Continuous Manufacturing Variability Study

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Abstract *— Continuous manufacturing variability is measured with the help of analysis of variance methodologies and statistical process control (SPC) tools such as control charts. The objective of this project was to assess variability within and between lots for two data sets with three process quality attributes: Assay, Content Uniformity and Tablet Weight. One data set included rejected quarantine hoppers (QH) and the other data set eliminated the rejected QH for the three lots This research could study variability with the usage of analysis of variance such as ANOVA, MANOVA, Post Hoc comparison test with Bonferroni correction among SPC control charts to illustrate mean and standard deviation variability. The analysis of variance concluded significant mean variability in the two data sets for Assay, CU and Tablet Weight in the three lots. Control charts supplemented the analysis of variance testing and provided an overview of process capability and mean variation for the chosen parameters.*

Key Terms *— Analysis of Variance, Continuous Manufacturing, Statistical Process Control, Variability.*

INTRODUCTION

The pharmaceutical industry is leaning to a newer, cleaner and more efficient technology called continuous manufacturing (CM) for its considerable benefits and modern approach. CM lots may differ from each other depending the run time of the line and variability may be affected due to this fact. This is the reason variability within and between lots was studied in this research. Limited information exists on CM variability for varying lot sizes for critical quality attributes such as assay, content uniformity (CU) and Tablet Weight.

RESEARCH OBJECTIVES

The objective of this research is to study variability within and between lots and for assay, content uniformity and tablet weight with two data sets, one that considered rejected QH and the other without rejected QH with the usage of analysis of variance such as ANOVA, MANOVA, Post Hoc with Bonferroni correction among SPC control charts to illustrate mean and standard deviation variability. The tablet samples were collected during the compression process of the continuous manufacturing line. To comprehend variability, data was collected from a sample size of 10 tablets per quarantine hopper. The objective is to quantify variability of CM lots effectively even with different lot sizes due to the different run time between lots. The parameters considered from this research were: Assay, Content Uniformity and Tablet Weight.

RESEARCH CONTRIBUTIONS

This project goal is to establish a method to analyze variability in CM lots that vary in run time and lot size. Continuous manufacturing is the latest technology for pharmaceutical production and data analysis from CM lots are starting to be studied to fully comprehend if there is impact in the process variability due to the uniqueness of each lot. Statistical process control tools such as control charts will clarify process capability and mean variation within a CM process parameter.

RESEARCH BACKGROUND

One transcendental challenge for Continuous Manufacturing (CM) is quality assurance. Continuous Manufacturing is a relatively new

concept of manufacturing where quality assurance and control is modified for a single production flow line. CM involves the creation and design of quality systems and documentation capable of maintaining and tracking critical process parameters to guarantee product quality and FDA regulations. The definition of a lot differs from batch and continuous processes and it's the only specified regulation or guidance of a CM line. Unlike batch manufacturing where materials are charged before the start of processing and discharged at the end of processing, CM is simultaneously charged and discharged from the process [1] affecting the standard batch definition of a lot. FDA refers a lot for a batch a specific identified portion of a batch having uniform character and quality within specified limits and for continuous process a lot is a specific identified amount produced in a unit of time or quantity in a manner that assures it's having uniform character and quality within specified limits. In conclusion batch and lot are applicable to continuous manufacturing.

CM recent movement to transform traditional manufacturing into a more efficient a fast way motivates by the many advantages of CM for example: waste reduction, smaller footprint, fewer steps and the most important of all consistent quality using process analytical technology (PAT) and on-line monitoring with a Real Time Release Testing (RTRT) approach. According to the FDA, PAT is a system for designing, analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality [2]. A PAT system in a CM line is in charge of monitoring and controlling the product critical quality attributes (CQAs) such as tablet ID, Content Uniformity and Assay. Content uniformity refers to the homogeneity of the active product ingredient (API) in a tablet or dosage unit. Assay refers to the API concentration in a tablet. The monitoring of these parameters ensures product quality and the safety of the patient that will consume said product.

In some cases, the PAT system can be based on near infrared technology in charge of collecting and analyzing spectra with the help of chemometric models designed for a specific material. RTRt in a CM line can be achieved with PAT to ensure the quality of in-process or final product based on process data such as chemometric models. chemometric models can predict critical quality attributes and guarantee the effectiveness of RTRt. Also, they can accurately predict tablet's assay and content uniformity in a CM line reducing the number of test and testing time it would have normally taken in a batch process.

