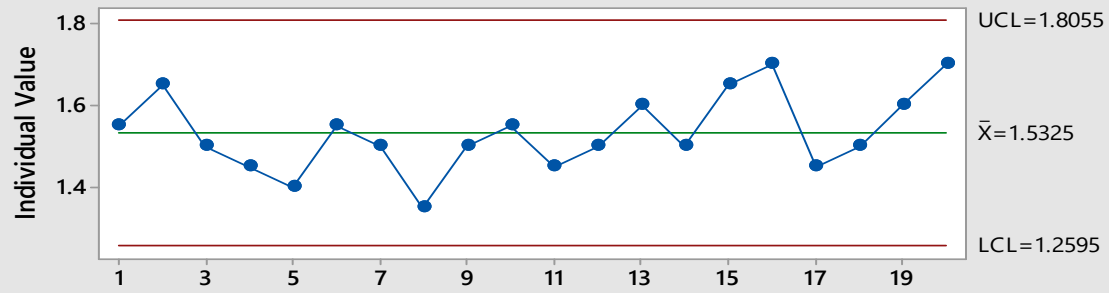
Method 3 – Process Capability

Determine whether the process parameters are in ‘statistical control’, whether the ‘normal distribution’ models the data well and whether these process parameters are ‘capable of consistently’ meeting specifications.

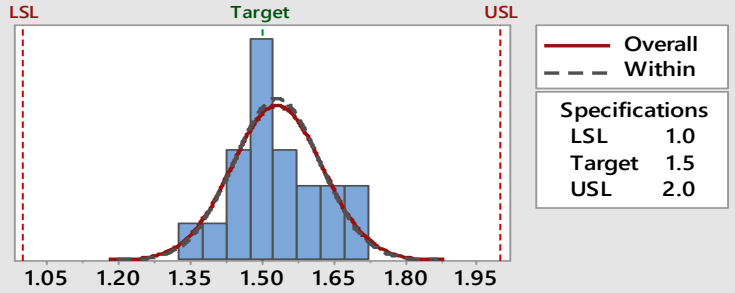


Process Capability Sixpack Report for Closure Time

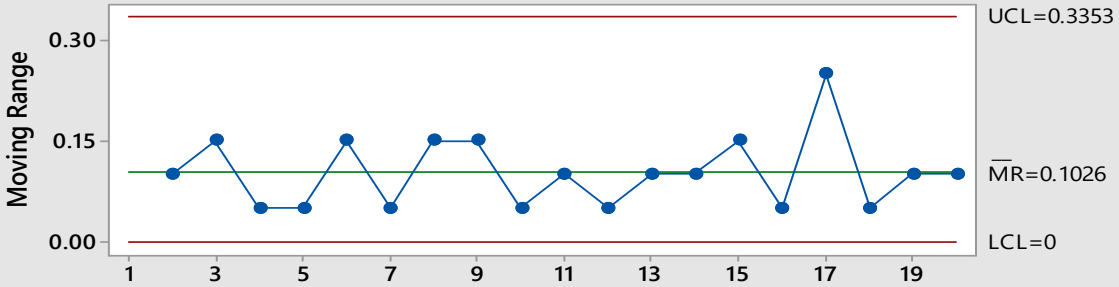
I Chart



Capability Histogram

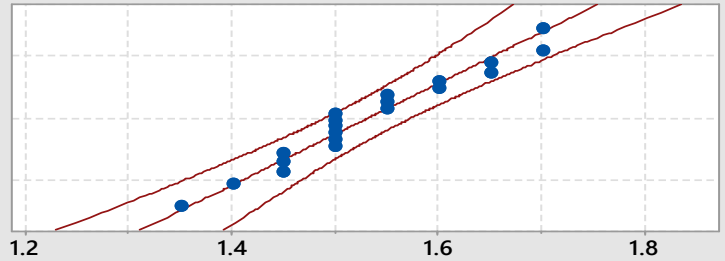


Moving Range Chart

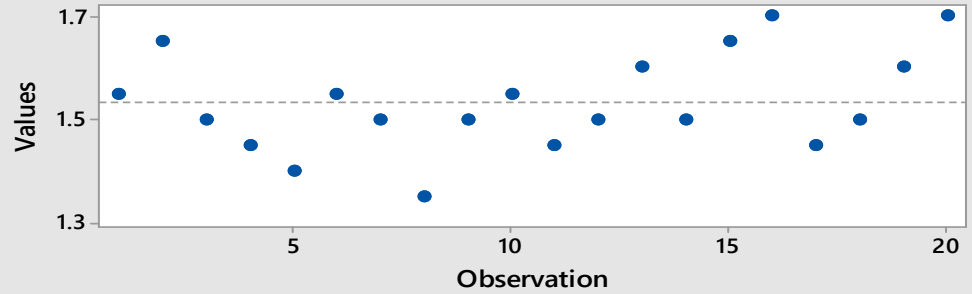


Normal Prob Plot

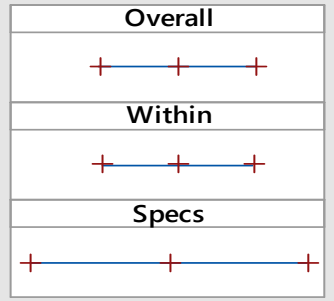
AD: 0.439, P: 0.264



Last 20 Observations



Capability Plot



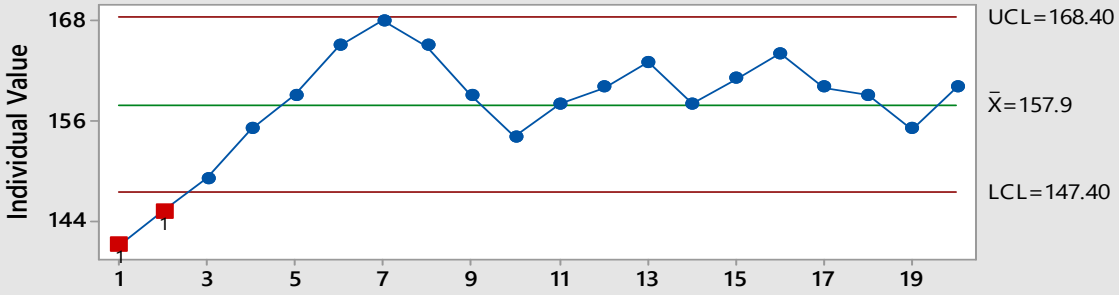
Within	
StDev	0.09099
Cp	1.83
Cpk	1.71
PPM	0.14

