CASE STUDY: PHARMACEUTICAL SECTOR

USING DMAIC TO REDUCE WASTE IN PILL MANUFACTURING

EXECUTIVE SUMMARY

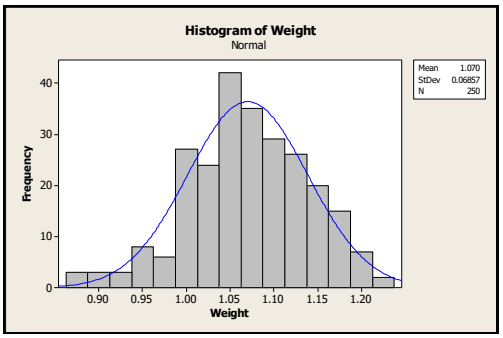
Secora was engaged by a large European Pharmaceutical Company to address a particular problem relating to its manufacturing processes. Specifically, production of a well-known brand of pills was at risk due to material variation in pill weight. Correct pill weight is critical to ensure correct medication.

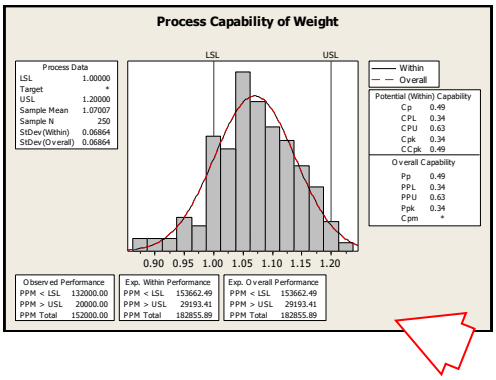
Secora utilized the traditional DMAIC approach in order to determine with accuracy the root causes of variation in pill weight. DMAIC is a tried and proven methodology for identifying variation in processes and was well understood and accepted by our client.

The results of each Phase are summarized in this section of the report. Detailed results are provided in the annexures.

DEFINE PHASE - Problem Statement, Business Case & Goal Statement

Problem Statement: The variation (designated as "Y1") in weight and pills not conforming to weight specifications (designated as "Y2") within (brand name confidential) is unacceptable.





Currently @18% of the (brand name confidential) pills need to be crushed and discarded

Business Case: Materials cost of discarded pills alone account for 800,000 (sFr.) a year. In addition, there are personnel, handling, documentation, regulation, and compliance costs which are estimated at 350,000 (sFr.). In total the cost of process inefficiency, variation and the resultant waste is estimated at 1,150,000 (sFr.) per year.

GOAL STATEMENT:

1. To reduce the variation (Y1) in the pill weight from 0.0686 to below 0.05
2. To increase the first pass rate from 85% to 99%
3. To be within in weight specifications (Y1).

MEASURE PHASE – Collect data and determine the baseline/current process performance

The client team believed a number of "causes" were responsible for the variation and non-compliance with the pill weight specifications. A data collection plan was developed, and potential causes measured over 250 batches on both manufacturing lines.

Initial Findings:

- Molecular size testing - possible statistical difference between manufacturing lines in molecular standard deviation, which could have a negative effect on pill variation and weight specification non-compliance.
- Pill compression time testing - the overall range (irrelevant of manufacturing line) within the compression time was quite large (0.187 to 0.20050). This could lead to the variation and specification non-compliance within the pill weight. Once again, we see differences between manufacturing line 1 and 2 both in range, standard deviation, and average. Once again, proving that the manufacturing lines (x2) could be responsible for the variation and non-compliance within the pill weight.
- Fill ratio - the overall range (irrelevant of manufacturing line) within the fill ratio was quite large (0.4540 to 0.5500). This could lead to the variation and specification non-compliance within the pill weight. Once again, we see differences between manufacturing line 1 and 2 both in range and standard deviation. Once again, proving that the manufacturing lines (x2) could be responsible for the variation and non-compliance within the pill weight
- Line speed testing - possible effect on variation and non-compliance with pill weight. CAUTION: Because the line speed can only be measured in whole numbers, it would be imprudent to make a decision at this stage. We will use other process engineering tools later to confirm or disapprove this factor.

Measure phase findings compiled: Differences in individual manufacturing lines, compression times, and fill ratio could have a direct impact on the variation and non-compliance within the pill weight. Furthermore, further investigation is required as to possible "interactions" between the factors (could one factor increase or decrease the other factors influence). Finally, line speed is measured must be analyzed in greater detail because measuring in whole numbers gives us little indication whether or not this factor has a positive or negative influence on the variation or non-compliance within the pill weight.

ANALYZE PHASE - Testing the perceived "causes" of variation

During the ANALYZE phase it is important to prove statistically that the various reasons the team believes is causing the variation and non-compliance within the pill weight. We prove or disprove, to a high probability, the inputs to the pill manufacturing process causing the variation we are attempting to reduce to a satisfactory level.

Findings:

- There is statistical proof that the manufacturing lines (1 and 2) operate differently and thus are a contributing factor to Y2 (non-compliance within pill weight). There is a 99.999% probability this factor is one of the root causes.
- We can say with high confidence that there is NO statistical proof that the manufacturing lines (1 and 2) are the cause for Y1 (variation within the pill weight). There is only a 74.40 – 79.10% probability this factor is one of the root causes.
- BOTH manufacturing lines are out of specification. Manufacturing line 1 produces @18% bad product and manufacturing line 2 @ 10% bad product.
- Molecular size does have an effect on both variation within the pill weight and non-compliance within the pill weight; BUT is only responsible for 4.3% of the total variation within the weight.
- We can say with a 99.999% confidence that line speed is also a root cause for the variation and non-compliance within the pill weight (25.40% to 26.16% of the variation).
- We can state with a 99.999% surety that compression time has a direct and linear effect on non-compliance within the pill weight (35.4% of the variation within pill weight).
- There is only a 61.7% chance that ambient moisture is responsible for the variation and non-compliance within the pill weight. Furthermore, it is responsible for less than 0.4% of the variation within the pill weight. We can comfortably ignore this factor from any further analysis.
- There is only an 81.9% chance that particle size is responsible for the variation and non-compliance within the pill weight. Furthermore, it is responsible for less than 1.4% of the variation within the pill weight. We can comfortably ignore this factor from any further analysis
- We can state with a 99.999% surety that fill ratio has a direct and quadratic effect on non-compliance within the pill weight. In addition, it also explains 33.0% of the variation within the pill weight.

As a result of this testing, it was confirmed that the following factors were causes of the variation in pill weight and specification and were therefore confirmed as candidates for optimization:

1. Manufacturing line
2. Compression time
3. Line speed
4. Fill ratio

IMPROVE PHASE - find solutions targeted at verified causes from the ANALYZE phase.

To show with data that solutions are developed which solve the problem and lead to improvement.

Steps:

- Decide whether to go proceed with DMAIC or move to DFSS - does it make sense to improve the existing process, or do you have to design an entirely new one?
- Identify solutions addressing important "causes" - which potential solutions are there? What criteria will you use to assess alternative solutions, and evaluate solutions?
- Minimize risks and implement solutions

Important considerations: What risk attaches to the selected solution, how to mitigate these risks? Should a pilot be run for the selected solution? What must be planned to implement the solution? How will results be checked?

Because we were able to identify with high certainty which factors have the largest and most significant impact on variation in pill weight and specification it was decided to conduct a Design of Experiment ("DOE") with these factors.

Findings:

1. There is a direct linear correlation between compression time and pill weight
2. Even though there is no direct correlation between fill ratio and pill weight, there is a squared relationship between fill ratio and pill weight
3. The cause line speed has been deleted from the model
4. We can explain 64.6% of the variation of the pill weight with these two factors
5. The mathematical model is sound because of the high P-Value (0.887) of the lack of fit.

To optimize the output (Y1) "pill weight" and to reduce the output (Y2) "pill weight variation", we ran the DOE model through the response optimizer for the optimal settings. To reach our goal of each pill weighing between 1.000 and 1.200 grams, we set compression time at 0.21300 and fill ratio at 0.46772. To prove this theory, we ran a pilot of thirty runs at these setting in order confirm (or deny) our pilot.

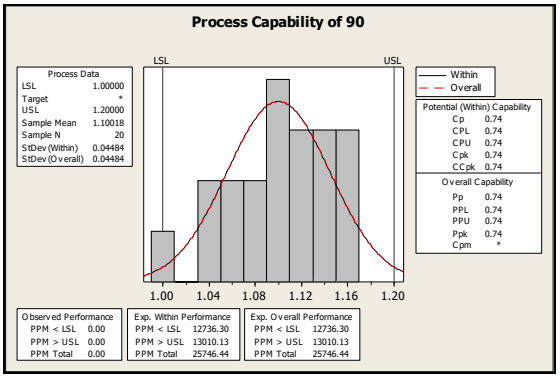
Improve phase conclusions: The pilot achieved both targets, i.e., Y1 (reduce variation from 0.0634 to 0.0500) and Y2 (Be within specification of pill weight 1.000 to 1.200). The pilot was successful.

CONTROL PHASE - to ensure sustainability of the process improvements, evaluate the accomplished results and finally close the project.

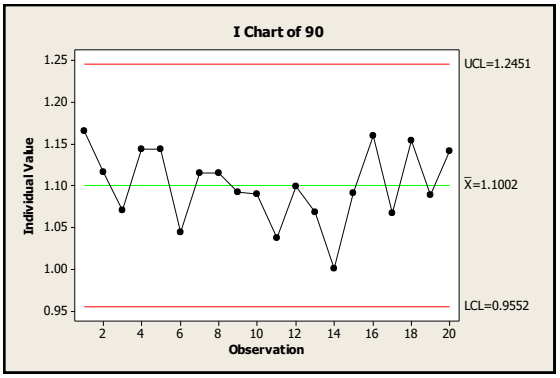
Process Management asks for establishing “leading indicators” (X) in addition to or instead of “lagging indicators” (Y) based on the analysis results. This means we are no longer ONLY monitoring the variation and non-compliance of the pill weight, but mainly the two critical factors we verified during the analyze and improve phase of the project, i.e., compression time and fill ratio.