A PAT system containing RTRt in a CM line functions as a control strategy for the CQA and contributes to the FDA goal they quality should be built-in or should be by design [3]. By PAT implementation a CM line can reduce production cycle time, improve energy and material use and most over helps continuous processes to handle variability and improve efficiency. Another significant goal for PAT framework is process understanding where sources of variability are well defined with their specific control strategy and CQAs are predicted over the design space of the process. Another benefit of PAT technology as a process control tool is Material Traceability and diversion of non-conforming material to assure batch uniformity. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [4].

Process understanding starts in assessing each unit operation CQAs and ensuring each CQA's is ensured and reproduced in each run. The combination of PAT System and RTRt technology enables a CM line the capacity to reject material instantly if the process falls out of specification bypassing traditional laboratory testing and additional time. To control variability and maintain product quality, process alarms have to be

considered amid process deviations adjustments by the CM line. System integration

FDA concerns in CM truly lie in assuring product quality and proving uniform character can be achieved for this type of process. Quality needs to be maintained in every phase of the CM line from feeding through coating and onto final product. The challenge lies in the adequate monitoring and sample collection in the process due to the constraint a CM line has due to its continuous design. A continuous process doesn't need to wait for a unit operation to finish in order to transfer the material to the next unit like in batch process because is already designed as a single flow production line. This may be beneficial to batch production because you can gather samples after each unit is finished and assure quality before it continues to the next equipment, although testing time will usually take longer in a laboratory setting. A CM line is able to achieve the adequate monitoring and testing in line, reducing testing time and speeding up the release time for a product. Process understanding can provide the information to choose testing locations, sampling frequency and size to assure the monitoring and control of the established process CQA's.

The challenges in implementing CM lies the control strategies of CM because they are clearly different from traditional batch processing. The definition of a Batch has to be determined by the company employing CM technology and it has to benefit their process design and control strategies. In addition, proper data storage needs to be assured due to the large amount data acquired such as spectra from the chemometric models. The creation of documentation specific for CM batches capable of documenting process results, events and comments. Assessment of the Impact found in the Startup and Shutdown in terms of quality. The process definition of State of control that depends on the control strategy and its implementation such as process monitoring, integration of controls, handling of deviation and disturbances in real time.

RESEARCH METHODOLOGY

The methodology employed in the research were descriptive statistics to provide the mean and standard deviations for the lots and parameters, analysis of variance to study process variability and statistical process control (SPC) focused in control charts to assess process control limits. Data acquisition was in the compression operation using PAT and RTRt methodology. The parameters considered for this research were tablet weight, content uniformity and assay and obtained from equipment situated in the compression stage of the process. Assay, Content Uniformity and tablet weight parameters are measured as part of an in-process test to assure product quality and RTRt capability of the line.

Data Acquisition

In continuous manufacturing lots are segmented in quarantine hoppers (QH) due to the nature of the process and they vary according to the run time of the line. The data collected for this research was obtained from three distinctive lots with different number of QH. Tablet sampling consisted of ten samples per quarantine hoppers. The equipment used to measure the parameters finalizes by measuring the last quarantine hopper of the lot a second time this explains the last quarantine hopper tendency of the data in the second and third lot, it doesn't apply to the first lot because its last two quarantine hoppers were discarded. Each lot is unique because they differ in run time causing that different number of quarantine hoppers. The first lot ran eight hours resulting in ten quarantine hoppers with the last two quarantine hoppers rejected for the measurement of the established parameters. The second lot ran 16 hours giving 26 quarantine hoppers where three quarantine hoppers were rejected and one was never documented due to inconsistencies in the process. The third lot ran 32 hours and 49 were obtained without any QH rejected.

The data will be analyzed twice to study the process behavior with and without the discarded

QH in lot one and two. The data for the first lot with the rejected QH consisted of ten QH totaling 100 tablet samples. The data for the first lot without the rejected QH equaled eight QH adding to 80 tablet samples. The data for the second lot with the rejected QH consisted of 26 QH with the accumulation of 260 tablet samples. The third lot consisted of 49 HQ but in the data analysis it may seem 50 QH equating to 500 tablet samples and this is due to the fact that the last QH was re-tested to finalize line production.