Overall	
StDev	0.09497
Pp	1.75
Ppk	1.64
Cpm	1.66
PPM	0.44

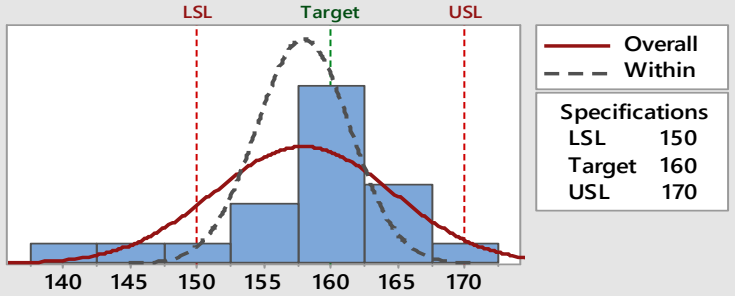
www.statisticaltechniques.com.au

Process Capability Sixpack Report for Temperature Degrees

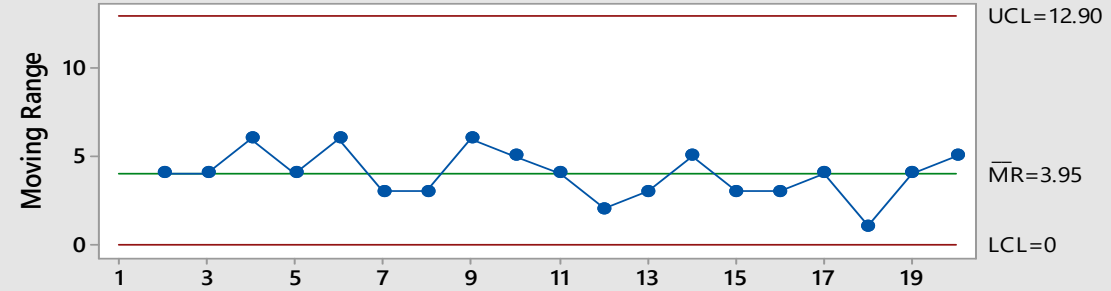
I Chart



Capability Histogram

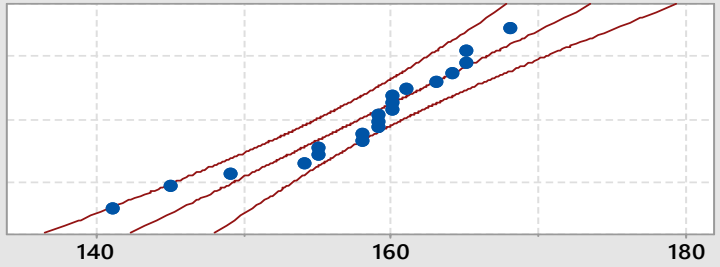


Moving Range Chart

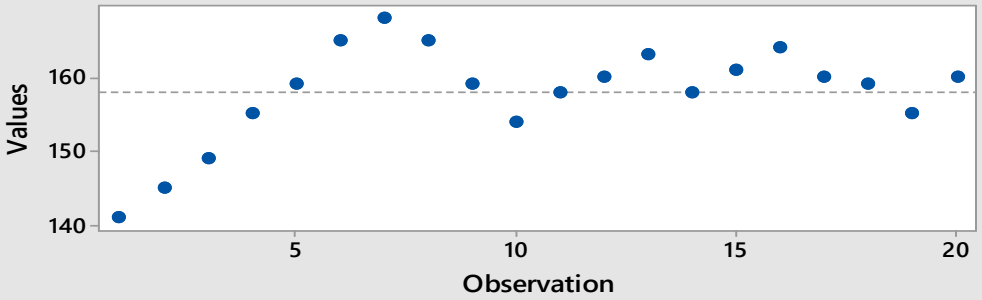


Normal Prob Plot

AD: 0.720, P: 0.051

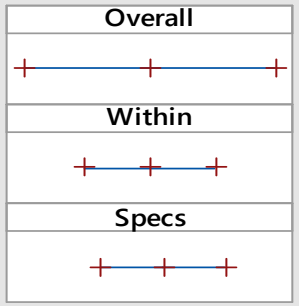


Last 20 Observations



Capability Plot

Within	
StDev	3.499
Cp	0.95
Cpk	0.75
PPM	12260.71

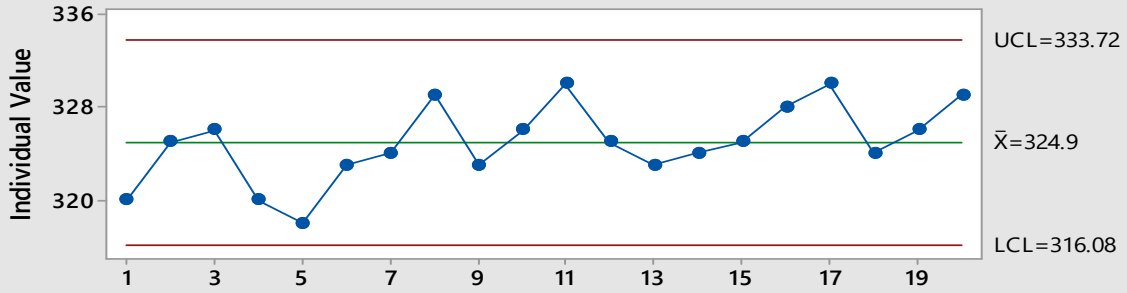


Overall	
StDev	6.711
Pp	0.50
Ppk	0.39
Cpm	0.47
PPM	155275.95

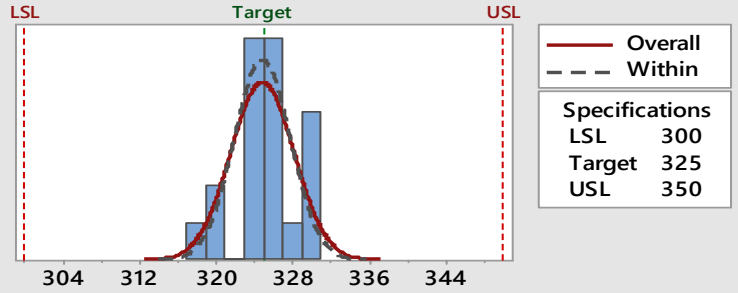
www.statisticaltechniques.com.au

Process Capability Sixpack Report for Pressure kPa

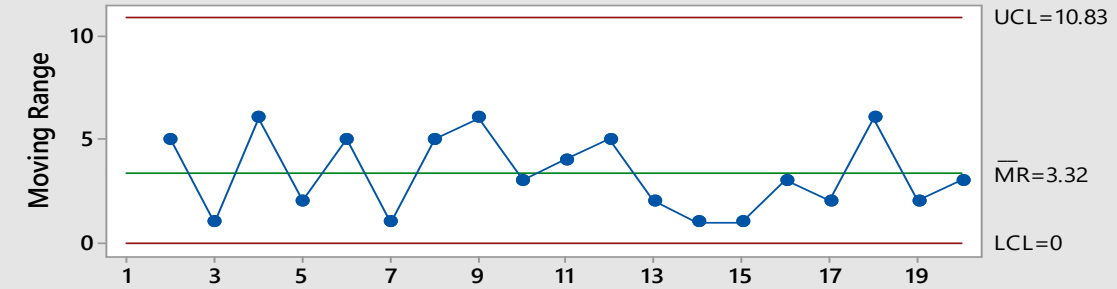
I Chart



Capability Histogram

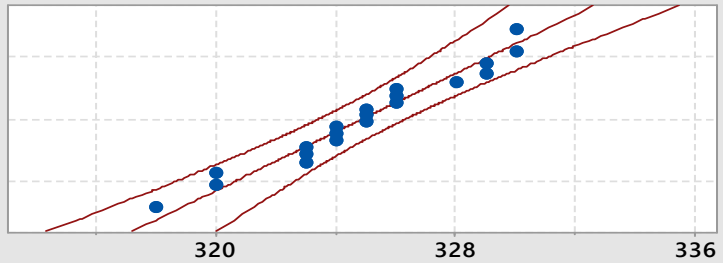


Moving Range Chart

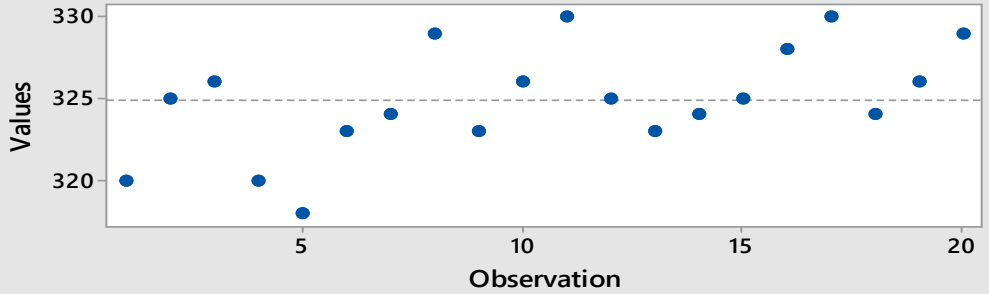


Normal Prob Plot

AD: 0.356, P: 0.422

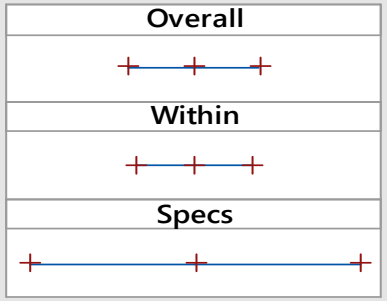


Last 20 Observations



Capability Plot

Within	
StDev	2.940
Cp	2.83
Cpk	2.82
PPM	0.00



Overall	
StDev	3.307
Pp	2.52
Ppk	2.51
Cpm	2.52
PPM	0.00

www.statisticaltechniques.com.au

Process Capability Study in Details

Determine whether process parameters are ‘capable of consistently’ meeting specifications

$$Cpu = \frac{USL - \bar{\bar{X}}}{3(\tilde{\sigma})}$$

$$Cpl = \frac{\bar{\bar{X}} - LSL}{3(\tilde{\sigma})}$$

$$Cpk = minimum\ of\ Cpu\ and\ Cpl$$

$$Ppu = \frac{USL - \bar{X}}{3(\sigma)}$$

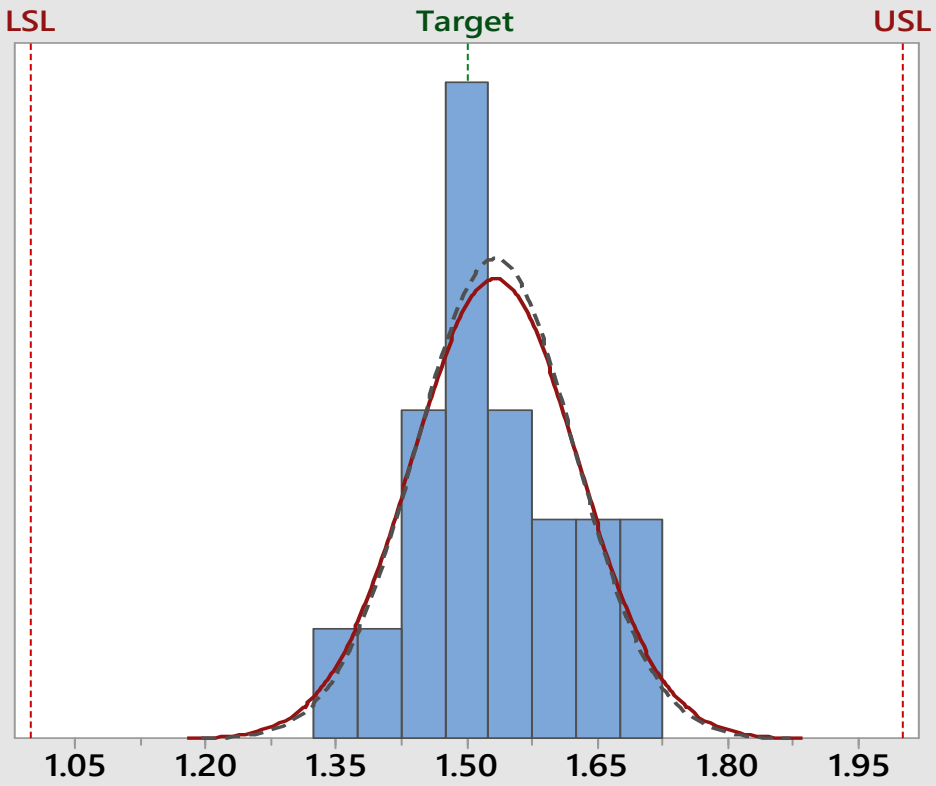
$$Ppl = \frac{\bar{X} - LSL}{3(\sigma)}$$

$$Ppk = minimum\ of\ Ppu\ and\ Ppl$$

$$\sigma = \sqrt{\frac{\sum_i^n (X_i - \bar{X})^2}{n-1}}$$

Process Capability Report for Closure Time

Process Data	
LSL	1
Target	1.5
USL	2
Sample Mean	1.5325
Sample N	20
StDev(Overall)	0.0949723
StDev(Within)	0.0909854



Overall
Within

Overall Capability	
Pp	1.75
PPL	1.87
PPU	1.64
Ppk	1.64
Cpm	1.66

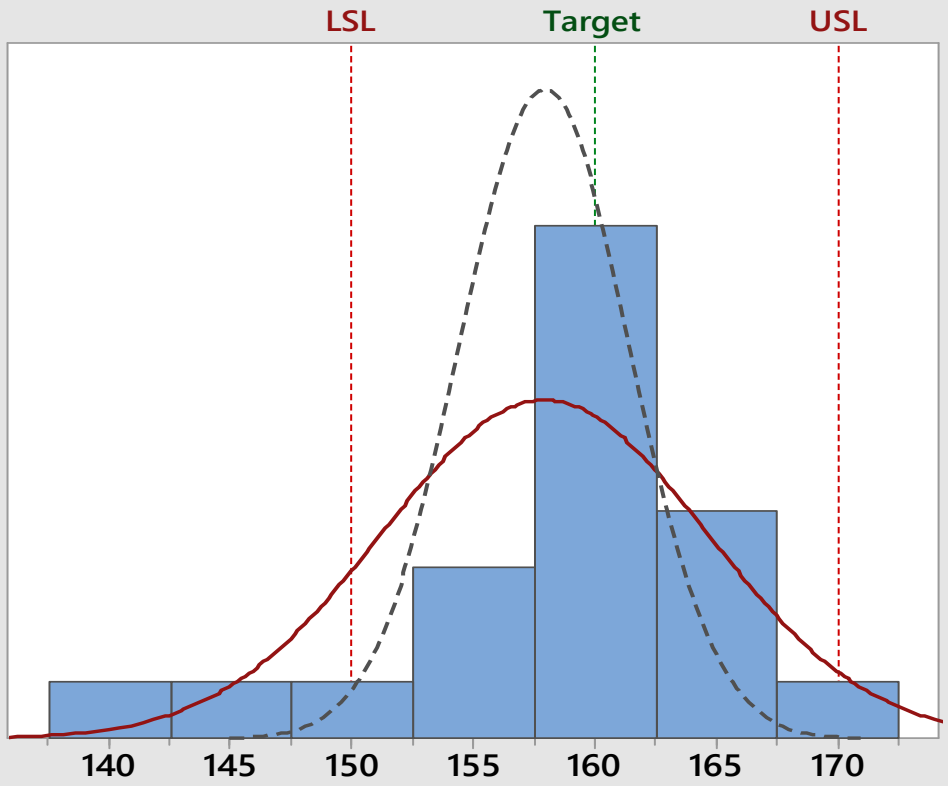
Potential (Within) Capability	
Cp	1.83
CPL	1.95
CPU	1.71
Cpk	1.71