To make sure we do not make any unnecessary changes to the process, and only make adjustments when warranted, control charts were built into the process, which allows the process owner to visually see if there is common cause variation or special cause variation, which will determine the correction plan.

Control charts and process capability are reviewed at 30-, 60- and 90-days post optimization. The 90-day results where:



Capability: Above 95%



Stability: in control

CONCLUSION: Project close out and follow up successful. Project CLOSED.

PROJECT OUTCOME

- 95% of pill wastage was eliminated, meaning an annual saving of 1,000,000 sFr
- Project term 21 weeks
- Commitment from team and advisors, 20 hours per week
- Project cost 175,000 sFr

THE DMAIC PROCESS IN DETAIL

1. DEFINE PHASE

Methodology

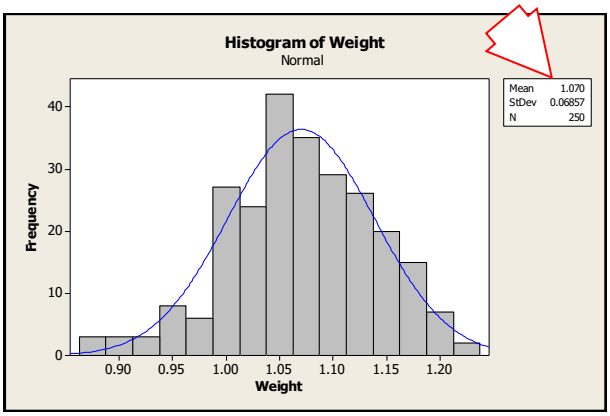
In the DEFINE phase we address the following:

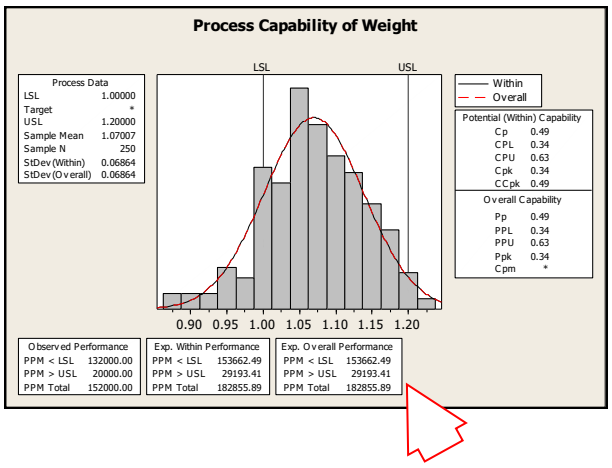
- Problem statement - What problem are you addressing with the project?
- Project metrics - How do you measure the influence of the problem and the success of the project? What is the "project Y" including a goal statement? What are the customer benefits from the project?
- Business benefit - What is the business impact of the problem that you are addressing? What are the financial benefits of the project?
- Process - What is the name of the process that you are addressing with the project?
- Participants - Who are the stakeholders to be addressed? Who are the project team members?

Application

Problem Statement:

The variation (designated as "Y1") in weight and pills not conforming to weight specifications (designated as "Y2") within (brand name confidential) is unacceptable.





Currently @18% of the (brand name confidential) pills need to be crushed and discarded

Project Metrics:

Y1 = Standard deviation of weight in grams
Y2 = Weight in grams

Business Case:

Materials cost of discarded pills alone account for 800,000 (sFr.) a year. In addition, there are personnel, handling, documentation, regulation, and compliance costs which are estimated at 350,000 (sFr.). In total the cost of process inefficiency, variation and the resultant waste is estimated at 1,150,000 (sFr.) per year.

Process boundaries:

Lower boundary: Raw material into mixer
Upper Boundary: Finished product inspection line

Included in scope of project:

Both manufacturing lines

Goal Statement:

1. To reduce the variation (Y1) in the pill weight from 0.0686 to below 0.05
2. To increase the first pass rate from 85% to 99%
3. To be within in weight specifications (Y1).

2. MEASURE PHASE

Methodology

In the second phase of the project, MEASURE, data was collected, and the baseline/current process performance determined. Key considerations:

- Decide which variables to include in data collection - since it is not possible to measure everything, what are likely to be the main causes?
- Verify measurement system and sampling approach - after it is clear what to measure, the next step is to decide on how to measure and how much data is needed.
- Collect data - execute the data collection plan.
- Baseline Capability - with data on the current process, make an analysis of the current performance (updating the project charter, as required).

Application

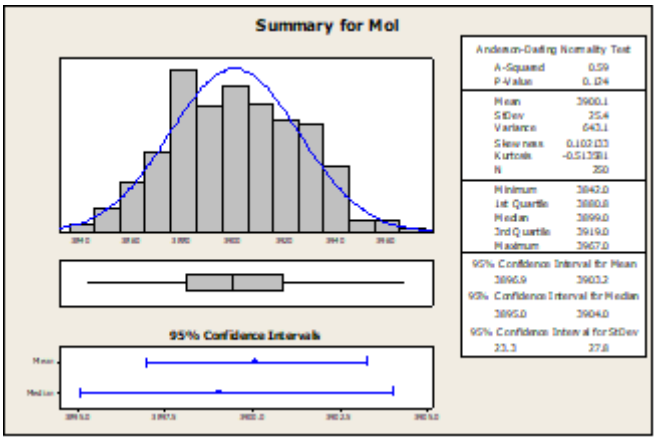
During the initial brainstorming session, the client team believed the following "causes" were responsible for the variation and non-compliance with the pill weight specifications:

1. Molecular size of material (designated as X1)
2. Manufacturing line (1 and 2) (designated as X2)
3. Line speed (designated as X3)
4. Compression time (designated as X4)
5. Ambient moisture in air (designated as X5)
6. Particle size of material (designated as X6)
7. Fill ratio (designated as X7)

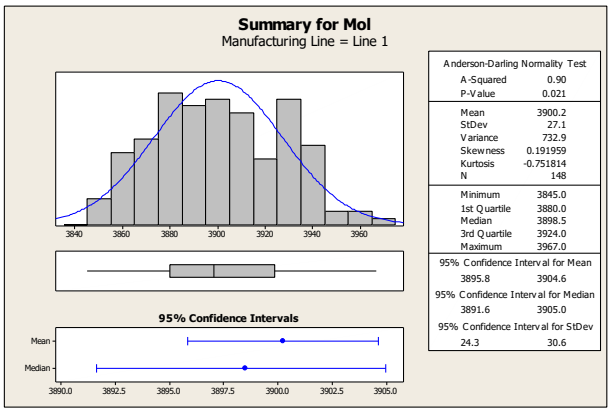
A data collection plan was developed, and these parameters were measured over the next 250 batches on both manufacturing lines. The purpose is to gain knowledge and to establish a base line from which we can work. What we are looking for are "major" differences between averages, standard deviations, ranges, variances, and medians. This is just a rudimentary look at the possible reasons for the variation and non-compliance within the pill weight.

Here are the initial results:

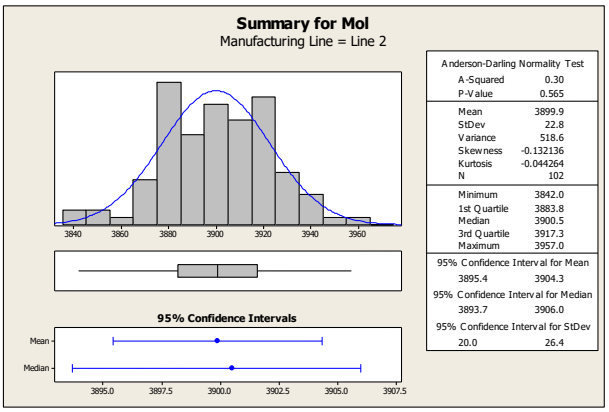
Molecular size (X1)



Molecular size overall



Molecular size manufacturing line 1

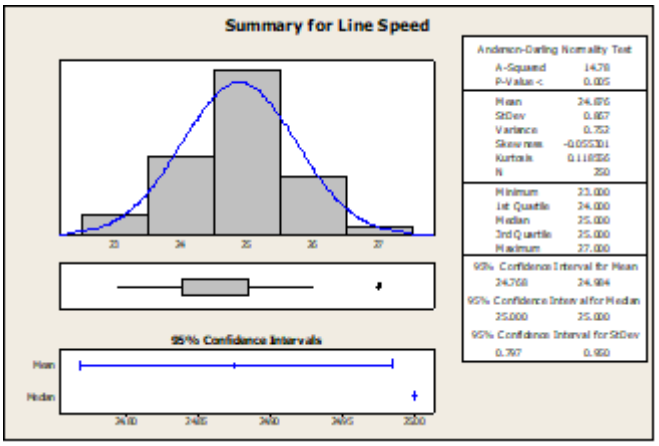


Molecular size manufacturing line 2

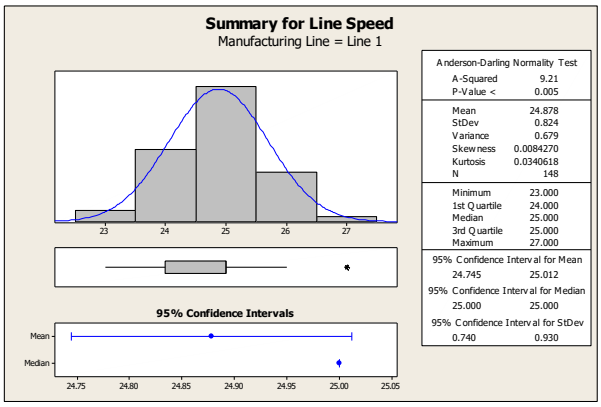
Initial findings:

- Possible statistical difference between manufacturing lines in molecular standard deviation, which could have a negative effect on pill variation and weight specification non-compliance.