Analysis of Variance

One of the objectives of the research is to measure variability within and between lots and this is possible with analysis of variance method or short for ANOVA. This statistical method is a general test that decomposes variance in terms of sums of squares by comparing the means of comparison groups. One-way ANOVA was utilized to compare assay, CU and tablet weight within lots and between lots for both sets of data. In total two one-way ANOVA were generated for the data with and without rejected lots. A level of significance of ninety-five percent was used for the ANOVAs. For the ANOVA analysis the F-test was conducted to accept or reject the null hypothesis. For the analysis of variance, the null hypothesis is the following: the mean of each parameter is the same for each lot. If the null hypothesis is rejected, the alternate hypothesis is: the mean of each parameter are different for each lot. Computer software named IBM SPSS was used to examine the data and generate the ANOVA for the three lots with assay, CU and tablet weight for the data with all the QH and without the rejected QH.

The importance of the ANOVA lies in the F-test because it determines if the null hypothesis is accepted or rejected. The ANOVA F-test helped to study the variability of each parameter's mean within and between lots. Within the ANOVA results is the p-value associated with the analysis of variance F-test. The p-value determines if there is a significant difference between the means of the assessed variables. The p-value calculated from the computer software is the value that really indicates to accept or reject the null hypothesis. If the p-value is more than 0.05, the null hypothesis is accepted and if it is less than 0.05 the alternate hypothesis is accepted.

MANOVA

The second variance analysis for the data was MANOVA short for multivariate analysis of variance. MANOVA is an ANOVA but it tests if there is a significant mean difference among groups containing different variables. MANOVA provided a multivariate analysis for the three lots with the three studied parameters. The MANOVA is like the ANOVA if the p-value is less than 0.05 the interaction is significant and if the p-value is more than 0.05, then the interaction is not significant. If the MANOVA shows significance in one of the variables a contrast test is performed to assess the location of the difference.

Post Hoc

If the MANOVA results show a significance variable difference a contrast analysis must follow to further investigate data interactions. Post Hoc analyzes the results of the experimental data. The Post Hoc test chosen for this research was multiple comparisons with Bonferroni correction to reduce the chances of obtaining false-positive results caused by the multiple comparison of a single data set. The Bonferroni correction adjusts the p-values increasing the accuracy of the significant interactions and eliminating inaccurate results and misleading inferences [5].

Statistical Process Control (SPC)

SPC determines process capability, monitors processes and detects if the process operates as expected or if correction action is required to eliminate existing variability's. SPC is a statistical tool to measure and monitor control processes by the application of control charts. Choosing the right control chart depends on the data and the sample collection of the process. The best control chart for the amount of data and sample size was X

Bar – S. To investigate process capability after QH rejection 9 control charts were generated for the three lots and for assay, CU and tablet weight. Control charts provide an overview of the process limits and capability by revealing common or special variation found in the data trend. Common cause variation or random variation is due to ordinary causes and it results in a stable process. Special cause variation results in an unstable process that needs to be improved by investigating the origins of the variation.

RESEARCH RESULTS

The results obtained for ANOVA, MANOVA and contrast were acquired with the help of a computer software called IBM SSPC. The control charts were obtained from additional computer software named Minitab. Two data sets were considered for all the analysis in this research, one with all the QH and the other without the rejected QH. The reasoning for the double analysis is to formulate an overview of the variability and to check if the process if mean variability still existed after forfeiting data from the rejected QH.

Results with Rejected QH

Descripted Statistics results were consulted to study the mean, standard deviation and range of Assay, CU and Tablet Weight in each lot. The descripted statistics included three charts plotting each parameter mean versus lot. The standard deviation in the first lot for CU was higher than one showing mean variation in the data this was caused by missing data from a the rejected QH 10. The standard deviation of Tablet Weight in lot one and 2 was more than 0.5 meaning mean variability and a wider range data. Then, a one-way ANOVA was conducted to investigate the p-value of the parameters in the three lots. The ANOVA resulted in p-values less than 0.05 for the three variables meaning that there is a significant difference in their means between and within groups or lots.

