Execution of Lean Techniques for Cost improvement in a Quality Area of a Small Regulated Company established in Puerto Rico

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Abstract *— A small regulated company established in Puerto Rico developed a cost improvement project on a Quality Area to stay competitive. The main objective was to reduce the number of samples sampled for X and Y areas. Also, according to the evaluation those samples quantities already stored were reduced and the sample orientation at storage was changed. The implementations were performed with data integrity, high quality, within Regulatory and Quality Management approvement. Plan Phase was used to investigate the situation where the Visual Management 5'S was applied. During the data analysis was implemented a solution plan on the Do Phase. Meanwhile on Check Phase it was evaluated that implementation accomplished the project milestones. Though on Act Phase a cost saving of $85,784.82 was met and around 50% of samples sampled were reduced. It was confirmed with a Hypothesis Test for the Mean with alpha 5% and it was found that the reduction was completed.*

Key Terms *— Cost saving, Deming Cycle, Quality, Visual Management 5'S Methodology.*

INTRODUCTION

Pharmaceutical Industries manufacture chemical medicines to improve the health and are controlled by several standards, procedures, laws, and regulations. Since these organizations are regulated accurate, reliable, and legible documentation is required within the good manufacturing practices (GMP). Several audits are performed to assure the accomplishment of the companies within the laws and regulations. These audits could be internal or external audits and should cover Manufacturing, Packaging, Quality, Compliance, Information Systems, Engineering, and Finances areas, among others. The audits could be first, second or third party, depending on who is auditing. There are three general types of audits that certify the compliance: product audits, process audits, and system audits. Accomplishment with the standards, laws, and regulations must be performed or minor and/or major observations could be submitted by the auditors. These observations could have a hard impact on the operations of the audited company. Even more on small sites which must be cost, quality and compliance competitive.

A small regulated company develops a cost improvement project on a Quality Area to stay competitive. This project was performed using lean techniques as Deming Cycle as the principal tool. Meanwhile the project could be accomplished using Visual Management 5'S Methodology.

LITERATURE REVIEW

Pharmaceutical Industries are regulated and follows standards, procedures, laws and regulations stipulated by its global company management and by the government where operates and merchandise. Different audits are performed to evaluate the conformance to these regulations. A National Sanitation Foundation (NSF) Health Sciences article states that within the past 10 years, the volume of data integrity-related warning letters has increased dramatically [1]. Also, an article from the American Pharmaceutical Review reports that numerous warning letters have been issued from the Food and Drug Administration (FDA) citing data integrity violations from January to June 2020. It is frustrating that in 2022, a year that remains COVID-19 pandemic issues and virtual audits, stills predominating data integrity observations; even more when a guide was published by the FDA titled *Data Integrity and Compliance with Drug cGMP; Questions and Answers – Guidance for Industry*

was released in December 2018 [2]. This guide was generated since the FDA found an incrementation on current Good Manufacturing Practices (cGMP) violations involving data integrity issues which impact the safety, efficacy, and quality of products, and therefore several regulatory actions including warning letters, import alerts and consent decrees were submitted.

It is a shame that the data integrity observations are given due to human manipulation and execution. Neumeyer dictates that common finding were violation to principles of ALCOA+, 21 CFR Part 11, and FDA's data integrity guidance document [3]. Neumeyer offered some of the findings as follow: deletion or manipulation of data, aborted sample analysis without justification, invalidated OOS results without justification, destruction or loss of data, failure to document work contemporaneously, and uncontrolled documentation. Apparently, the regulated organizations have a lot of hard work to do, and the problem may be solved working on the culture of the company and its people.

Besides, Schniepp brought into attention that the industries has changed dramatically in the last years due to the grow of the generic-drug industry combined with the emergence of biosimilars, virtual companies, contract manufacturing organizations, rapid advances in automation and information technology, and the globalization of the industry [4]. All these changes lead to a reinterpretation of the integrity of data throughout the product life which increased violations to data integrity driving at a near future to a reeducation to improve the quality of the products. Schniepp bets the quality of the products into the use of ALCOA+ elements to avoid regulatory observations due to data integrity issues. ALCOA means that data should be attributable, legible, contemporaneous, original, and accurate. The plus, +, adds that data also needs to be complete, consistent, enduring, and available. This statement of ALCOA+ is the base to data integrity, but people culture loses the path of the principles of integrity of data, therefore Schniepp article could be seen as superficial.