Performance			
	Observed	Expected Overall	Expected Within
PPM < LSL	0.00	0.01	0.00
PPM > USL	0.00	0.43	0.14
PPM Total	0.00	0.44	0.14

www.statisticaltechniques.com.au

Process Capability Report for Temperature Degrees

Process Data	
LSL	150
Target	160
USL	170
Sample Mean	157.9
Sample N	20
StDev(Overall)	6.71134
StDev(Within)	3.49944



Overall
Within

Overall Capability	
Pp	0.50
PPL	0.39
PPU	0.60
Ppk	0.39
Cpm	0.47

Potential (Within) Capability	
Cp	0.95
CPL	0.75
CPU	1.15
Cpk	0.75

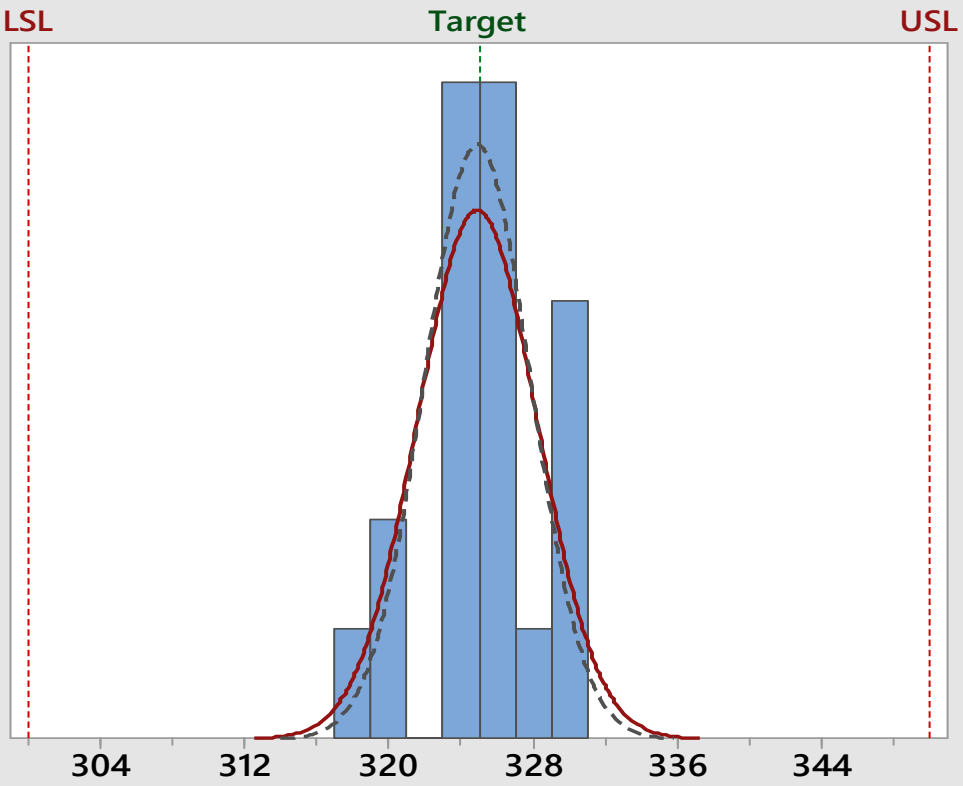
Performance

	Observed	Expected Overall	Expected Within
PPM < LSL	150000.00	119575.42	11988.30
PPM > USL	0.00	35700.53	272.41
PPM Total	150000.00	155275.95	12260.71

www.statisticaltechniques.com.au

Process Capability Report for Pressure kPa

Process Data	
LSL	300
Target	325
USL	350
Sample Mean	324.9
Sample N	20
StDev(Overall)	3.30709
StDev(Within)	2.93953



Overall
Within

Overall Capability	
Pp	2.52
PPL	2.51
PPU	2.53
Ppk	2.51
Cpm	2.52

Potential (Within) Capability	
Cp	2.83
CPL	2.82
CPU	2.85
Cpk	2.82

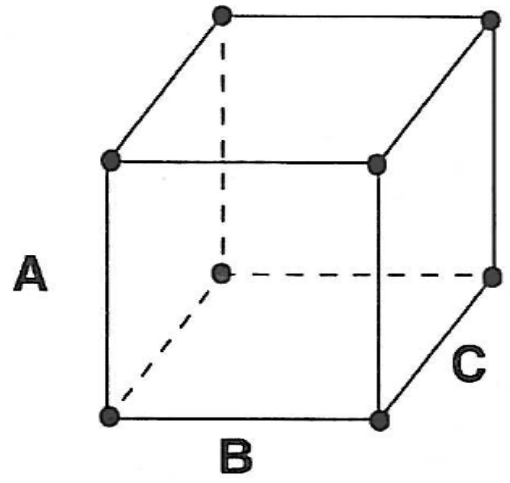
Performance

	Observed	Expected Overall	Expected Within
PPM < LSL	0.00	0.00	0.00
PPM > USL	0.00	0.00	0.00
PPM Total	0.00	0.00	0.00

www.statisticaltechniques.com.au

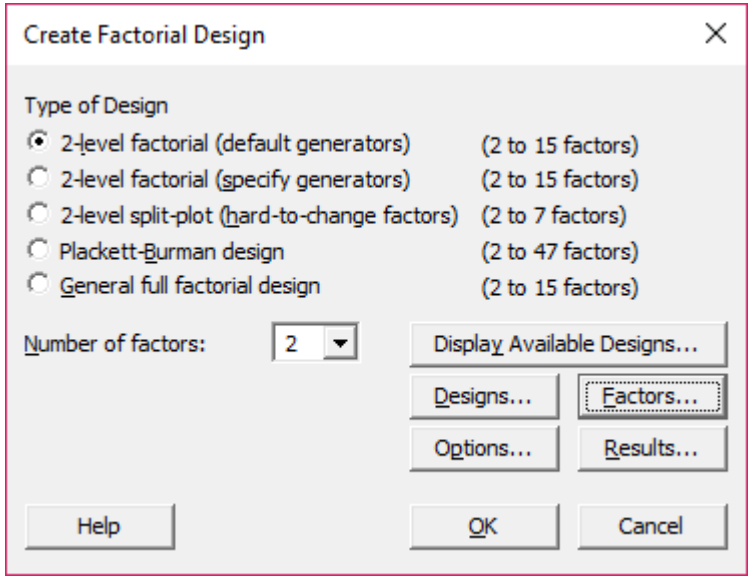
Method 4 – Design of Experiments

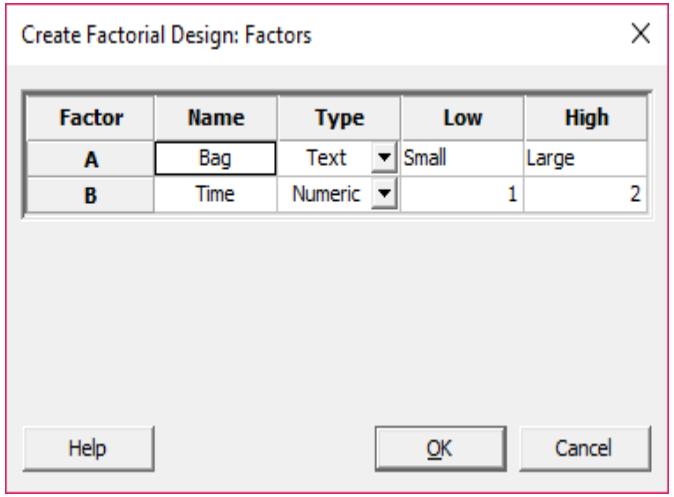
Determine the parameters which affect seal strength and their optimal values using a two level full factorial design of experiments.

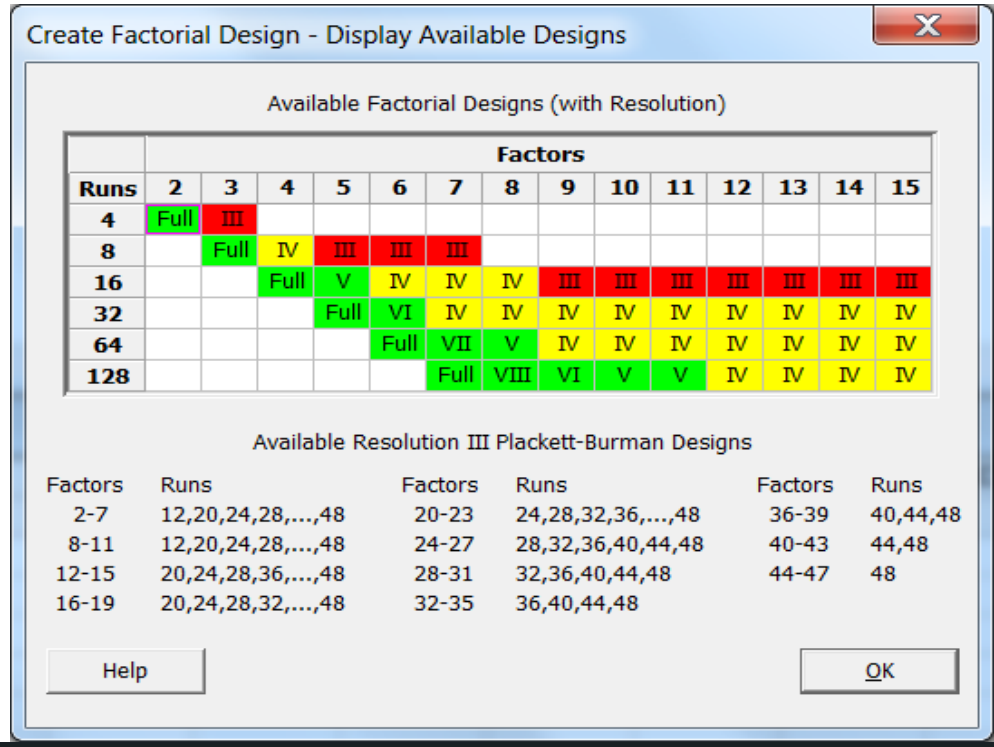


Select and Create the Design

- Create an experimental design in a worksheet to record the response variable. Create a 2 level factorial design, with three replicates