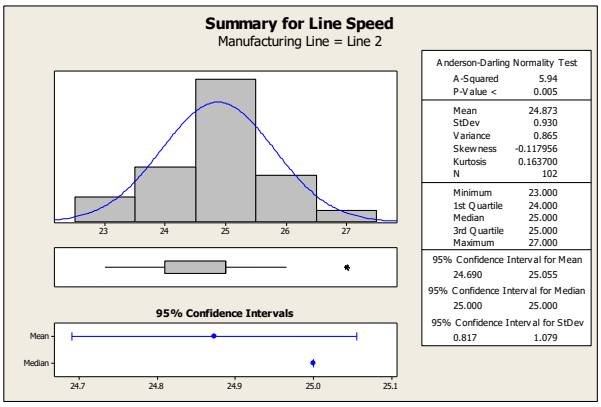
Line speed (X3)



Line speed overall



Line speed
Manufacturing line 1

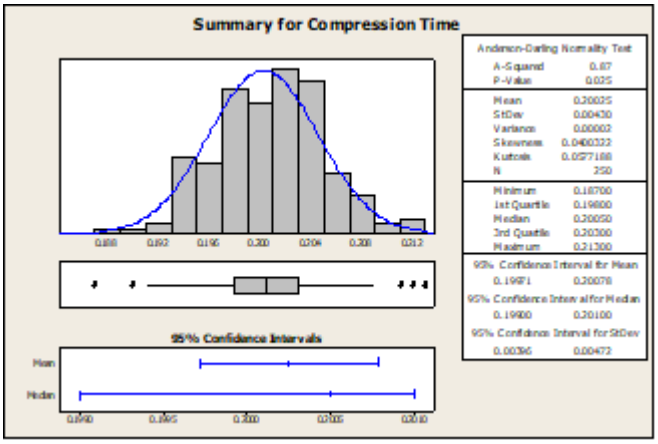


Line speed
Manufacturing line 2

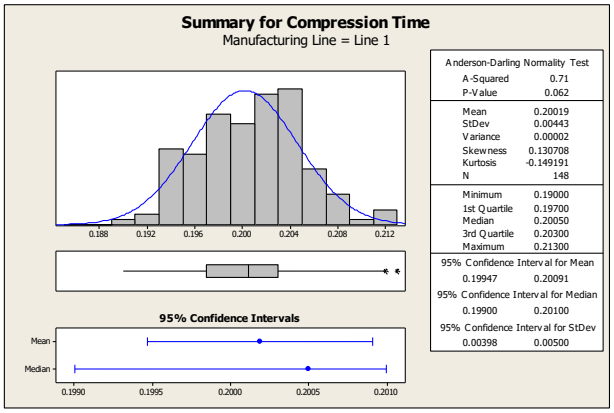
Initial findings:

- Possible effect on variation and non-compliance with pill weight.
- CAUTION: Because the line speed can only be measured in whole numbers, it would be imprudent to make a decision at this stage. We will use other process engineering tools later to confirm or disapprove this factor.

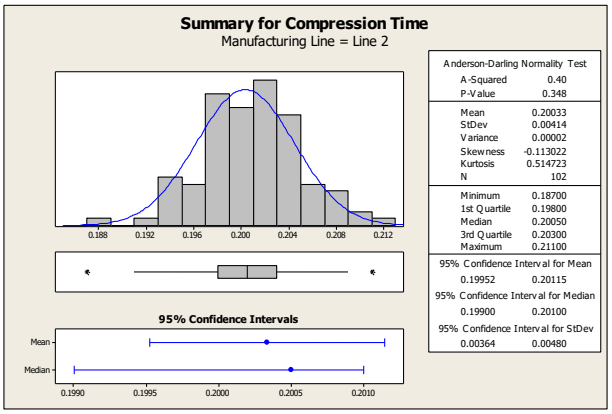
Compression time (X4)



Compression time overall



Compression time
Manufacturing line 1



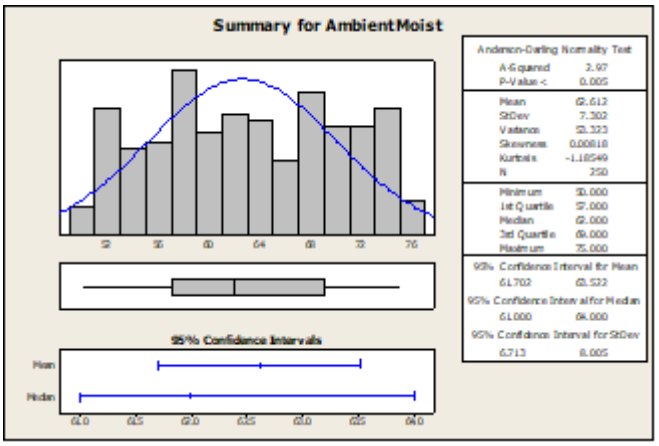
Compression time
Manufacturing line 2

Initial findings:

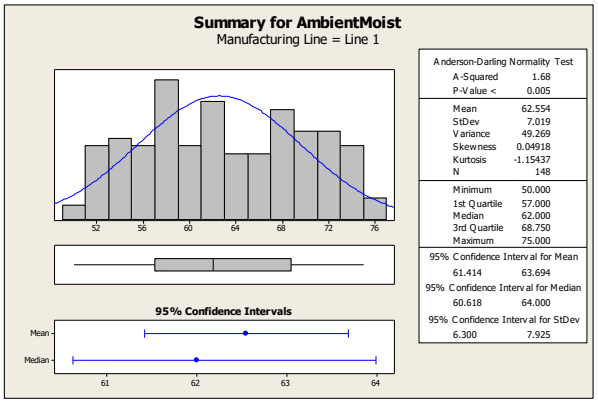
1. The overall range (irrelevant of manufacturing line) within the compression time was quite large (0.187 to 0.20050). This could lead to the variation and specification non-compliance within the pill weight.

2. Once again, we see differences between manufacturing line 1 and 2 both in range, standard deviation, and average. Once again, proving that the manufacturing lines (x2) could be responsible for the variation and non-compliance within the pill weight.

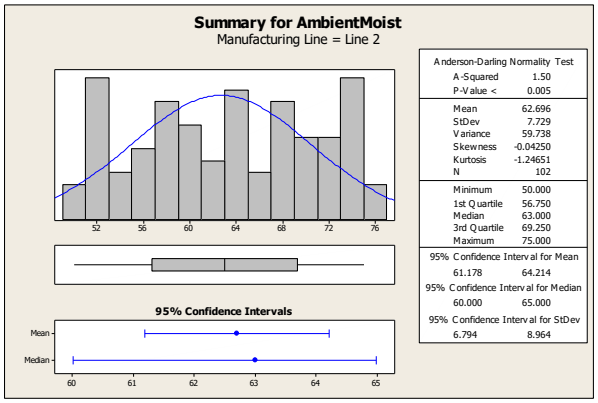
Ambient moisture (X5)



Ambient moisture overall



Ambient moisture
Manufacturing line 1

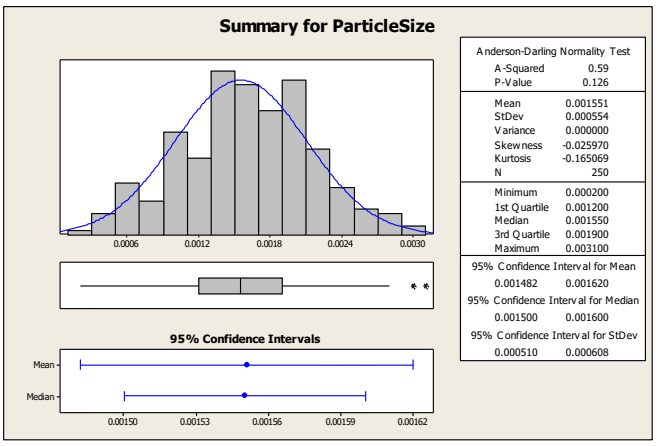


Ambient moisture
Manufacturing line 2

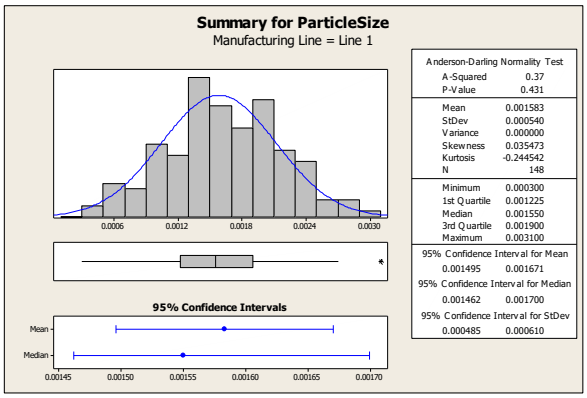
Initial findings:

Nothing of interest.