Schniepp acknowledges on the article the data integrity issues and suggest different solutions to solve the problem. Schniepp relates the issues to the evolution and/or transformation of the drug manufacture of the medicines and the reinterpretation of the data integrity regulations established. The approaches to find a solution to data integrity problems are focused from different perspectives. A solution could be the focus on ALCOA+ principles as Schniepp mentions on the article.

In brief, audits are performed on regulated companies to evaluate the conformance of them to regulations. The last years between the observations found by the audit companies predominate data integrity failures. Possible solutions to work on integrity of data could be accept the data integrity issue and use it to educate instead of judging the personnel. The data integrity principles ALCOA+ should be the base of the integrity of data.

The audit background is important for this project since the processes should be performed meeting with regulations and data integrity. The small regulated site established on Puerto Rico had suffer several changes in the last years and audits are more frequent than usual despite the observations had been minors. The factor that impacts the site is the competitiveness with other sites around United States that manufacture similar products. The parent site always evaluates costs and in the process several consolidations of products and sites had been take place. The small sites need to stay competitive accomplishing quality and overall performance. Therefore, improvement projects are important to maintain these small sites competitive within quality and profitability.

METHODOLOGY

The application of lean will be used to accomplish with standards and regulations within data integrity and to enhance the quality of the products, cost improvements and the efficiency of the personnel. The Deming Cycle is a four-step model for continuous improvement of a process and

is also known as Plan-Do-Check-Act (PDCA) Cycle. The cycle consists in find out the issue and evaluate how to correct them, then executes a study to correct the issue, review the results and learn from the study is crucial prior to start all over again the cycle with a final studied solution.

Plan Phase consists in investigate the situation around the problem. The lean technique project charter was used to evaluate the situation where the objective is defined as well as the project milestones. The milestones of this project are to meet the objective within 12 weeks with a profitability of approximately $80,000 for the current year. Also, it is expected to reduce 50% of the samples sampled for X and Y areas. Also, Visual Management 5'S Methodology was used as a guide to complete this project. The 5'S Methodology which are sort, set in order, shine, standardize, and sustain. This method works organizing the samples, discarding samples that are no longer necessary to make more space available for storage, changing orientation of samples stored to maximize storage, reducing number of samples to be stored and discarding the overage of samples previously received, standardizing the changes offering education to the personnel, and using a checklist form to maintain the improvement.

ANALYSIS AND RESULTS

The second phase of the Deming Cycle Do is to identify the problem during the data analysis and at the same time implements a solution plan.

In order to *Sort* as the first step of 5'S method, X area was evaluated to reduce the number of samples sampled on Packaging Area for all the products manufactured on site. The decision was consulted with Quality Management to assure compliance with Regulatory and to complies with data integrity to avoid observations during an audit. Refer to Table 1 for detailed information.

Also, following the first step of 5'S method the Y area was evaluated to reduce the number of samples sampled on Packaging Area for product A manufactured on site. The decision was consulted with Quality Management to align sample quantity with Regulatory and to complies with data integrity to avoid observations during an audit. Refer to Table 2 for detailed information.

Table 1
Samples Evaluation on X Quality Area

Product	X Area			
	Total lots to be manufactured in 2022	**Total of samples sampled originally**	**Total of samples that could be sampled after evaluation**	**Total of samples returned to lot to be commercialized**
A	21	174	87	87
B	15	24	12	12
C	5	12	6	6
D	5	39	21	18

Table 2
Samples Evaluation on Y Quality Area

Product	Y Area			
	Total lots to be manufactured in 2022	**Total of samples sampled originally**	**Total of samples that could be sampled after evaluation**	**Total of samples returned to lot to be commercialized**
A	21	1106	506	600

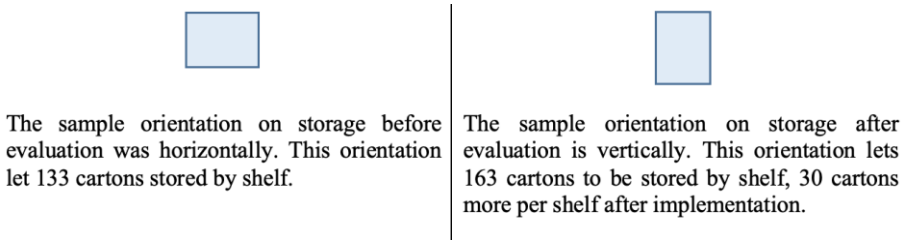
Meanwhile performing the second step of 5'S method *Set in order* samples on X and Y Area were organized. Product A was reviewed, and samples were regrouped on the free spaces of the same sample shelf. This reorganization gets some shelves available for future storage. Also, *Shine*, the third step of 5'S method, was employed on X area

discarding samples that are ready for destruction as per procedure.