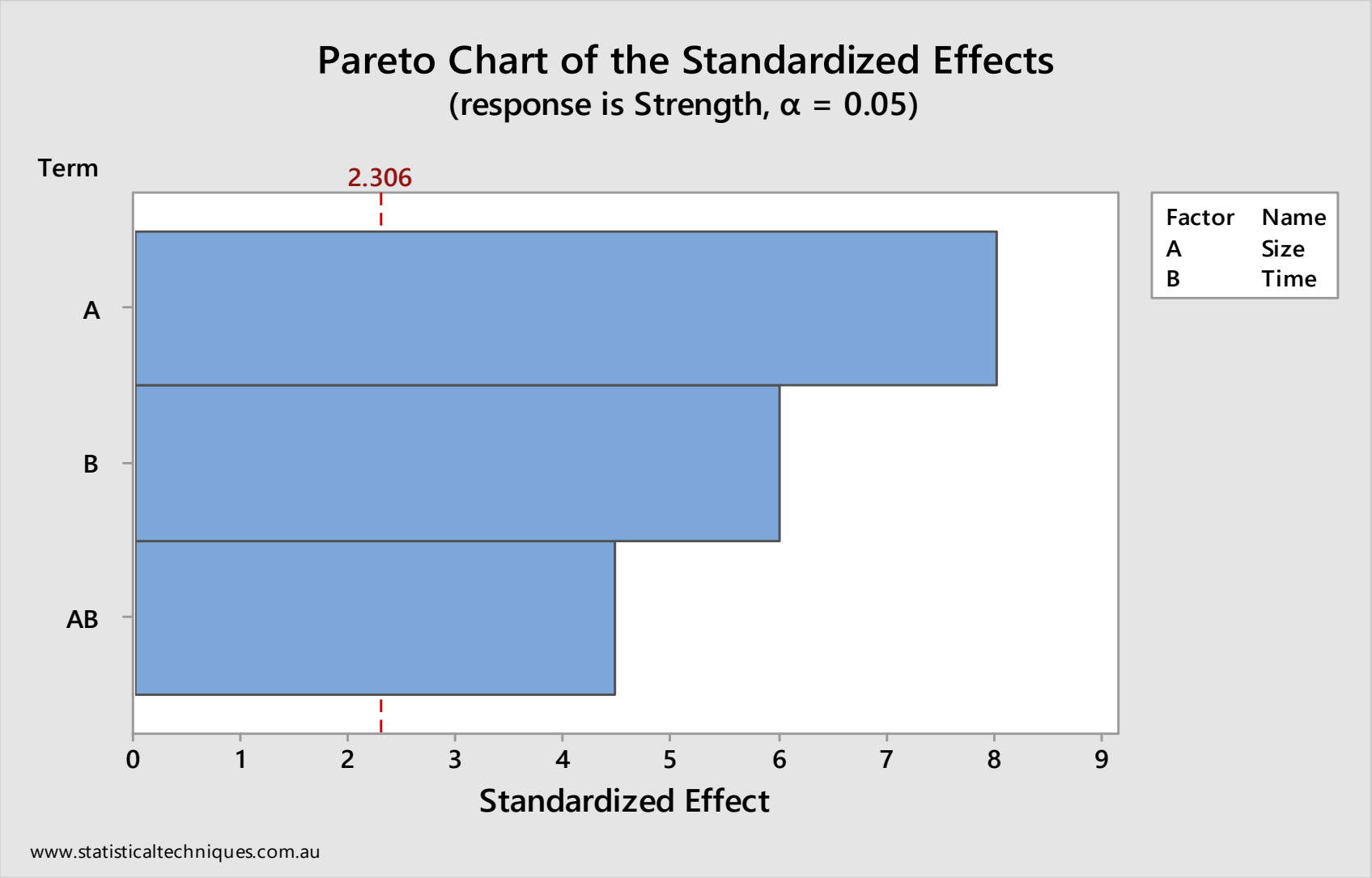


View the Design

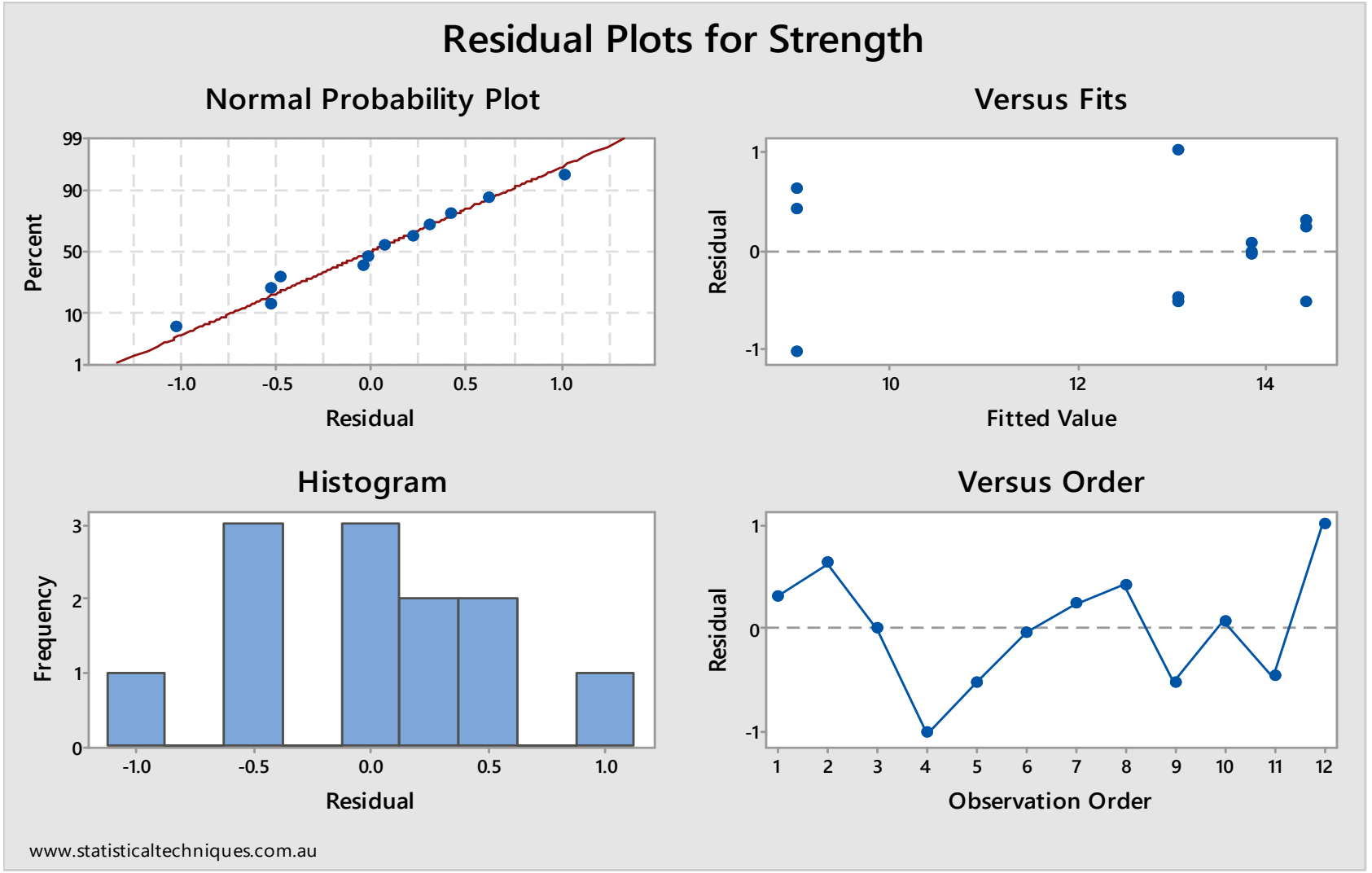
Worksheet 11 ***

	C1	C2	C3	C4	C5-T	C6	C7	C8	C9	C
	StdOrder	RunOrder	CenterPt	Blocks	Size	Time	Strength			
1	2	1	1	1	Large	1	14.72			
2	11	2	1	1	Small	2	9.62			
3	4	3	1	1	Large	2	13.81			
4	3	4	1	1	Small	2	7.97			
5	1	5	1	1	Small	1	12.52			
6	12	6	1	1	Large	2	13.78			
7	10	7	1	1	Large	1	14.64			
8	7	8	1	1	Small	2	9.41			
9	6	9	1	1	Large	1	13.89			
10	8	10	1	1	Large	2	13.89			
11	5	11	1	1	Small	1	12.57			
12	9	12	1	1	Small	1	14.06			
13										