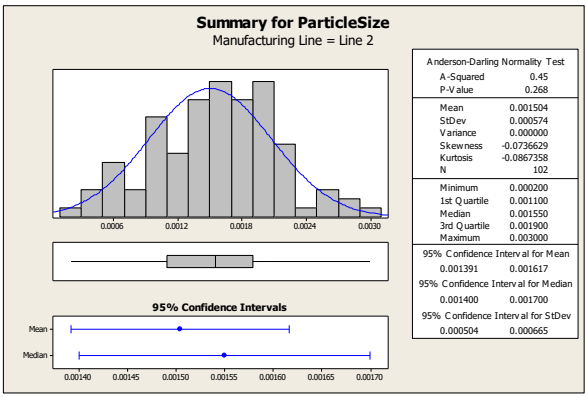
Particle size (X6)



Particle size overall



Particle size
Manufacturing line 1

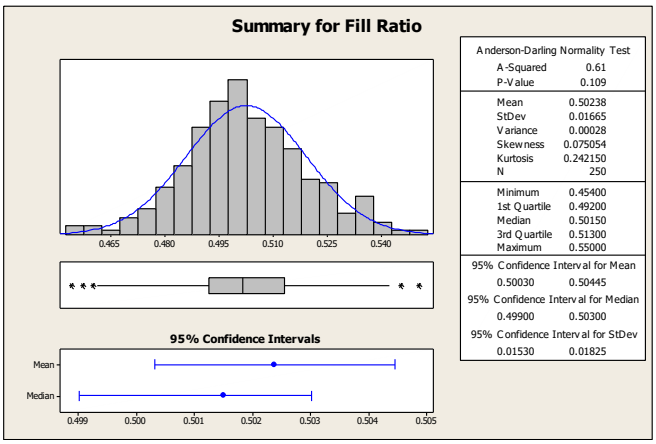


Particle size
Manufacturing line 2

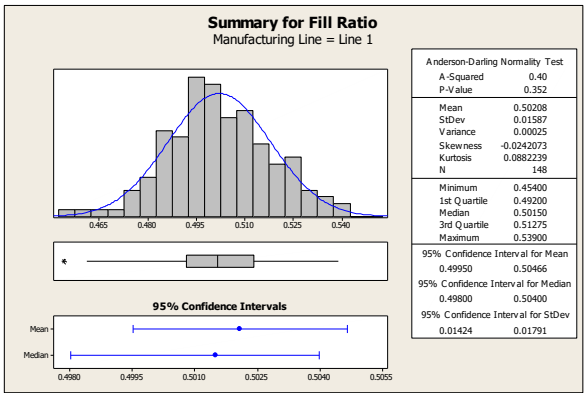
Initial findings:

Nothing of interest

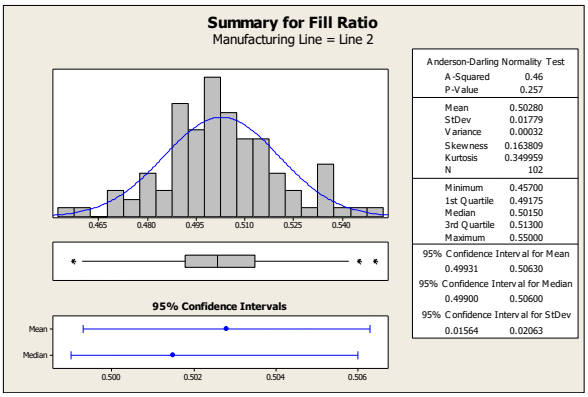
Fill ratio (X7)



Fill ratio overall



Fill ratio
Manufacturing line 1



Fill ratio
Manufacturing line 2

Initial findings:

- The overall range (irrelevant of manufacturing line) within the fill ratio was quite large (0.4540 to 0.5500). This could lead to the variation and specification non-compliance within the pill weight.

- Once again, we see differences between manufacturing line 1 and 2 both in range and standard deviation. Once again, proving that the manufacturing lines (x2) could be responsible for the variation and non-compliance within the pill weight.

Measure phase findings compiled

- At this stage it seems that the differences in individual manufacturing lines, compression times, and fill ratio could have a direct impact on the variation and non-compliance within the pill weight.
- Furthermore, we need to investigate possible “interactions” between the factors (could one factor increase or decrease the other factors influence).
- Finally, how we measure the factor line speed must be analyzed in greater detail (measuring in whole numbers gives us little indication whether or not this factor has a positive or negative influence on the variation or non-compliance within the pill weight).

3. ANALYZE PHASE

Methodology

During the ANALYZE phase the aim is to prove statistically the various "causes" the team believes is resulting in the variation and non-compliance within the pill weight. At the end of the analyze phase each factor will have a probability forecast attached to it. What this means, is that a % number will be attributed to each reason (factor) which will indicate the probability of this factor being the root cause for the variation and non-compliance within the pill weight (example: If line speed turns out to be one of the root causes, then line speed could have a 98% number behind it. This means, there is a 98% surety that line speed is the root cause, with only a 2% chance of it not being the root cause).

Application

We started out with a simple mathematical equation:

$$Y = (f)\ x$$

(Y1, Y2 = (f) x1, x2, x3, x4, x5, x6, x7)

Y1 = Variation within the pill weight
Y2 = Non-compliance within pill weight
X1 = Molecular size of material
X2 = Manufacturing line (1 and 2)
X3 = Line speed
X4 = Compression time
X5 = Ambient moisture in air
X6 = Particle size of material
X7 = Fill ratio

We prove or disprove this equation by using various statistical tools - see Annexure 1. These are the statistical tools available to us, however we will NOT necessarily use all of them (just as a mechanic may not use all their tools to repair a car).

We start the testing by analyzing X2 (manufacturing lines 1 and 2). We are start with X2 instead of X1 because of the type of data. X1, X3, X4, X5, X6, X7 are all continuous data types, while X2 is discrete. The different data types dictate the use of different process improvement tools.

The client teams claim (this is also the Ho) - "…the manufacturing lines produce differently (one may be heavier than the other), and this is the reason why we have Y1 (Variation within pill weight) and Y2 (non-compliance within pill weight)".

To prove this, we will use various statistical tools and run charts (2 sample t-test, Moods-Median, F-test, Levens, I-Chart, I-MR-Chart).

Results:

Two sample t-test:

Two-sample T for Weight

Manufacturing

Line	N	Mean	StDev	SE Mean
Line 1	148	1.0406	0.0559	0.0046
Line 2	102	1.1129	0.0626	0.0062

Difference = mu (Line 1) - mu (Line 2)
Estimate for difference: -0.072300
95% CI for difference: (-0.087516, -0.057084)
T-Test of difference = 0 (vs not =): T-Value = -9.37 P-Value = 0.000 DF = 200

Based on the P-Value we can say with high confidence there is statistical proof that the manufacturing lines (1 and 2) operate differently and thus are a contributing factor to Y2 (non-compliance within pill weight). There is a 99.999% probability this factor is one of the root causes.

Test for equal variances:

Test for Equal Variances: Weight versus Manufacturing Line

95% Bonferroni confidence intervals for standard deviations

Manufacturing Line	N	Lower	StDev	Upper
Line 1	148	0.0494166	0.0558970	0.0642461
Line 2	102	0.0540570	0.0626124	0.0742318

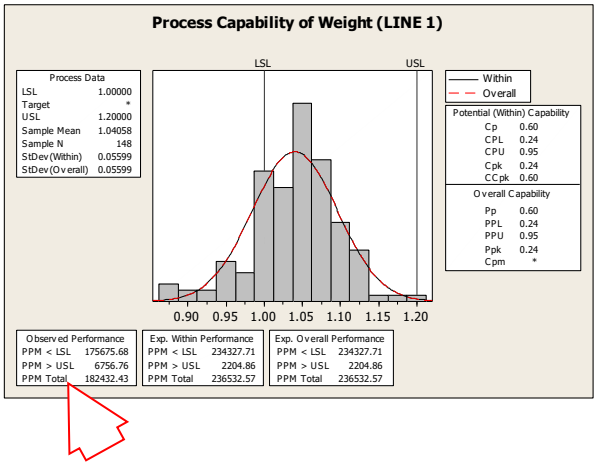
F-Test (normal distribution)
Test statistic = 0.80, p-value = 0.209

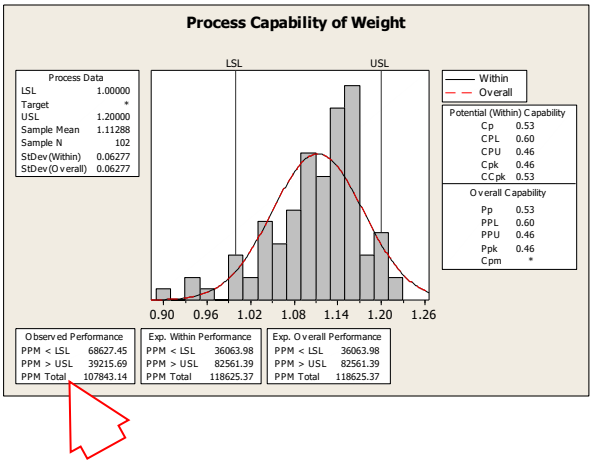
Levene's Test (any continuous distribution)
Test statistic = 1.30, p-value = 0.256

Based on both P-Values we can say with high confidence that there is NO statistical proof that the manufacturing lines (1 and 2) are the cause for Y1 (variation within the pill weight). There is only a 74.40 – 79.10% probability this factor is one of the root causes.

To make absolutely sure the manufacturing lines is one of the root causes for the non-compliance within the pill weight, and to see which one is the major culprit, we will perform a process capability study.

Here are the results:





Conclusion: BOTH manufacturing lines are out of specification. Manufacturing line 1 produces @18% bad product and manufacturing line 2 @ 10% bad product.

This type of analysis was done on all factors (X1, X3, X4, X5, X6, X7) with the following graphs and results:

X1 (Molecular size):

Polynomial Regression Analysis: Weight versus Mol

The regression equation is
Weight = 21764 - 16.78 Mol + 0.004313 Mol**2 - 0.000000 Mol**3

S = 0.0675064 R-Sq = 4.3% R-Sq(adj) = 3.1%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	3	0.04984	0.0166145	3.65	0.013
Error	246	1.12105	0.0045571		
Total	249	1.17089			

Sequential Analysis of Variance

Source	DF	SS	F	P
Linear	1	0.0013154	0.28	0.598
Quadratic	1	0.0229867	4.95	0.027
Cubic	1	0.0255413	5.60	0.019

Conclusion for X1 Molecular size:

Even though X1 does have an effect on both variation within the pill weight and non-compliance within the pill weight, it is only responsible for 4.3% of the total variation within the weight. We are looking for factors with more than 25%. (This decision was based on economically viable and cost-effective possible improvements).