To further study variability simultaneously through the three lots a MANOVA was generated. The descripted statistics included three charts plotting each parameter mean versus lot.

Table 1
Descriptive Statistics

Lots		N	Min	Max	Mean	Std. Dev
Lot 1	Assay (%LC)	99	99.4	101.4	100.34	0.4583
	CU (%LC)	100	0	101.8	99.03	10.0391
	Tablet Weight (mg)	100	1224.6	1265	1246.52	8.5518
Lot 2	Assay (%LC)	259	99.3	101.4	100.56	0.4144
	CU (%LC)	260	98.3	103.7	100.65	1.025
	Tablet Weight (mg)	260	1223.4	1286.4	1251.56	11.091
Lot 3	Assay (%LC)	500	99	101.9	100.85	0.4154
	CU (%LC)	499	98.2	104	100.82	0.7583
	Tablet Weight (mg)	500	1227.8	1270.1	1249.92	7.1898

Table 2
ANOVA

ANOVA		Sum of Squares	df	Mean Square	F	Sig.
Assay (%LC)	Between Groups	29.022	2	14.511	82.171	0.00000
	Within Groups	150.986	855	0.177		
	Total	180.008	857			
CU (%LC)	Between Groups	269.046	2	134.523	10.929	0.00000
	Within Groups	10536.121	856	12.309		
	Total	10805.167	858			
Tablet Weight (mg)	Between Groups	1851.021	2	925.511	12.222	0.00000
	Within Groups	64894.933	857	75.723		
	Total	66745.954	859			

The MANOVA was analyzed like the ANOVA, the p-values show if the means significantly differ or not from each other. The MANOVA concludes like ANOVA, it shows p-values less than 0.5. The means from the three parameters differ significantly per lot. The MANOVA analysis is composed of two tables the first is the Multivariate Testsa where three statistics tests named Pillai's Trace, Wilks'Lambda, Hotelling's Trace and Roy's Largest Root analyze the data providing significance level values

Table 3

Multivariate Comparison

Multiple Comparisons with Bonferroni Correction					
Dependent Variable	**(I) Lots**	**(J) Lots**	**Mean Dif. (I-J)**	**Std. Error**	**Sig.**
Assay (%LC)	Lot 1	Lot 2	-.215*	0.0495	0.00000
		Lot 3	-.508*	0.0461	0.00000
	Lot 2	Lot 1	.215*	0.0495	0.00000
		Lot 3	-.294*	0.0321	0.00000
	Lot 3	Lot 1	.508*	0.0461	0.00000
		Lot 2	.294*	0.0321	0.00000
CU (%LC)	Lot 1	Lot 2	-.615*	0.1013	0.00000
		Lot 3	-.787*	0.0944	0.00000
	Lot 2	Lot 1	.615*	0.1013	0.00000
		Lot 3	-.172*	0.0657	0.02700
	Lot 3	Lot 1	.787*	0.0944	0.00000
		Lot 2	.172*	0.0657	0.02700
Tablet Weight (mg)	Lot 1	Lot 2	-5.057*	1.0293	0.00000
		Lot 3	-3.446*	0.9584	0.00100
	Lot 2	Lot 1	5.057*	1.0293	0.00000
		Lot 3	1.611*	0.6671	0.04800
	Lot 3	Lot 1	3.446*	0.9584	0.00100
		Lot 2	-1.611*	0.6671	0.04800

The Multivariate Testsa significance values are less than one showing mean difference. The second table is the Tests of Between-Subjects Effects; it is similar to ANOVA because it uses sum of squares calculations. The p-values for the analysis between and within lots are less than 0.05 signifying mean variation for the three parameters.

Post Hoc

The MANOVA results concluded that there is a significant mean difference but it doesn't tell you where, for this reason a Post Hoc analysis of Multiple Comparisons was realized. The multiple comparison test using the Bonferroni Correction contrasted each lot with each other resulting in a table with the mean difference gathered from the mean comparisons. The multiple comparison tables conclude that Assay, CU and Tablet Weight contains a significant mean difference because the significant level is less than 0.05 when each lot is contracted to each other such as Lot 1 vs Lot 2, Lot 1 vs Lot 3.