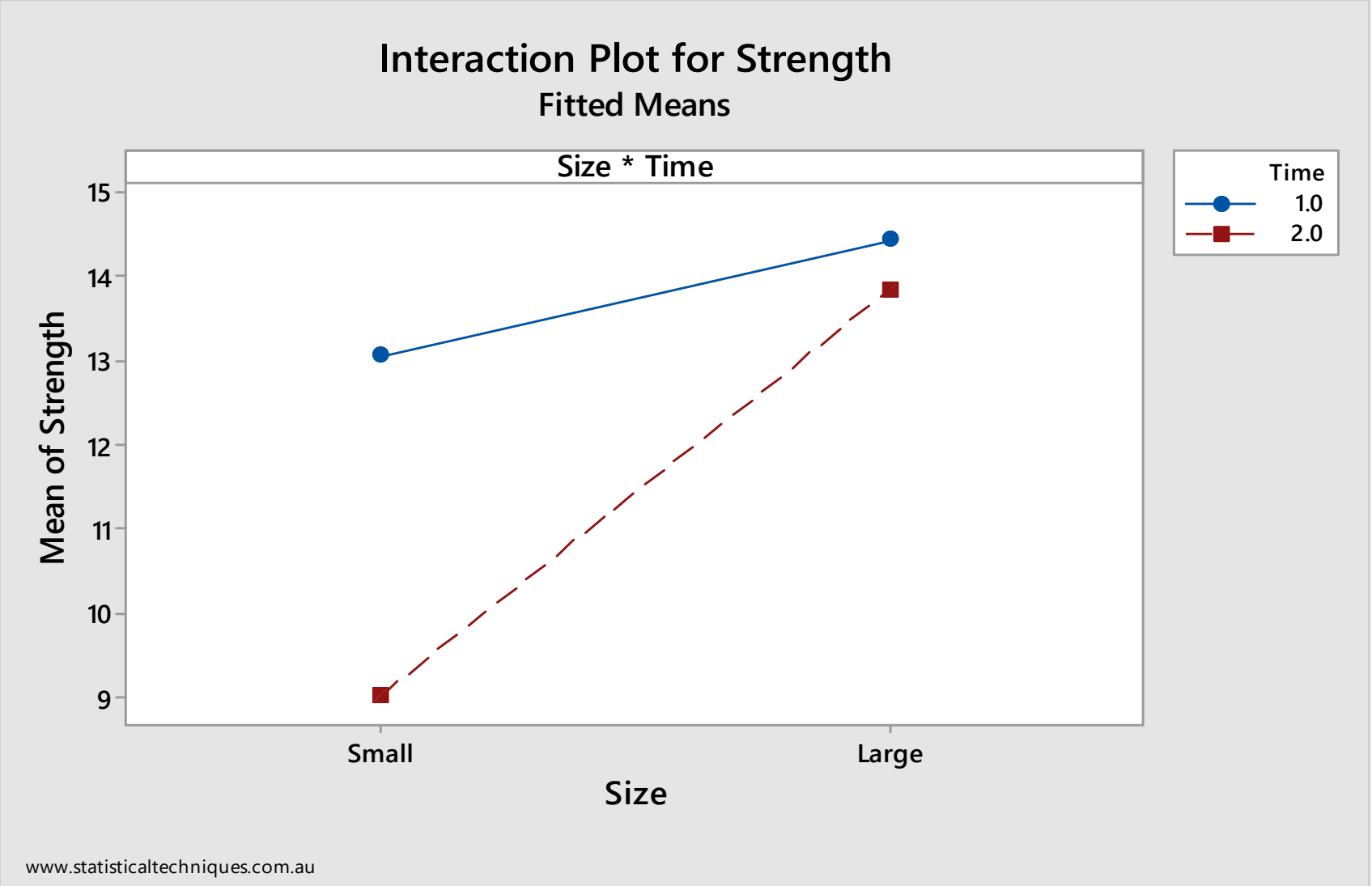
Analyse the Design



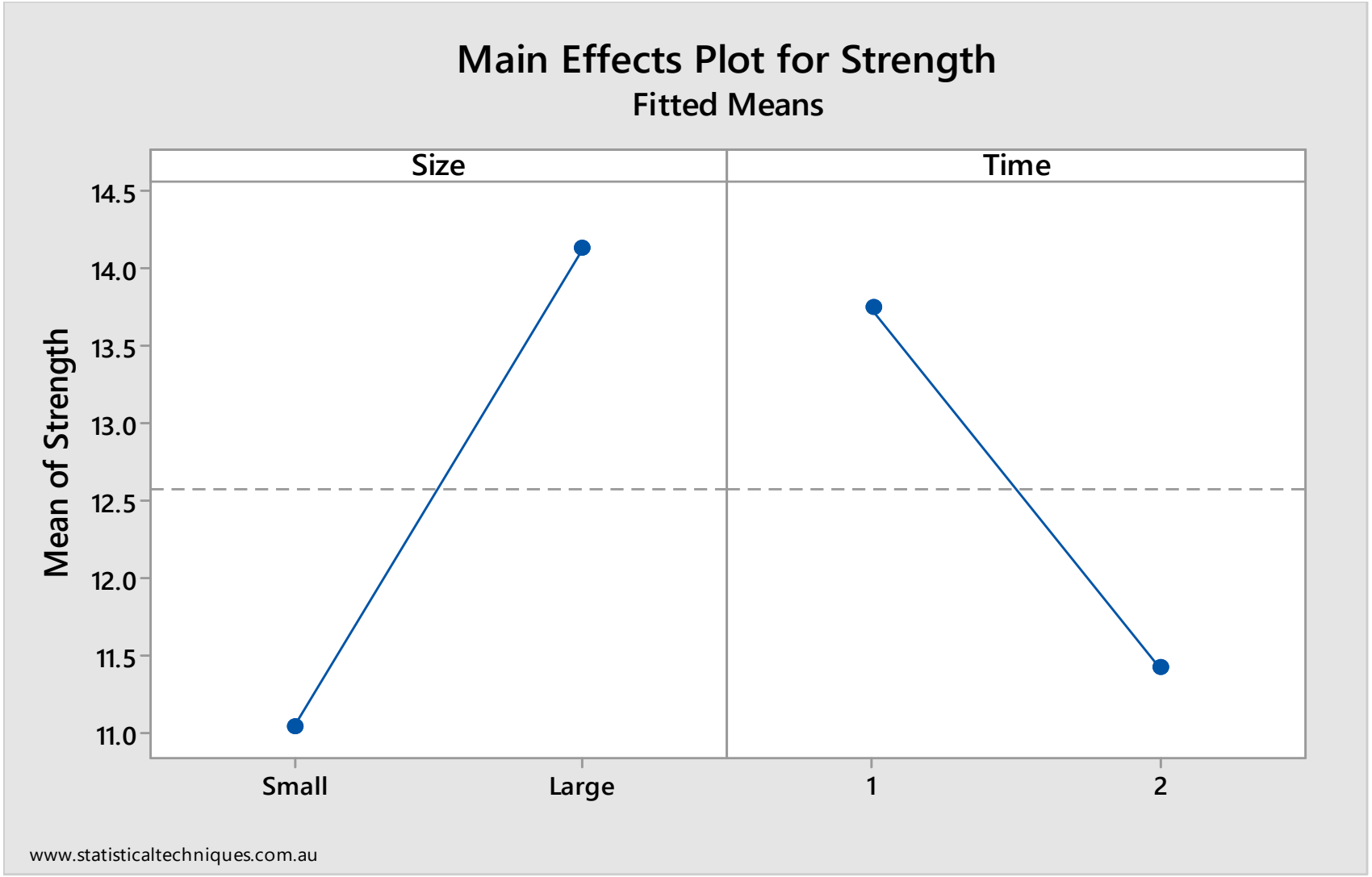
Check the Model



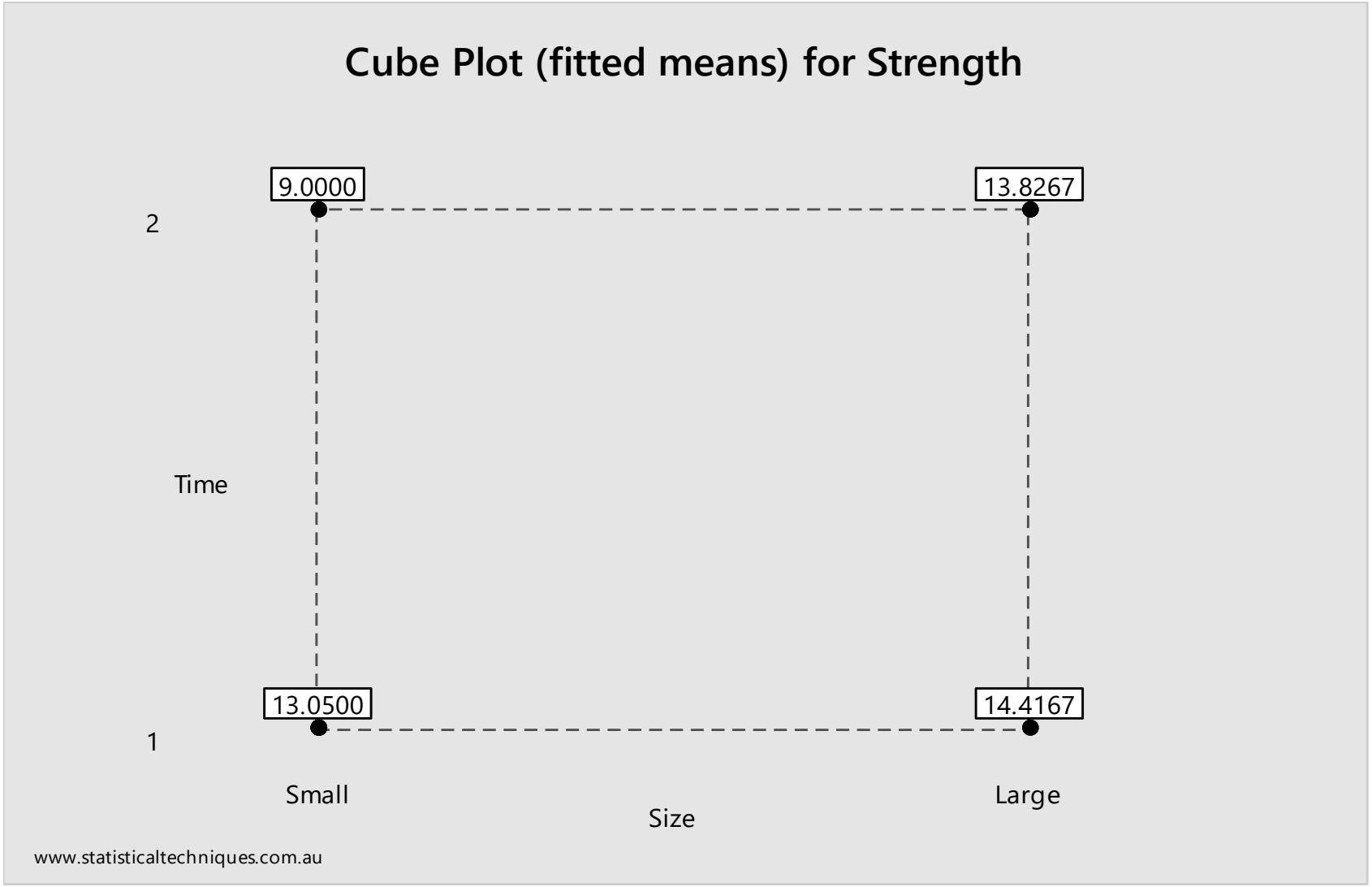
Check for Interactions



Interpret Results

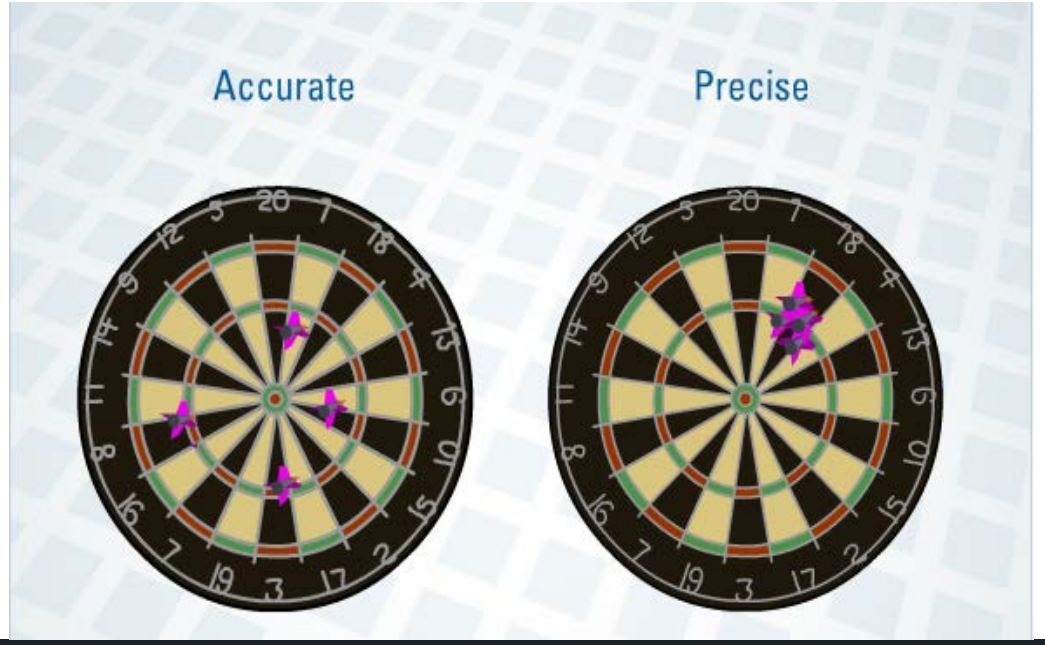


Draw Conclusions



Method 5 – Measurement System Analysis

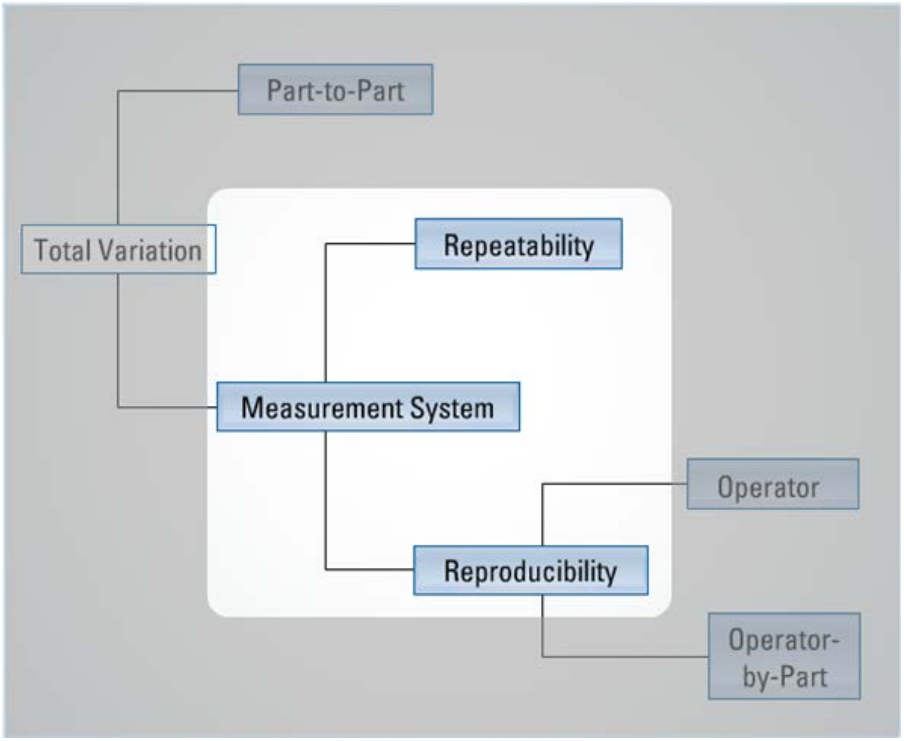
Determine whether measurements are accurate and precise and if measurements can be trusted – are repeatable and reproducible.



Measurement System Analysis

- Five main measurement studies for Continuous Variables
    1. Type one Gage Study
    2. Gage Run Chart
    3. Gage Linearity & Bias Study
    4. Gage R&R Study (Crossed)
    5. Gage R&R Study (Nested)

- Another study for Attribute Variable
    1. Attribute Agreement Analysis



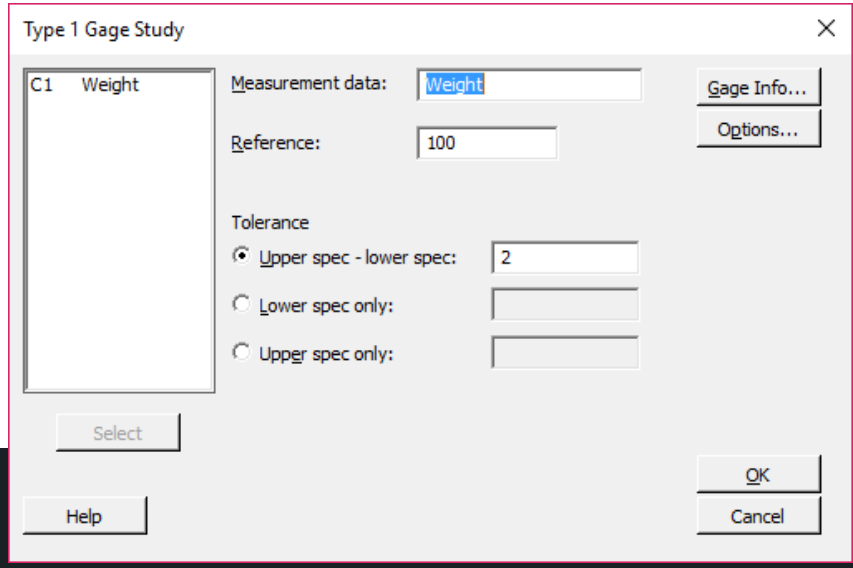
Measurement System Analysis

- Before proceeding, quality engineers need to determine whether the measurements from the digital scale can be trusted.
- To determine acceptability, the engineers use a type one and a gauge repeatability and reproducibility study, and an …
- Attribute study to show inspectors consistently agree with their own appraisals, amongst each other and against a standard.

Type One Study

- Through repeated measurements of a known standard, the type one study can determine bias and how capable the gauge is of measuring.

- One operator weighs a 100 gram which is a known standard weight thirty times and records the results into a Minitab worksheet.