X3 (Line speed)

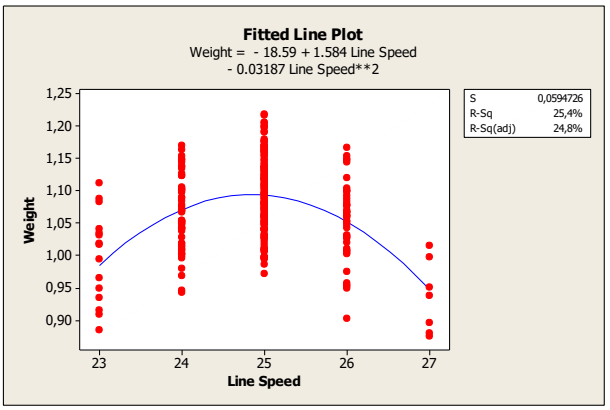
Polynomial Regression Analysis: Weight versus Line Speed

The regression equation is
Weight = 45.24 - 6.123 Line Speed + 0.2779 Line Speed**2
- 0.004145 Line Speed**3

S = 0.0593552 **R-Sq = 26.0%** R-Sq(adj) = 25.1%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	3	0.30423	0.101409	28.78	**0.000**
Error	246	0.86667	0.003523		
Total	249	1.17089			



Sequential Analysis of Variance

Source	DF	SS	F	P
Linear	1	0.000000	0.00	0.992
Quadratic	1	0.297255	84.04	**0.000**
Cubic	1	0.006970	1.98	0.161

One-way ANOVA: Weight versus Line Speed_1

Source	DF	SS	MS	F	P
Line Speed_1	4	0.30634	0.07659	21.70	**0.000**
Error	245	0.86455	0.00353		
Total	249	1.17089			

S = 0.05940 R-Sq = **26.16%** R-Sq(adj) = 24.96%

Individual 95% CIs For Mean Based on Pooled StDev

Level	N	Mean	StDev	--+---------+---------+---------+-------
23	15	0.9980	0.0698	(----*----)
24	59	1.0621	0.0552	(--*--)
25	125	1.0960	0.0601	(-*)
26	44	1.0530	0.0598	(-*--)
27	7	0.9352	0.0557	(-------*------)

--+---------+---------+---------+-------
0.900 0.960 1.020 1.080

Pooled StDev = 0.0594

Conclusion for X3 Line speed:

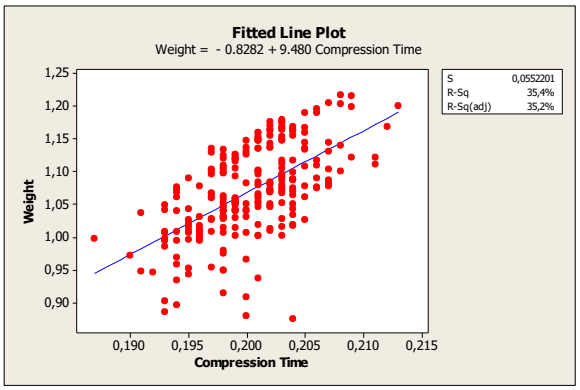
Because speed is “normally” a continuous data type it lends itself to various analytical tools. However, because our measurement system can only measure the line speed in whole numbers, we also looked at this factor through “discrete” eyes and used the appropriate discrete analysis tools. Based on both views (continuous and discrete) we can say with a 99.999% confidence that line speed is also a root cause for the variation and non-compliance within the pill weight and is responsible for an estimated 25.40% to 26.16% of the variation.

X4 (Compression time)

Regression Analysis: Weight versus Compression Time

The regression equation is
Weight = - 0.8282 + 9.480 Compression Time

S = 0.0552201 **R-Sq = 35.4%** R-Sq(adj) = 35.2%



Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	0.41468	0.414677	135.99	**0.000**
Error	248	0.75622	0.003049		
Total	249	1.17089			

Conclusion for X4 Compression Time: We can state with a 99.999% surety that compression time has a direct and linear effect on non-compliance within the pill weight. In addition, it also explains 35.4% of the variation within the pill weight.

X5 (Ambient moisture)

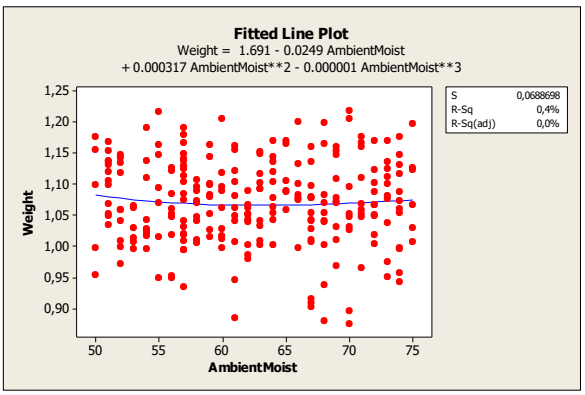
Polynomial Regression Analysis: Weight versus Ambient Moist

The regression equation is
Weight = 1.691 - 0.0249 Ambient Moist + 0.000317 Ambient Moist**2
- 0.000001 Ambient Moist**3

S = 0.0688698 **R-Sq = 0.4%** R-Sq(adj) = 0.0%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	3	0.00410	0.0013679	0.29	**0.834**
Error	246	1.16679	0.0047430		
Total	249	1.17089			



Sequential Analysis of Variance

Source	DF	SS	F	P
Linear	1	0.0004618	0.10	**0.755**
Quadratic	1	0.0036022	0.76	**0.383**
Cubic	1	0.0000397	0.01	**0.927**

Conclusion for X5 Ambient Moisture:

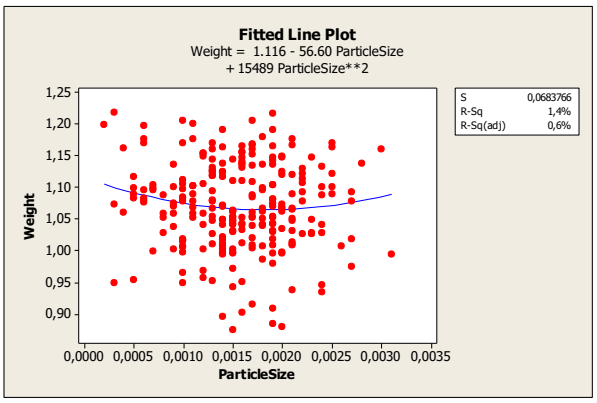
There is only a 61.7% chance that X5 is responsible for the variation and non-compliance within the pill weight. Furthermore, it is responsible for less than 0.4% of the variation within the pill weight. We can comfortably ignore this factor from any further analysis.

X6 (Particle size)

Polynomial Regression Analysis: Weight versus Particle Size

The regression equation is
Weight = 1.116 - 56.60 Particle Size + 15489 Particle Size**2

S = 0.0683766 **R-Sq = 1.4%** R-Sq(adj) = 0.6%



Analysis of Variance

Source	DF	SS	MS	F	P
Regression	2	0.01608	0.0080391	1.72	**0.181**
Error	247	1.15482	0.0046754		
Total	249	1.17089			

Sequential Analysis of Variance

Source	DF	SS	F	P
Linear	1	0.0058974	1.26	0.264
Quadratic	1	0.0101808	2.18	0.141

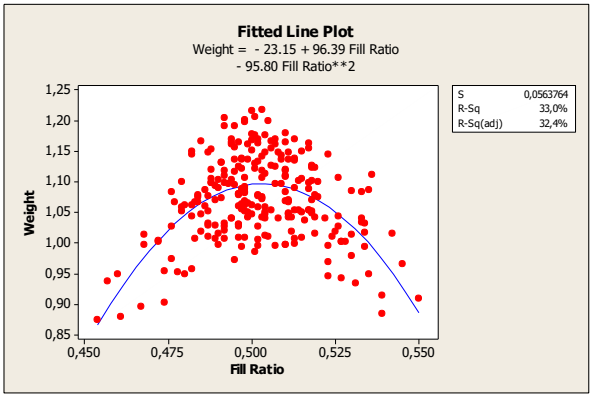
Conclusion for X6 Particle Size:

There is only an 81.9% chance that X6 is responsible for the variation and non-compliance within the pill weight. Furthermore, it is responsible for less than 1.4% of the variation within the pill weight. We can comfortably ignore this factor from any further analysis.

X7 (Fill ratio)

Polynomial Regression Analysis: Weight versus Fill Ratio

The regression equation is
Weight = - 23.15 + 96.39 Fill Ratio - 95.80 Fill Ratio**2



S = 0.0563764 R-Sq = 33.0% R-Sq(adj) = 32.4%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	2	0.38585	0.192927	60.70	0.000
Error	247	0.78504	0.003178		
Total	249	1.17089			