Results without Rejected QH

The mean, standard deviation and range of Assay, CU and Tablet Weight was specified for each lot using descriptive statistics. The standard deviations for CU for the three lots are close and larger than one showing mean variability and a wide data range. The standard deviation of Tablet weight in the three lots is higher than one showing high mean variability and that the data set points are not uniform. A one-way ANOVA was generated to further study variability and displayed p-values less than 0.05 for the three parameters concluding that their means significantly differ from each other. A MANOVA was generated to examine variability from the three lots all together. The MANOVA is analyzed like the ANOVA, the p-values show if the means significantly differ or not from each other. The MANOVA concludes like ANOVA, it shows p-values less than 0.5. The means from the three parameters differ significantly per lot. The MANOVA analysis is composed of two tables the first is the Multivariate Testsa where three statistics tests named Pillai's Trace, Wilks' Lambda, Hotelling's Trace and Roy's Largest Root analyze the data providing significance level values. The Multivariate Testsa significance values are less than one showing mean difference.

Table 4
Descriptive Statistics

Lots		N	Min	Max	Mean	Std. Dev
Lot 1	Assay (%LC)	80	100.27	100.483	100.376	0.4782
	CU (%LC)	80	100.548	100.652	100.6	0.4034
	Tablet Weight (mg)	230	100.819	100.891	100.855	0.4154
Lot 2	Assay (%LC)	230	100.548	100.652	100.6	0.4034
	CU (%LC)	500	100.819	100.891	100.855	0.4154
	Tablet Weight (mg)	810	100.704	100.766	100.735	0.449
Lot 3	Assay (%LC)	500	100.819	100.891	100.855	0.4154
	CU (%LC)	810	100.704	100.766	100.735	0.449
	Tablet Weight (mg)	80	99.765	100.157	99.961	0.8799

Table 5
ANOVA

ANOVA		Sum of Squares	df	Mean Square	F	Sig.
Assay (%LC)	Between Groups	21.688	2	10.844	61.879	0.000
	Within Groups	141.422	807	0.175		
	Total	163.11	809			
CU (%LC)	Between Groups	52.538	2	26.269	36.386	0.000
	Within Groups	581.894	806	0.722		
	Total	634.432	808			
Tablet Weight (mg)	Between Groups	1970.404	2	985.202	13.735	0.0000
	Within Groups	57886.79	807	71.731		
	Total	59857.19	809			

The second table is the Tests of Between-Subjects Effects. The p-values from the Test of Between-Subjects Effects Table show mean variability of the three variables between and within lots.

Post Hoc

The MANOVA results concluded that there is a significant mean difference but it doesn't tell you where, for this reason a Post Hoc analysis of Multiple Comparisons was realized. The multiple comparison tests using the Bonferroni Correction contrasted each lot with each other resulting in a table with the mean difference gathered from the mean comparisons.

Table 6
Multivariate Comparison

Multiple Comparisons with Bonferroni Correction					
Dependent Variable	(I) Lots	(J) Lots	Mean Dif. (I-J)	Std. Error	Sig.
Assay (%LC)	Lot 1	Lot 2	-.224*	0.0542	0.000000
		Lot 3	-.481*	0.0503	0.000000
	Lot 2	Lot 1	.224*	0.0542	0.000000
		Lot 3	-.257*	0.0333	0.000000
	Lot 3	Lot 1	.481*	0.0503	0.000000
		Lot 2	.257*	0.0333	0.000000
CU (%LC)	Lot 1	Lot 2	-.672*	0.1103	0.000000
		Lot 3	-.865*	0.1023	0.000000
	Lot 2	Lot 1	.672*	0.1103	0.000000
		Lot 3	-.194*	0.0677	0.013000
	Lot 3	Lot 1	.865*	0.1023	0.000000
		Lot 2	.194*	0.0677	0.013000
Tablet Weight (mg)	Lot 1	Lot 2	-5.674*	1.0993	0.000000
		Lot 3	-4.783*	1.02	0.000000
	Lot 2	Lot 1	5.674*	1.0993	0.000000
		Lot 3	0.891	0.675	0.562000
	Lot 3	Lot 1	4.783*	1.02	0.000000
		Lot 2	-0.891	0.675	0.562000

The multiple comparison tables conclude that Assay, CU contains a significant mean difference because the significant level is less than 0.05 when each lot is contracted to each other such as Lot 1 vs Lot 2, Lot 1 vs Lot 3. There is a significant mean difference for Tablet Mean between Lot 1 vs Lot 2, Lot 1 vs Lot 3, Lot 2 vs Lot 1 and Lot 3 vs Lot 1. The is no significance mean difference between is significance level is larger than 0.05 in Lot 2 vs Lot 3 and Lot 3 vs Lot 2.