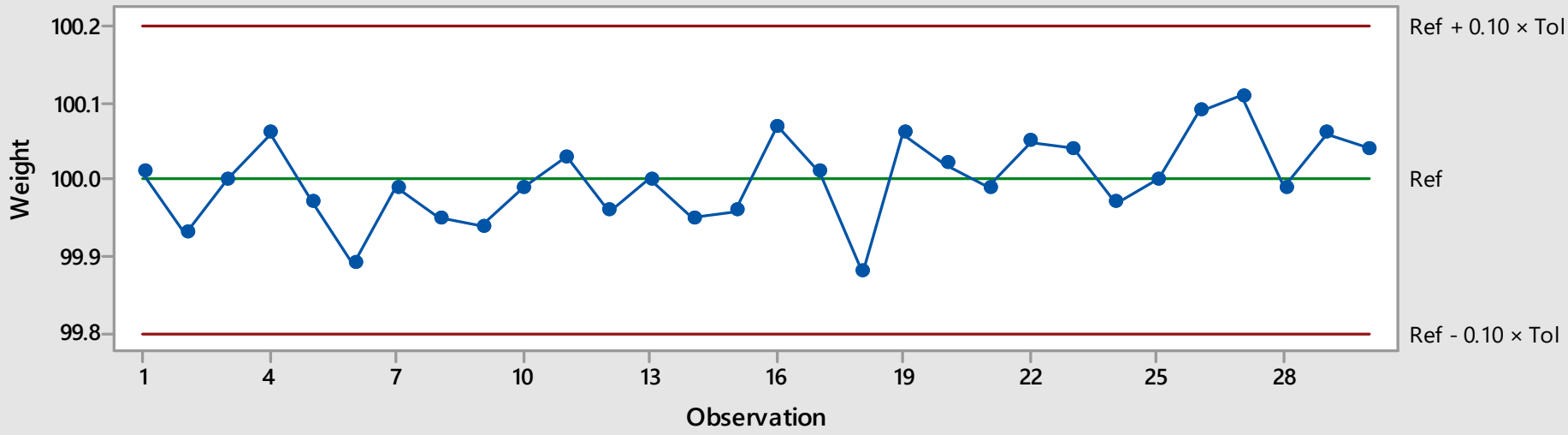


Type 1 Gage Study for Weight

Gage name: Type One Study - GMP and Engineering Forum
Date of study: 16 July 2018

Reported by: Bass Masri
Tolerance: 2
Misc: Statistical Techniques

Run Chart of Weight



Basic Statistics	
Reference	100
Mean	100.00
StDev	0.055
6 × StDev (SV)	0.331
Tolerance (Tol)	2

Bias	
Bias	0.00
T	0.033
PValue	0.974
(Test Bias = 0)	

Capability	
Cg	1.21
Cgk	1.20

%Var(Repeatability)	16.57%
%Var(Repeatability and Bias)	16.60%

www.StatisticalTechniques.com.au

Interpretation and Conclusion

- The output shows that for a tolerance of +/- 1 gram the digital scale is acceptable with Cgk that is greater than 1. All measured values are within +/- 10% of the tolerance, at an average of 100 grams.

- The null hypothesis is that there is no bias in measurements from the reference value. The p value (0.974) is greater than 0.05 so we can conclude there is no bias and proceed to the gauge study.

Repeatability & Reproducibility Study

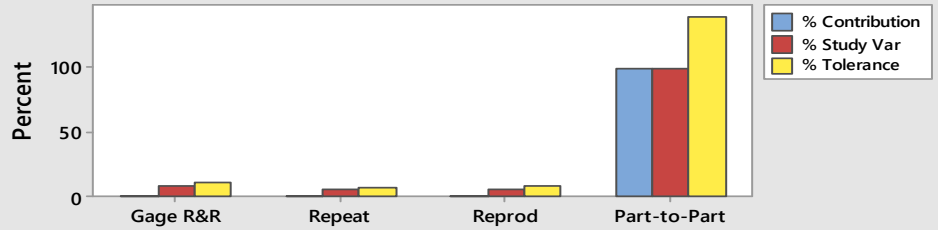
- Gage R&R studies determine how much of the observed process variation is due to the measurement system: equipment, operators environment and procedures and how much is due to part variation.
  - Repeatability is variation observed when the same operator measures the same part repeatedly with the same device.
  - Reproducibility is the variation observed when different operators measure the same parts using the same device.