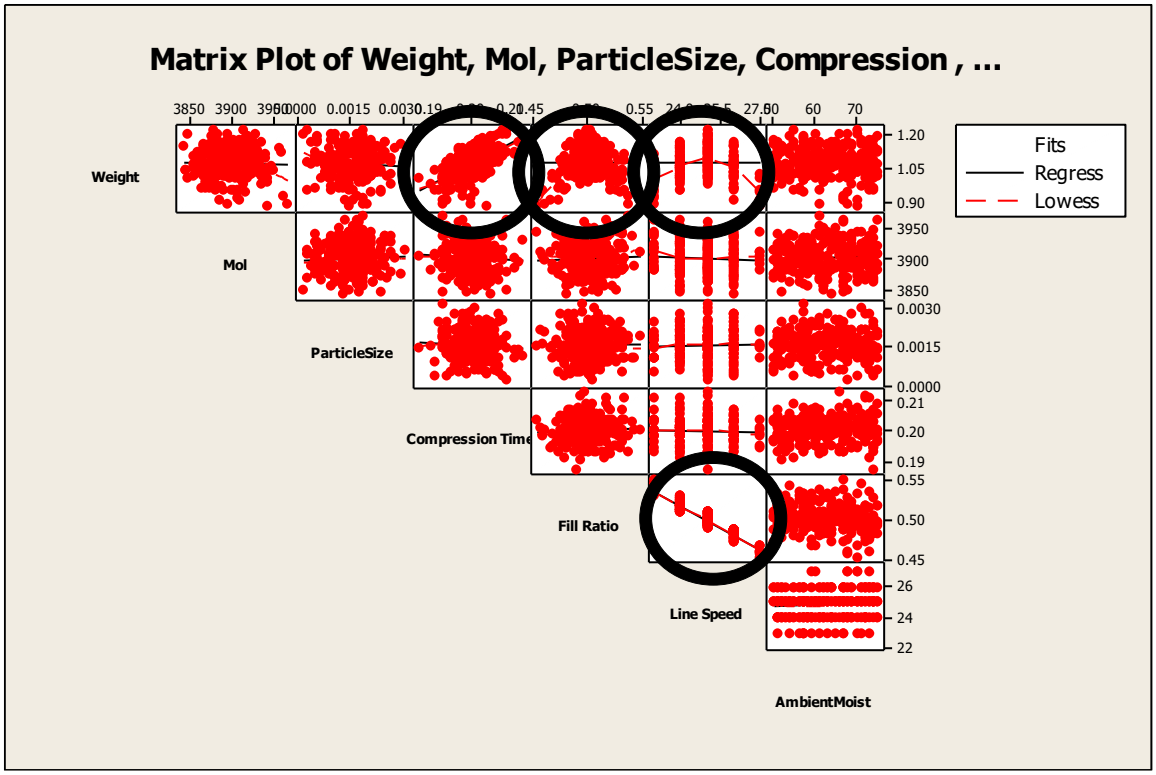
Sequential Analysis of Variance

Source	DF	SS	F	P
Linear	1	0.000020	0.00	0.948
Quadratic	1	0.385834	121.40	0.000

Conclusion for X7 Fill Ratio: We can state with a 99.999% surety that fill ratio has a direct and quadratic effect on non-compliance within the pill weight. In addition, it also explains 33.0% of the variation within the pill weight.

Now that we have analyzed each factor on its own, it is time to see if there are any types of **interactions** between factors.

First, we look at the possible interactions graphically.



This graph confirms two issues.

1. That compression time, fill ratio, and line speed all have an effect on pill weight (top 3 black circles)
2. That there is a possible interaction between fill ratio and line speed (bottom black circle)

Next, we will confirm this mathematically with a multiple regression.

Regression Analysis: Weight versus Compression, Fill Ratio, Line Speed

The regression equation is
Weight = - 0.991 + 9.49 Compression Time + 0.118 Fill Ratio + 0.0040 Line Speed

Predictor	Coef	SE Coef	T	P	VIF
Constant	-0.9909	0.6371	-1.56	0.121	
Compression Time	9.4949	0.8165	11.63	0.000	1.0
Fill Ratio	0.1181	0.6366	0.19	0.853	**9.1**
Line Speed	0.00403	0.01222	0.33	0.742	**9.1**

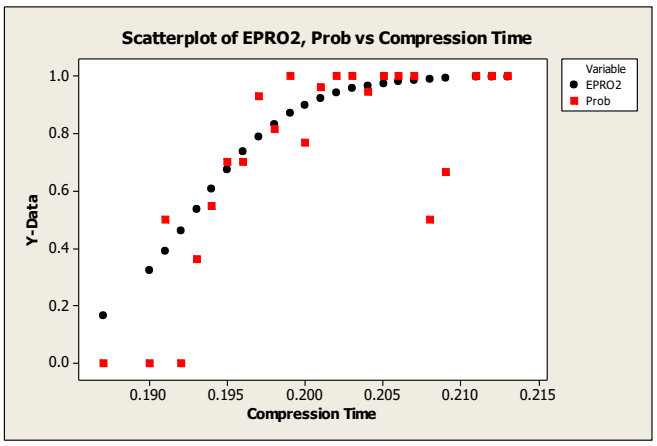
S = 0.0554157 R-Sq = 35.5% R-Sq(adj) = 34.7%

Analysis of Variance

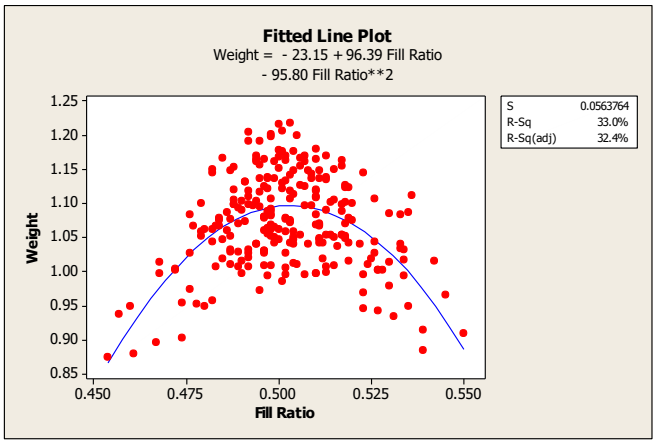
Source	DF	SS	MS	F	P
Regression	3	0.41545	0.13848	45.10	0.000
Residual Error	246	0.75544	0.00307		
Total	249	1.17089			

Based on the VIF (variation inflation factor) we can see there is a correlation between fill ratio and line speed. Any VIF number above 5.0 is significant. This is important for later in the improve phase.

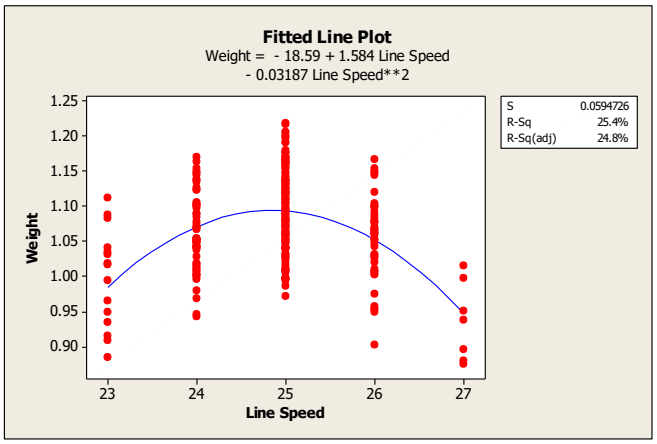
To look at the effect of each factor (compression time, line speed, and fill ratio), we will look at the logarithmic or regression curve for each factor.



Compression time:
On this graph we can see that the lower the compression time, the higher the probability of a bad pill. Any compression time above 0.200 increases the probability of success.



Fill ratio:
Based on this quadratic equation, we can see that below 0.480 and above 0.520 there is a significant higher chance of a defective pill.



Line speed:
Based on this quadratic equation, we can see that line speeds below 24 and above 26 increases the chance of a defective pill. (CAUTION: Because we are doing the equation with whole numbers, we need to be cautious of the decisions we make. In addition, because there is a high correlation with fill ratio these results may be a little blurred).

Analyze phase conclusions:

Criteria to confirm as root cause:

X1 = Molecular size of material 97.300% confirmation of root cause 04.300% cause of variation	**X2 = Manufacturing line (1 and 2)** 99.999% confirmation of root cause (No % of variation here because of type of data)	**X3 = Line speed** 99.999% confirmation of root cause 25.400% cause of variation	**X4 = Compression time** 99.999% confirmation of root cause 35.400% cause of variation
X5 = Ambient moisture in air 16.600% confirmation of root cause 00.400% cause of variation	**X6 = Particle size of material** 81.900% confirmation of root cause 01.400% cause of variation	**X7 = Fill ratio** 99.999% confirmation of root cause 33.000% cause of variation	

1. Minimum 95.000% confirmation of root cause
2. Minimum 25.000% cause of variation

Factors confirmed as root causes of variation and therefore candidates for optimization:

1. Manufacturing line
2. Compression time
3. Line speed
4. Fill ratio

5. IMPROVE PHASE

In the fourth phase of the project, IMPROVE, we identify solutions targeted at the verified causes from the ANALYZE phase.

To show, with data, that the solutions solve the problem and lead to improvement, we:

- Decide whether to go on with DMAIC or DFSS, i.e., does it make sense to improve the existing process, or do you have to design an entirely new one?
- Identify solutions addressing important Xs - which potential solutions are there? What criteria will you use to assess alternative solutions, and evaluate solutions?
- Minimize risks and implement solutions

Which risks does the selected solution hold and how to mitigate them? Do you need to pilot the selected solution? What must be planned to implement the solution? How will you check on the results?

Because we were able to identify with high certainty which factors have the largest and most significant impact on Y1 and Y2, a DOE (design of experiment) was conducted with these factors:

- Design of Experiments (DOE) is a tool to model a continuous output variable (Y) with continuous or discrete input/process variables (Xs).
- DOE describes a way
- To set up the experimental data collection (experimental plan).
- To analyze the results from the conducted experiment (DOE analysis).
- The analysis of DOE has three main outputs:
- Model – an equation of the form: Y=b0+b1X1+b2x2+b3x1x2…
- P-values of terms – how significant are the factors (Xs)?
- R-sq, unexplained – how much of the observed variation does the model explain, what portion remains unexplained?

By developing a DOE experimental plan, the following criteria's must be observed:

1. Decide how to measure the process output (Y) or outputs (Ys)
    - Our Y1 = Variation Y2 = Non-compliance with Specification
2. Select the factors to test in the experiment (Xs)
    - Our X1 = Compression time, X2 = Line Speed, X3 = Fill Ratio
    - We will run this experiment ONLY on manufacturing line 2
3. Select factor levels for the Xs (initially 2 levels per factor)
    - We will conduct a full factorial (ALL LEVELS)
    - No center points
4. Decide on the number of replications of runs
    - No Replications
    - No Repeats
5. Select the appropriate experimental design
    - Full Factorial

6. Randomize the runs
    - Not possible

7. Finalize the experimental plan and check whether it is possible in reality to test all the combinations
    - Yes, all combinations are possible

DOE results

Initial model before

Response Surface Regression: Weight versus Compression, Fill Ratio, Line Speed
The analysis was done using coded units.