Control Charts

SPC methodology provided a process capability overview of the process through the use of Control Charts. The control chart selected for this research was X Bar – S because the studied data is high volume and the sample size is 10. They are 3 control charts per lot for each parameter totaling 9 control charts for the data without the rejected quarantine hoppers.

Assay

Assay in the first Lot has only one point outside the control limits in the sample mean possibly indicating special variation but in the sample standard deviation the data shifted from below towards on top of the total sample mean. In the second Lot for Assay in the sample mean vs sample control charts, there were three points outside control limits indicating special cause variation. In the Sample standard deviation control chart, the data seemed predictable in nature. The third lot sample mean control chart had the most outside control limits points, 10 in total from the three lots. This indicated special variation but in the sample standard deviation the data showed consistency and not a single a point was outside the control limits.

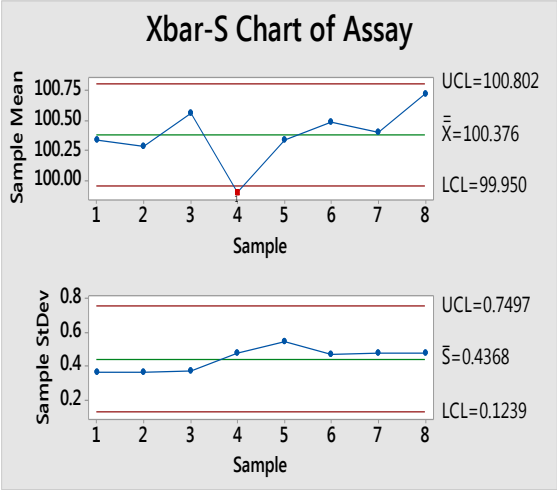

Figure 1
Lot 1 Assay

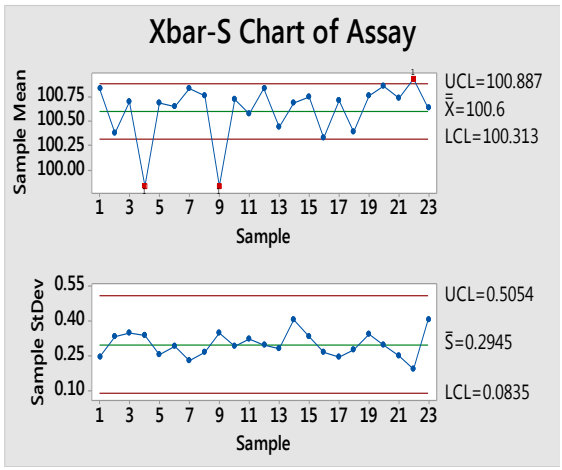

Figure 2
Lot 2 Assay

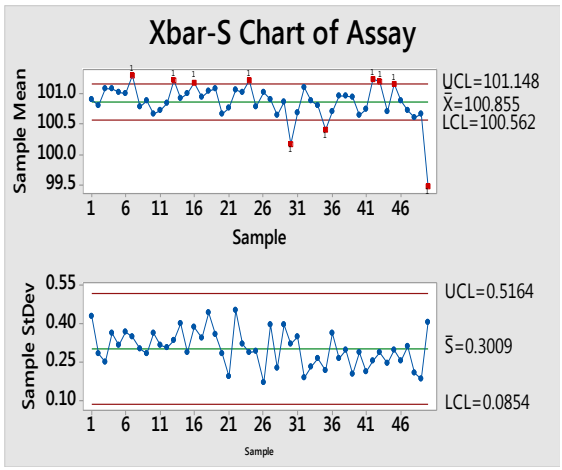

Figure 3
Lot 3 Assay

Content Uniformity

The X Bar – S control chart of Content Uniformity sample mean in the First Lot had 2 points outside the control limits and in the sample standard deviation showed a shift in data points possible indicating special cause variation. The sample mean control chart in the second lot had six points outside the control limits. In addition, the sample standard deviation chart for the second lot had 4 data points outside the control limits. Lot 2 needs further research to study the special cause variation found in the data.