Gage R&R (ANOVA) Report for Measurements

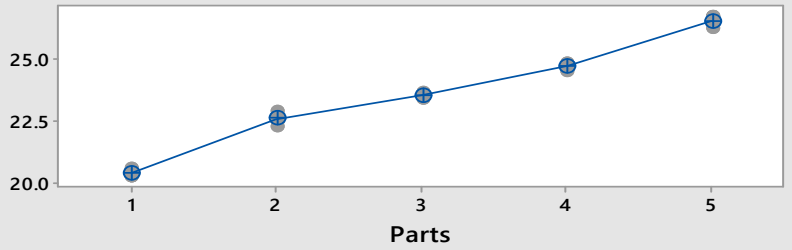
Gage name: Gage R&R Study - GMP and Engineering
Date of study: 16 July 2018

Reported by: Bass Masri
Tolerance: +/- 5 Grams
Misc: Statistical Techniques

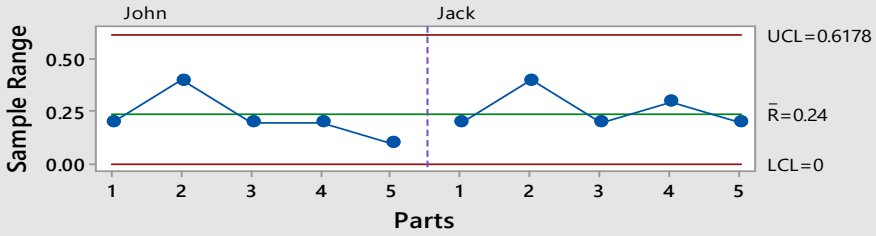
Components of Variation



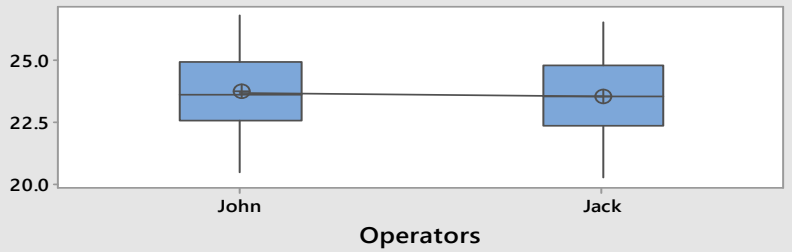
Measurements by Parts



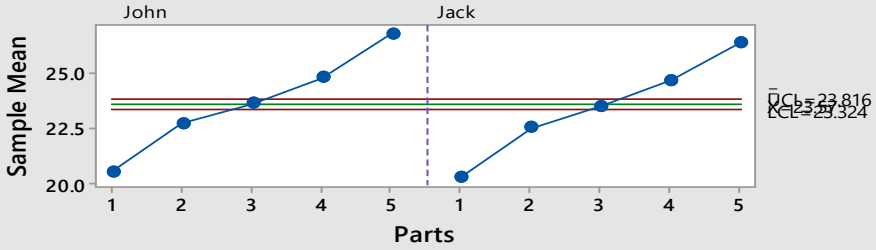
R Chart by Operators



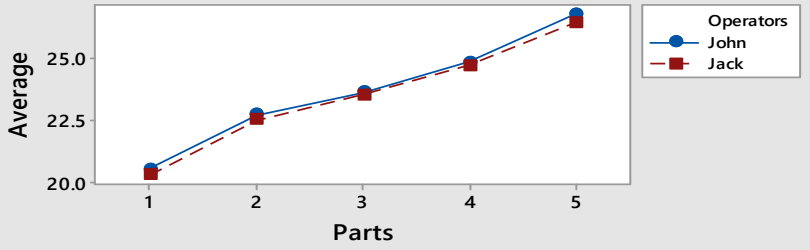
Measurements by Operators



Xbar Chart by Operators



Parts * Operators Interaction



www.statisticaltechniques.com.au

Interpretation and Conclusion

- Engineers run a gauge study using two inspectors and five parts selected from across the range of the part values 20-30 grams.
- Gauge repeatability and reproducibility or measurement system variation is around 8% of process variation (study variation).
- Most of the study variation comes from the part to part variation. Therefore they can trust their measurement system and proceed.

Attributes Agreement Analysis

- In the last step of the process, operators visually assess the seal as closed or open (conforming or non-conforming, binary variable).
- Two appraisers' rated 50 bags [to reflect the range of parts] as either good-to-go (G) or not good-to-go (NG).
- Each appraiser [Fred and Lee] rate each bag twice, in a random order to mimic the typical production environment.

Attributes Agreement Analysis

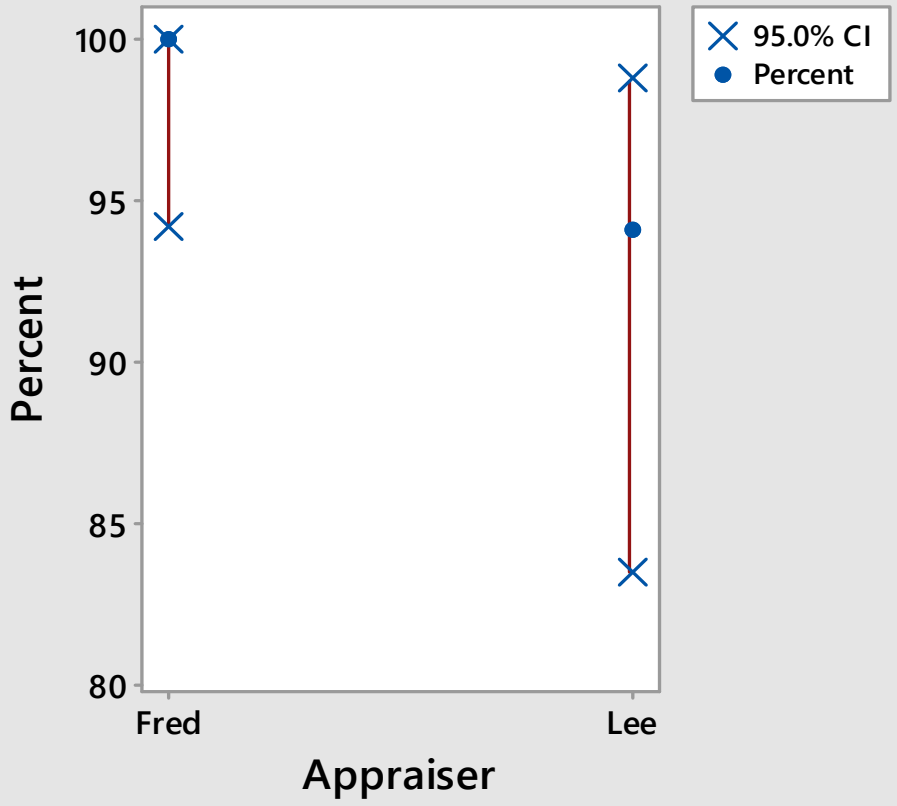
- Attribute Agreement Analysis shows operators consistently agree with their own appraisals, amongst each other and against a standard.

1. Within Appraiser: Does each appraiser rate the same parts, the same way, each time?
2. Between Appraisers: Do the appraisers ratings consistently agree with each other?
3. Appraiser versus Standard: Does each appraiser evaluate parts accurately against a standard?

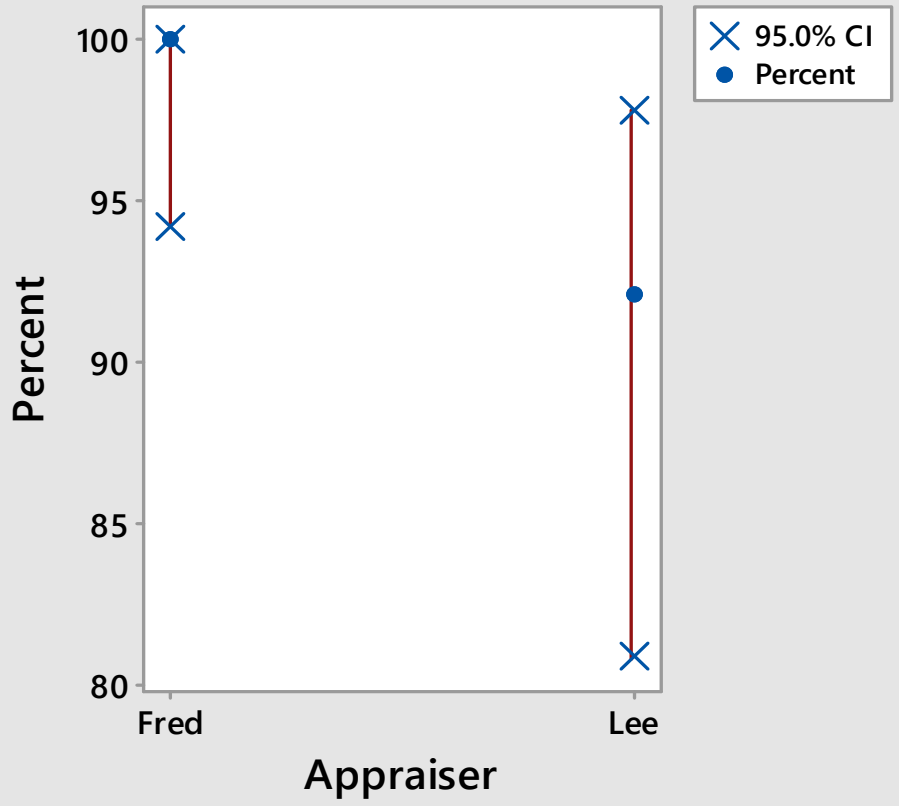
Assessment Agreement

Date of study: 16 July 2018
Reported by: Bass Masri
Name of product: Attribute Agreement Study
Misc: Statistical Techniques

Within Appraisers



Appraiser vs Standard



Interpretation and Conclusion

- The Assessment Agreement graph shows the consistency of each appraiser's answers and the agreement against a standard.
- Fred rated all 50 parts consistently and correctly across both trials. From the session output Lee incorrectly rated 3 of 50 parts.
- Lee rated parts incorrectly across the trials and may need training against approved procedures to assess product more effectively.

Method 6 – Sampling Plans

The Quality team want to inspect for the correct weight of bags and to ensure the seal on the bag is closed.

Sampling plans

- Measurement studies were successfully completed so we can trust the measurements of weight and inspector results, we now need to determine the sample size required to randomly select from the lot.

- It is not always possible, efficient or cost effective to inspect the entire lot. To determine an appropriate sample size the team use international standard sampling procedures…

1. Variables Method

ISO 3951 (AS2490)

2. Attribute Method

ISO 2859-1 (AS1199.1)

Zero Acceptance Plans

Variables Method

- **Variables Method:** Weight is a variable that is measured so the continuous variables method is used. This method has the advantage of requiring a much smaller sample size than the attributes method. But the variables method does require some very basic computation.

- **Sample Size Question**: Quality Assurance engineers want to evaluate the weight of bags without having to inspect the entire population. What is an appropriate sample size for a lot size of 1000 bags?

Variables Method

From the supply agreement the maximum bag weight should not exceed 1 kg, in lots of 1000 items and inspected using a Normal Inspection with an AQL of 1%. Using this information we need a random sample size of **n=35** to demonstrate an AQL of 1% for a lot size of 1000.