Estimated Regression Coefficients for Weight

Term	Coef	SE Coef	T	P
Constant	1.09410	0.004630	236.328	0.000
Compression Time	0.12011	0.009061	13.255	0.000
Fill Ratio	0.02420	0.026520	0.912	0.362
Line Speed	0.01841	0.021966	0.838	0.403
Compression Time*Compression Time	-0.01699	0.016954	-1.002	0.317
Fill Ratio*Fill Ratio	-0.17394	0.199158	-0.873	0.383
Line Speed*Line Speed	0.06598	0.137898	0.479	0.633
Compression Time*Fill Ratio	0.04472	0.074279	0.602	0.548
Compression Time*Line Speed	0.02102	0.059752	0.352	0.725
Fill Ratio*Line Speed	0.10809	0.327045	0.331	0.741

S = 0.04104 R-Sq = 65.5% R-Sq(adj) = 64.2%

Analysis of Variance for Weight

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	9	0.76667	0.766672	0.085186	50.58	0.000
Linear	3	0.41545	0.298995	0.099665	59.17	0.000
Square	3	0.34954	0.031944	0.010648	6.32	0.000
Interaction	3	0.00168	0.001685	0.000562	0.33	0.801
Residual Error	240	0.40422	0.404222	0.001684		
Lack-of-Fit	205	0.32997	0.329970	0.001610	0.76	0.877
Pure Error	35	0.07425	0.074251	0.002121		
Total	249	1.17089				

Final model after

Response Surface Regression: Weight versus Compression Time, Fill Ratio

The analysis was done using coded units.

Estimated Regression Coefficients for Weight

Term	Coef	SE Coef	T	P
Constant	1.09287	0.003120	350.299	0.000
Compression Time	0.11745	0.007830	15.001	**0.000**
Fill Ratio	0.00507	0.007492	0.676	**0.500**
Fill Ratio*Fill Ratio	-0.20924	0.014527	-14.404	**0.000**

S = 0.04082 R-Sq = 65.0% **R-Sq(adj) = 64.6%**

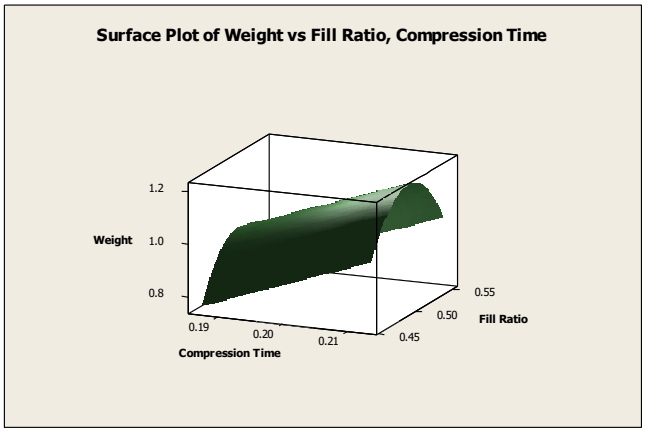
Analysis of Variance for Weight

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	3	0.76089	0.760890	0.253630	152.18	0.000
Linear	2	0.41512	0.377998	0.188999	113.40	0.000
Square	1	0.34577	0.345773	0.345773	207.46	0.000
Residual Error	246	0.41000	0.410003	0.001667		
Lack-of-Fit	211	0.33575	0.335752	0.001591	0.75	**0.887**
Pure Error	35	0.07425	0.074251	0.002121		
Total	249	1.17089				

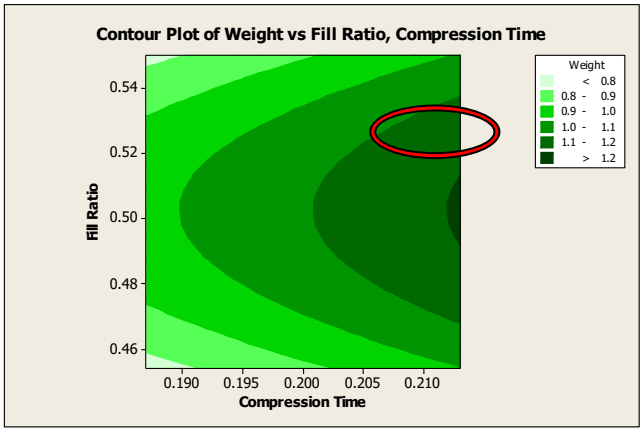
Explanation:

1. We have a direct linear correlation between Compression time and pill weight
2. Even so there is no direct correlation between fill ratio and pill weight, there is a squared relationship between fill ratio and pill weight
3. The term (factor) line speed has been deleted out of the model
4. We can explain 64.6% of the variation of the pill weight with these two factors
5. The mathematical model is sound because of the high P-Value (0.887) of the lack of fit

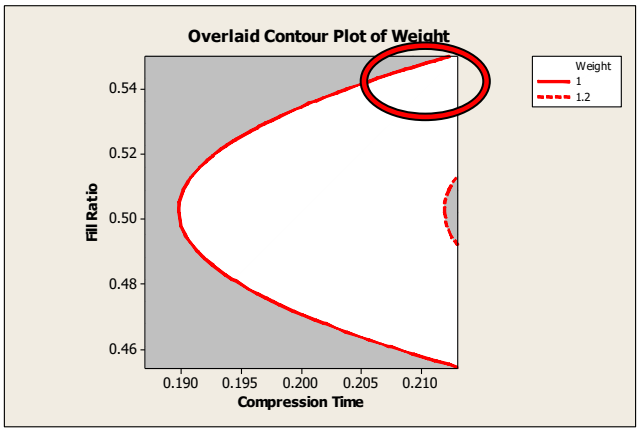
Graphical Explanation:



On this Surface plot graph, we can see as compression time increases, so does the pill weight. We also see that fill ratio has a curved relationship with will weight.



On this contour plot we can see where our optimum settings should be for Compression time and fill ratio, if we want to be between 1.0 – 1.2 (see red circle). We can go with a lower compression time, as long as we increase the fill ratio. Or we can lower the fill ratio as long as we increase compression time.



On this overlaid contour plot we can see once again where our optimum settings should be for Compression time and fill ratio (the white area), if we want to be between 1.0 – 1.2 (see red circle).

To optimize the output (Y1) “pill weight” and to reduce the output (Y2) “pill weight variation”, we will run our DOE model through the response optimizer for the optimal settings.

Response optimizer results:

Response Optimization

	Goal	Lower	Target	Upper	Weight	Import
Weight	Target	1	1.1	1.2	1	1

Global Solution

Compression = 0.21300
Fill Ratio = 0.46772

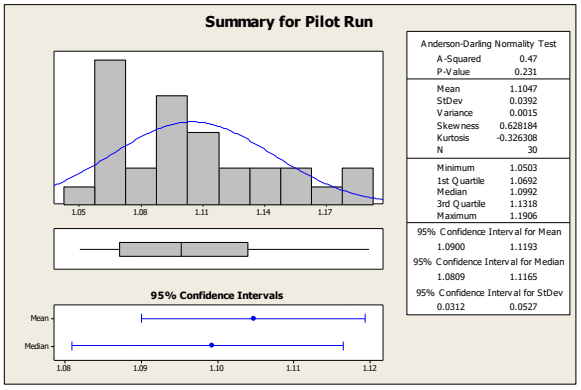
Predicted Responses

Weight = 1.10000, desirability = 1.00000
Composite Desirability = 1.00000

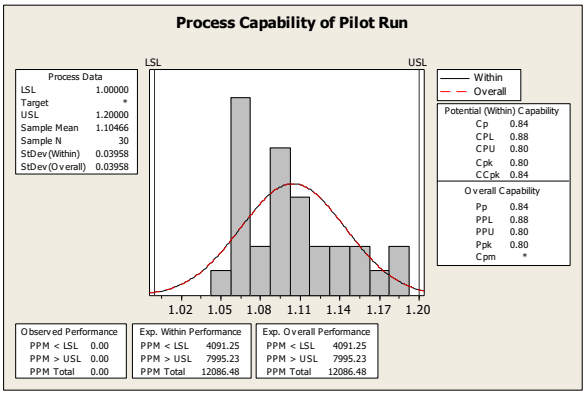
To reach our goal of each pill weighing between 1.000 and 1.200 grams, we need to set compression time at: 0.21300 and fill ratio at 0.46772

To prove this theory, we will run a pilot of thirty runs at these setting and confirm (or deny) our suggestions.

Here are the results:



After the pilot, we have an average pill weight of 1.1047, a standard deviation of 0.0392, and no pills underweight (below 1.000) or overweight (above 1.200).



During our pilot we have a process capability of Cpk 0.84 (almost doubled). Our defect rate is 0.00%

Improve phase conclusions:

We have reached both targets of Y1 (reduce variation from 0.0634 to 0.0500) and Y2 (Be within specification of pill weight 1.000 to 1.200).

Pilot phase successful.

1. CONTROL PHASE

In the fifth and last phase of the project, CONTROL, you want to ensure sustainability of the process improvements, evaluate the accomplished results, and finally close your project. Therefore, you need to:

- Draw up a process management plan - what are critical steps of the new process? Who is responsible if an error occurs? Which actions must be taken?
- Standardize the new process - how to make sure that essential elements of the new process are performed consistently in the best possible way?
- Implement a control system and assess process results - how to show, with data, that the developed solutions really contributed to improvements of your process? How to monitor that these improvements will endure?
- Document lessons-learned of your project and close the project - how did DMAIC help you to accomplish results? What problems did appear? What may be transfer opportunities? How to hand-over your process to the process owner? How to celebrate project closure?