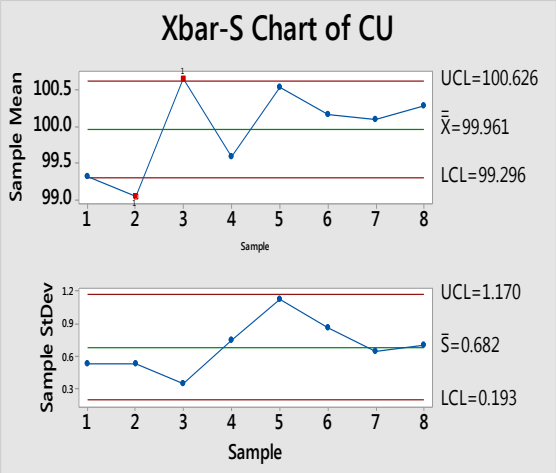

Figure 4
Lot 1 CU

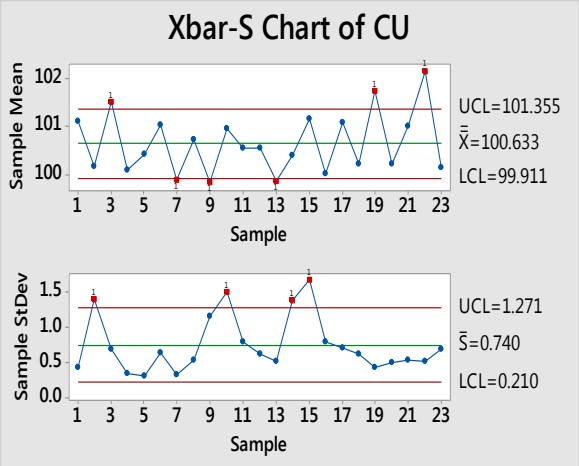

Figure 5
Lot 2 CU

CU in the third lot had 8 points outside the control limits in the sample mean chart and only one point outside the control limits for the sample deviation chart. The third lot sample mean chart had 8 points outside the control limits indicating mean variability and the sample standard deviation had only one point in the upper control limit line. The first lot sample mean chart for Tablet Weight represented inconsistency in the data and the sample standard deviation chart had one point outside of the control limits indicating clear variation. In the second lot the sample mean chart shows 6 points outside the control limits and the sample standard deviation chart displays 3 points outside the control limits. Both charts indicate parameter variation within the second lot.

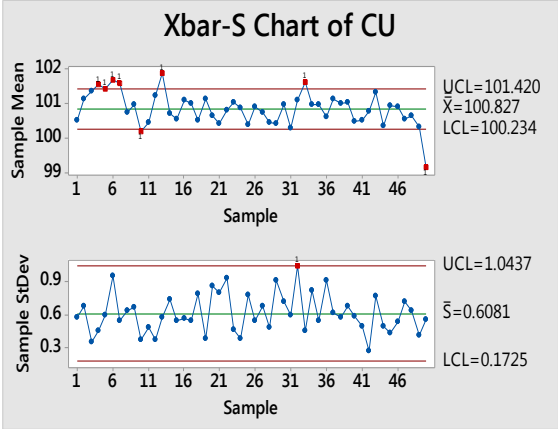

Figure 6
Lot 3 CU

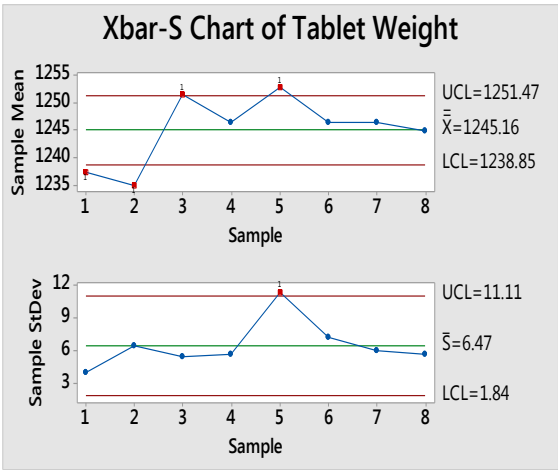

Figure 7
Lot 1 Tablet Weight

The mean chart demonstrated 7 points outside of the control limits and the sample standard deviation has only one point outside of the control limits. This means that variability exists in tablet weight mean of Lot 3.