Batch/Lot Size	General Inspection		
	I	II	III
2 to 8			C
9 to 15		B	D
16 to 25	B	C	E
26 to 50	C	D	F
51 to 90	D	E	G
91 to 150	E	F	H
151 to 280	F	G	I
281to 500	G	H / I*	J
501 to 1,200	H	J	K
1,201 to 3,200	I	K	L
3,201 to 10,000	J	L	M
10,001 to 35,000	K	M	N
35,001 to 150,000	L	N	P
150,001 to 500,000	M	P	
500,001 and over	N		

Sample Size Code	Sample Size	VARIABLES- Acceptance Quality Limit, AQL, (Normal Inspection)										
		AQL 0.1	AQL 0.15	AQL 0.25	AQL 0.4	AQL 0.65	AQL 1.0	AQL 1.5	AQL 2.5	AQL 4.0	AQL 6.5	AQL 10
		k	*k*	*k*	*k*	*k*	*k*	*k*	*k*	*k*	*k*	*k*
B	3								1.12	0.958	0.765	0.566
C	4						1.45	1.34	1.17	1.01	0.814	0.617
D	5					1.65	1.53	1.40	1.24	1.07	0.874	0.675
E	7			2.00	1.88	1.75	1.62	1.50	1.33	1.15	0.955	0.755
F	10		2.24	2.11	1.98	1.84	1.72	1.58	1.41	1.23	1.03	0.828
G	15	2.42	2.32	2.20	2.06	1.91	1.79	1.65	1.47	1.30	1.09	0.886
H	20	2.47	2.36	2.24	2.11	1.96	1.82	1.69	1.51	1.33	1.12	0.917
I	25	2.50	2.40	2.26	2.14	1.98	1.85	1.72	1.53	1.35	1.14	0.936
J	35	2.54	2.45	2.31	2.18	2.03	1.89	1.76	1.57	1.39	1.18	0.969
K	50	2.60	2.50	2.35	2.22	2.08	1.93	1.80	1.61	1.42	1.21	1.00
L	75	2.66	2.55	2.41	2.27	2.12	1.98	1.84	1.65	1.45	1.24	
M	100	2.69	2.58	2.43	2.29	2.14	2.00	1.86	1.67	1.48		
N	150	2.73	2.61	2.47	2.33	2.18	2.03	1.89	1.70			
P	200	2.73	2.62	2.47	2.33	2.18	2.04	1.89				

Variables Method

- Randomly select a sample n=35 from the population and compute the sample mean, sample standard deviation and quality statistic.

Sample size	n= 35
Sample mean	x= sum of x's /n = 0.66
Sample Standard deviation	s= sqrt [sum(xi-x)2/(n-1)] = 0.10
Specification (upper limit)	U= 1
Quality Statistic	Qu= (U-x)/s = (1-0.66)/0.10 = 3.34
Acceptability constant	K= 1.89
Acceptability Criterion	3.34>1.89

- Since the quality statistic is greater than the acceptability constant K the entire lot can be accepted. The team can be (95%) confident that the weight of at least 99% of the bags will be conforming.

Acceptance Sampling by Variables

Accept or Reject Decision Using Weight (Kg)

Sample Size	35
Mean	0.663429
Standard Deviation	0.100585
Upper Specification Limit (USL)	1
Z.USL	3.34614
Critical Distance (k Value)	1.89

Decision: Accept lot.

Attributes Method

- The attributes inspection method consists of examining items and classifying them as either conforming or nonconforming.

- To compute the sample size for an attribute variable the team use the sampling procedure for inspection by Attributes. The advantage of attribute over variable sampling is that there is less time taken to inspect and compute statistics but at a cost of an increased sample.

- A sampling plan requires the acceptance and rejection criteria to be specified in advance. The acceptance and rejection criteria may be detailed in a supplier contract, quality document or test protocol.

Attributes Method

- Seal strength is assessed by **visual inspection** of the seal. If the seal appears closed, then the seal is considered sufficient to ensure integrity. If a seal is open then the bag is considered nonconforming.

- **Sample Size Question:** The Quality Assurance team want to evaluate the seals in a lot of bags without having to inspect the entire population. What is an appropriate sample size for a lot of 1000 bags?

Attributes Method

Using the same quality specifications, from table 2A we see a sample size of n=80 items is required to demonstrate an acceptable quality level of 1% for a lot size of 1000

Table 1 - Sample size code letters (see 10.1 and 10.2)

Lot size		General inspection levels		
		I	II	III
2 to	8	A	A	B
9 to	15	A	B	C
16 to	25	B	C	D
26 to	50	C	D	E
51 to	90	C	E	F
91 to	150	D	F	G
151 to	280	E	G	H
281 to	500	F	H	J
501 to	1 200	G	J	K
1 201 to	3 200	H	K	L
3 201 to	10 000	J	L	M
10 001 to	35 000	K	M	N
35 001 to	150 000	L	N	P
150 001 to	500 000	M	P	Q
500 001 and over		N	Q	R

Table 2A – Single sampling plans for normal inspection - master table (AS1199.1)

Sample Size Code	Sample Size	Acceptance Quality Limit, AQL, in percent nonconforming items (Normal Inspection)																			
		0.10		0.15		0.25		0.40		0.65		1.0		1.5		2.5		4.0		6.5		10	
		Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
A	2															↓		↓		0	1	↓	
B	3																	0	1	↑			
C	5															0	1	↑		↓		1	2
D	8													0	1	↑		↓		1	2	2	3
E	13											0	1	↑		↓		1	2	2	3	3	4
F	20									0	1	↑		↓		1	2	2	3	3	4	5	6
G	32						↓	0	1	↑		↓		1	2	2	3	3	4	5	6	7	8
H	50				↓	0	1	↑		↓		1	2	2	3	3	4	5	6	7	8	10	11
J	80		↓	0	1	↑		↓		1	2	2	3	3	4	5	6	7	8	10	11	14	15
K	125	0	1	↑		↓		1	2	2	3	3	4	5	6	7	8	10	11	14	15	21	22
L	200	↑		↓		1	2	2	3	3	4	5	6	7	8	10	11	14	15	21	22		
M	315	↓		1	2	2	3	3	4	5	6	7	8	10	11	14	15	21	22				
N	500	1	2	2	3	3	4	5	6	7	8	10	11	14	15	21	22	↑					
P	800	2	3	3	4	5	6	7	8	10	11	14	15	21	22	↑							
Q	1250	3	4	5	6	7	8	10	11	14	15	21	22	↑									
R	2000	5	6	7	8	10	11	14	15	21	22	↑											

80 bags are drawn at random and inspected. No bags were found open, so the lot is accepted.

Attribute Method – Zero Acceptance

- Where no failures are permissible, Zero Acceptance Sampling Plans (Nicholas Squeglia) may be used. Note that Zero Acceptance Sampling is specific to the 'Normal Inspection' (not tightened or reduced).

- This method has an advantage over AS1199, as its the simplest plan to interpret as the acceptance number is zero in all cases.

- This plan is suited to low cost items. The disadvantage, is that if one unit fails the entire lot is rejected.

Attribute Method – Zero Acceptance

Using the C=0 sampling plan to demonstrate an acceptable quality limit of 1% for lot size of 1000.

Lot Size	Index Values (Associated AQLs)															
	.010	.015	.025	.040	.065	.10	.15	.25	.40	.65	1.0	1.5	2.5	4.0	6.5	10.0
	Sample Size															
2 to 8	*	*	*	*	*	*	*	*	*	*	*	*	5	3	2	2
9 to 15	*	*	*	*	*	*	*	*	*	*	13	8	5	3	2	2
16 to 25	*	*	*	*	*	*	*	*	*	20	13	8	5	3	3	2
26 to 50	*	*	*	*	*	*	*	*	32	20	13	8	5	5	5	3
51 to 90	*	*	*	*	*	*	80	50	32	20	13	8	7	6	5	4
91 to 150	*	*	*	*	*	125	80	50	32	20	13	12	11	7	6	5
151 to 280	*	*	*	*	200	125	80	50	32	20	20	19	13	10	7	6
281 to 500	*	*	*	315	200	125	80	50	48	47	29	21	16	11	9	7
501 to 1200	*	800	500	315	200	125	80	75	73	47	34	27	19	15	11	8
1201 to 3200	1250	800	500	315	200	125	120	116	73	53	42	35	23	18	13	9
3201 to 10,000	1250	800	500	315	200	192	189	116	86	68	50	38	29	22	15	9
10,001 to 35,000	1250	800	500	315	300	294	189	135	108	77	60	46	35	29	15	9
35,001 to 150,000	1250	800	500	490	476	294	218	170	123	96	74	56	40	29	15	9
150,001 to 500,000	1250	800	750	715	476	345	270	200	156	119	90	64	40	29	15	9
500,001 and over	1250	1200	1112	715	556	435	303	244	189	143	102	64	40	29	15	9

The advantage using C=0 plan over AS1199 is the number sampled has reduced from 80 to 34.

Summary

- Three process variables: time, temperature and pressure are used to illustrate statistical methods in manufacturing process validation.

1. Statistical Distributions,
2. Statistical Process Control,
3. Process Capability,
4. Design of Experiments,
5. Measurement Systems Analysis and
6. Sampling Plans…

Minitab Project Files

- Keen to give it a go?

  A copy of the Minitab file is available on request!

- Don’t have Minitab? Download a free 30-day trial from www.minitab.com

C:\Users\Zinadine\
uments\My Work\

Further Resources

- Introduction to ‘Statistical Quality Control’ by Douglas C. Montgomery, Fifth Edition.

- Need assistance with quality analysis and strategic research? Contact Bass Masri Bass.Masri@outlook.com

- Global Harmonization Task Force SG3 Edition 2 - January 2004 – Process Validation Guidance.

C:\Users\Zinadine\
uments\My Work\

PART 820 -- QUALITY SYSTEM REGULATION

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Subpart G--Production and Process Controls Sec. 820.75 Process Validation

(a) Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented.

(b) Each manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.

(1) Each manufacturer shall ensure that validated processes are performed by qualified individual(s).

(2) For validated processes, the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process or the major equipment used shall be documented.

(c) When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented.

PART 820 -- QUALITY SYSTEM REGULATION

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Subpart O--Statistical Techniques **Sec. 820.250 Statistical techniques.**

(a) Where appropriate, each manufacturer shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics.

(b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented.

GUIDE TO INSPECTIONS OF QUALITY SYSTEMS

Production and Process Controls

4. If the results of the process reviewed cannot be fully verified, confirm process was validated by reviewing the validation study.

If the chosen process requires process validation, review the established Process Validation Procedure(s).

Verify via a review of the Process Validation Study Summary and Approval that objective evidence has demonstrated that the process will consistently generate a product or result meeting its predetermined specifications.

GUIDE TO INSPECTIONS OF QUALITY SYSTEMS

NOTE: If there are indications of unresolved, potential problems with a validated process, in addition to a review of process monitoring and control activities, a comprehensive validation study review should be conducted.

1. The instruments used to generate the objective evidence were properly calibrated and maintained prior to the study;
2. Predetermined product specifications were established;
3. Test sample sampling plans were based upon a statistically valid rationale;
4. Objective evidence demonstrates predetermined product specifications were met consistently;
5. Process tolerance limits were challenged;
6. Process equipment was properly installed, adjusted and maintained;
7. Process monitoring instruments are properly calibrated and maintained;
8. Changes to the validated process were appropriately challenged; and,
9. Process operators are appropriately qualified.

Q&A