To ensure the process remained stable and efficient after the close of the project, a process management plan was implemented.

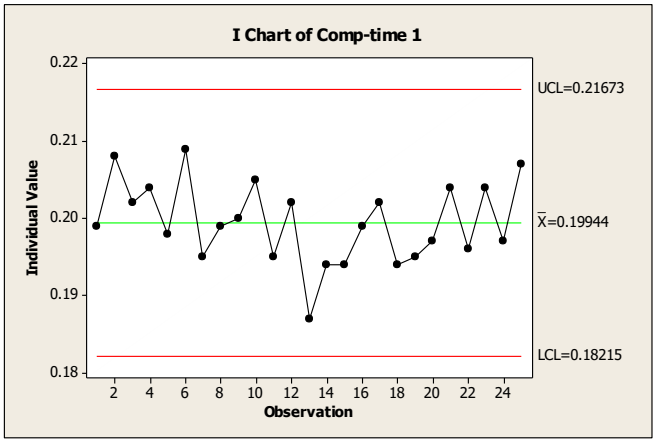
A process management makes sure that:

- The improved process is established
- Responsibilities are clarified
- Important process measurements for ongoing monitoring have been established
- A reaction plan is in place

Process Management asks for establishing “leading indicators” (X) in addition to or instead of “lagging indicators” (Y) based on the analysis results. This means we are no longer ONLY monitoring the variation and non-compliance of the pill weight, but mainly the two critical factors we verified during the analyze and improve phase of the project, i.e., compression time and fill ratio.

To make sure we do not make any unnecessary changes to the process, and only make adjustments when warranted, control charts were built into the process, which allows the process owner to visually see if there is common cause variation or special cause variation, which will determine the correction plan.

SPC chart of Compression time:



As long as the data points are within the "control" limits (not to be confused with specification limits), we consider this factor in control, i.e., stable.

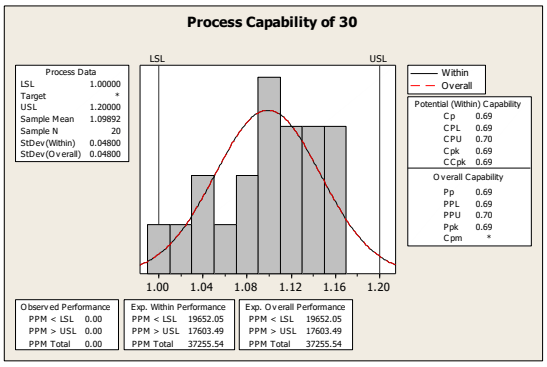
For both critical factors, a reaction plan was developed, and all involved process team members were trained on when to use it.

The last part of the project is to do 30, 60, and 90 follow-ups before considering the project successful.

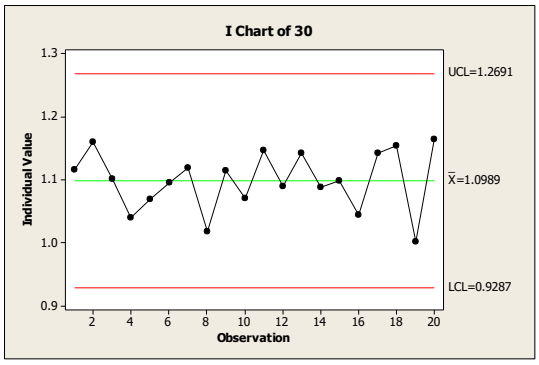
We look at two characteristics:

1. Process capability on the Y
2. Process stability on the Y

30-day results:

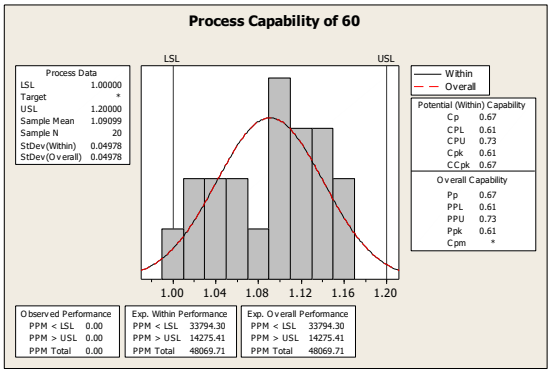


Capability: above 95%

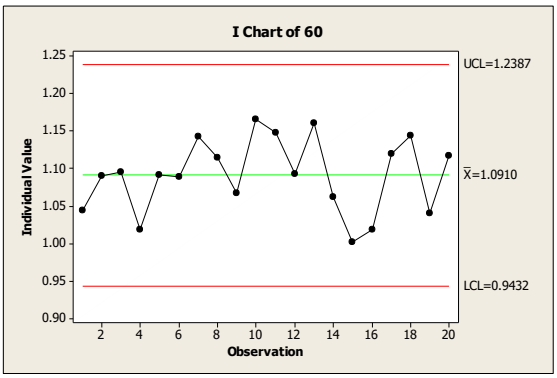


Stability: In control

60-day results:

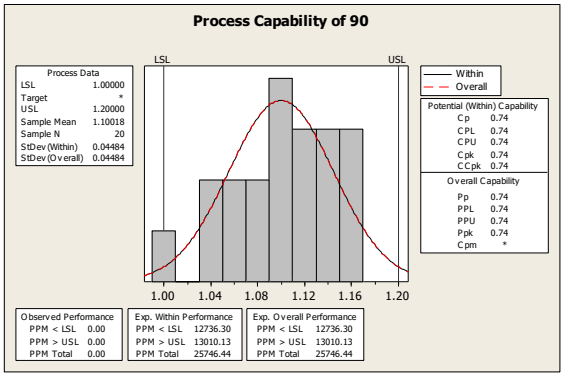


Capability: above 95%

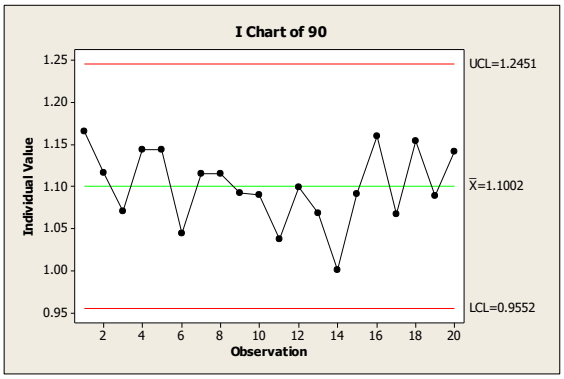


Stability: In control

90-day results:



Capability: above 95%



Stability: in control

Conclusion:

Project close out and follow up successful. Project **CLOSED**.

ANNEXURE 1

Statistical analysis tools overview:

- Basic statistics
- Regression
- Analysis of variance
- DOE (factorial, response surface, mixture, and Taguchi designs)
- Control charts
- Quality tools (planning tools, process capability, and gage study)
- Reliability/survival (distribution analysis, regression with life data, and accelerated life testing)
- Multivariate
- Time series
- Tables
- Nonparametrics
- Power and sample size

Detail statistical and graphical tools:

Graphical:

Scatter Plots, Matrix Plots, Marginal Plots, Histogram, Dot Plot, Stem Leaf, Probability, Empirical CDF, Box Plot, Interval, Individual Value, Bar, Pie, Time Series, Area Graph, Contour Plot, 3D Scatter Plot, 3D Surface Plot, Main Effects Plots, Interaction Plots, Pareto, Run Chart, Multi-vari Chart.

Trend Analysis:

Time Series Plot, Decomposition, Moving average, Single Exp. Smoothing, Double Exp. Smoothing, Winters' method (additive), Winters' method (multiplicative), Autocorrelation, Partial Autocorrelation, Cross Correlation, ARIMA (Autoregressive Integrated Moving Average)

Correlation and Regression Testing:

Simple linear regression, Multi-linear regression, Stepwise regression, Best sublets regression, Fitted line Plot, Partial Least Squares, Binary- Ordinal- Nominal Logistical regression, Correlation Analysis, Covariance Analysis.

Hypothesis Testing:

1 sample z, 1 sample t, 2 sample t, Paired t-test, ANOVA (one-way, two-way, balanced, general linear, fully nested), Balanced MANOVA, General MANOVA, Test for Equal Variances, 1 proportion test, 2 proportion test, Chi-Square.

Non-parametrics:

One-Sample Sign, One-Sample Wilcoxon, Mann Whitney, Kruskal-Wallis, Mood's Median test, Friedman.

Multivariate:
Principal Components, Factor analysis, Cluster observations, Cluster variables, Cluster K-means, Discriminant analysis.

Reliability/Survival:
Test plans (Demostrated test plans, Estimation test plans, Accelsrated life test plans), Distribution analysis (right censoring), Distribution analysis (arbitrary censoring), Parametric Growth curve, Nonparametric Growth curve, Probit analysis.

Measurement System Analysis:
Gage Study (Gage Run Chart, Gage Linearity and Bias, Gage R&R Crossed, Gage R&R Nested), Attribute Agreement Study, Attribute Gage Study.

Power and Sample Size:
1-sample Z, 1-sample t, 2-sample t, 1 proportion, 2 proportion, One-Way ANOVA, 2-level Factorial, Plackett-Burman

Design of Experiments (DOE):
2-level Factorial (to include historical), 2-level Fractional Factorial (to include historical), Plackett-Burman Design, General full Factorial, Central Composite Response Surface Design (to include historical), Box-Behnken Response Surface Design, Mixture Design (Simplex Centroid, Simplex Lattice, Extreme Vertices), Taguchi (2,3,4,5 and mixed level design).

Capability Analysis:
Normal, Between, Non-normal, Multiple Variables (normal), Multiple Variables (non-normal), Binominal, Poission.

Control Charts:
Xbar-R, Xbar-S, I-MR-R/S (Between/Within), Xbar, R, S, Zone, P, NP, C, U, EWMA, CUSUM, Tsquared, Multivariate EWMA