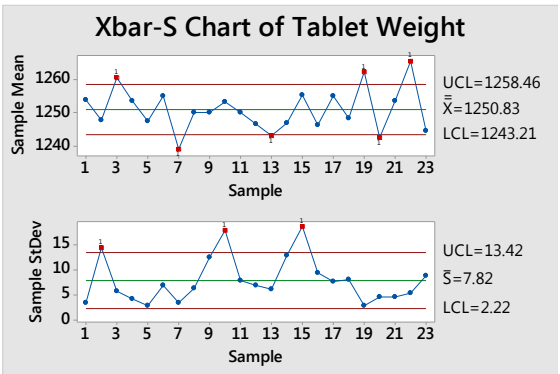

Figure 8
Lot 2 Tablet Weight

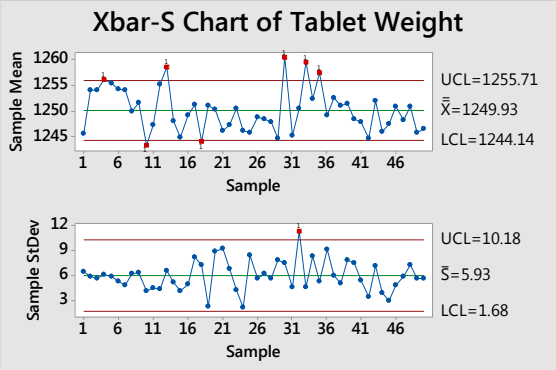

Figure 9
Lot 3 Tablet Weight

CONCLUSIONS

Variability within and between lots and for assay, CU and tablet weight was successfully studied using analysis of variance such as ANOVA, MANOVA, Post Hoc with Bonferroni correction among SPC control charts to illustrate mean and standard deviation variability. Research results proved Assay, CU and Tablet mean variation within lots and between lots. Further analysis needs to be conducted to find the origin of this variability. CM lot analysis can be supplemented with other types of test to fully grasp the inconsistency of lot sizes. SPC with control chart complemented the analysis of variance conducted in this research and could visually illustrate what the ANOVA and MANOVA were concluding.

The analysis of variance for the three lots considering two sets of data, the first data with the rejected QH and the second data without the rejected QH. The sample size difference from each lot doesn't affect the analysis of variance because these types of analysis adjust according to size of the data. The ANOVA for the first data set showed that the means from Assay, CU and Tablet Weight differed across Lots. The ANOVA from second data still indicated a considerate mean difference for Assay, CU and Tablet Weight across lots. The MANOVA for both data sets also concluded that the means for the three parameters differed between and within lots. The post hoc test with the Bonferroni correction contrasted the parameters between lots and could quantify the mean differences. This comparison test demonstrated that for the first data set, all the means for the three parameters in the three lots showed a significant mean difference. The comparison test for the second data set concluded that there was a mean difference in assay and content uniformity for all lots. Tablet weight showed no significant mean difference when Lot 2 was contrasted with Lot 3 and mean difference for the other lots comparisons.

The analysis of variance obtained from the first data set presented more mean variability than the second data set point. This is possibly caused by inclusion of the rejected QH data in the variance analysis. The rejected QH may have been rejected for out of specification data and negatively affected the trend variation in the results producing larger mean difference values. The second data set without the rejected quarantine hoppers produced more uniform results but the mean of the parameters was still significantly different. Assay was the most consistent parameter of the three and through lots. Assay mean variation increased by lot size but this can be attributed to special or random variation. The assay standard deviation remained predicable and stable in all lots. Content uniformity varied more than assay in terms of mean difference and also, variability increased with lot size. The standard deviation of CU seemed more stable in the first lot because the standard deviation varies significantly in the second and third lot. In the control charts, Tablet Weight presented the most inconsistent data out of the three parameters and variability increased with lot size in the sample mean and standard deviation control charts.

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