The samples for Product A from X and Y Areas should be placed on a storage at a given temperature and relative humidity. The storage available to placed samples for Product A are 88 shelves. Quality Management was consulted to ask for an authorization to reduce the sample quantities that exceeds the original amount after the evaluation on samples already stored. An authorization was granted by Quality Management to discard the overage samples while increase the total shelves available to store samples to be manufactured during 2022.

The quantity of Product A stored for X area prior 2022 were 21 lots where each lot was stored on five shippers given a total of 105 shippers. Each shelf is occupied by three shippers. Then after evaluation these sample lots were reduced to be store on three shippers. This reduction makes available 16 shelves for samples storage. Furthermore, the quantity of Product A stored on Y area that could be discarded was 3959 cartons. Since each shelf is occupied by 133 cartons then 29 shelves more were available for samples storage. The reorientation on X samples storage was executed to improve the number of samples to be store on a shelf. Refer to Figure 1 below for detailed information.

Check is the third phase of the Deming Cycle. During this phase is important to monitor the impact of the details implemented during the Do Phase to assure the objectives are accomplished. During the evaluation of improvement objectives, it was obtained that for X area around $63000 could be generated from the commercialization of products A, B, C, and D during 2022 after the implementation of samples reduction during Packaging sampling for X area samples. Refer to Table 3 below for a detailed information.



The sample orientation on storage before evaluation was horizontally. This orientation let 133 cartons stored by shelf.

The sample orientation on storage after evaluation is vertically. This orientation lets 163 cartons to be stored by shelf, 30 cartons more per shelf after implementation.

Figure 1
Samples Orientation on Storage of Product A for Y Area

Table 3
Cost Saving of Products on X Quality Area

Product	X Area			
	Total lots to be manufactured in 2022	Total of samples returned to lot to be commercialized	Price per carton	Total cost savings for 2022
A	21	87	$31.56	$57660.12
B	15	12	$13.97	$2514.60
C	5	6	$15.65	$469.50
D	5	18	$28.02	$2521.80
			Total	$63223.66

Table 4
Cost Saving of Product A on Y Quality Area

Product	Y Area			
	Total lots to be manufactured in 2022	Total of samples returned to lot to be commercialized	Price per carton	Total cost savings for 2022
A	1	600	$31.56	$18936.00

Table 5
Cost of Samples Storage of Product A for X and Y Area at External Storage

Area	Months to store Product A by area	Cost per month for External Storage	Total cost for External Storage by area
X area	36	$55.80	$2008.80
Y area	30		$1674.00
		Total	$3682.80

Product	X Area					Y Area				Total Cost Saving $
	Total Lots to be manufactured in 2022	Total of Samples Sampled Originally	Total of Samples that Could be Sampled after Evaluation	Total of Samples Returned to Lot to be Commercialized	%Reduction	Total of Samples Sampled Originally	Total of Samples that Could be Sampled after Evaluation	Total of Samples Returned to Lot to be Commercialized	%Reduction	
A	21	174	87	87	50.0%	1106	506	600	54.2%	$ 76,596.12
B	15	24	12	12	50.0%					$ 2,514.60
C	5	12	6	6	50.0%					$ 469.50
D	5	39	21	18	46.2%					$ 2,521.80
Cost Saving of External Storage not used since project implementation offers 45 shelves to store samples of Product A for X and Y Areas which consists on 51% of storage.										$ 3,682.80
									Total	$ 85,784.82

Figure 2
Summary of Samples Evaluation on X and Y Quality Areas

Hypothesis Test for the Mean

It is expected to have a %Reduction of 50%

Sample Size N = 5	%Reduction
1	50.0%
2	50.0%
3	50.0%
4	46.2%
5	54.2%

Hypothesis

H_0: $\mu = 50\%$
H_1: $\mu \neq 50\%$

Test with Known Variance (Normal Distribution)		Test with Unknown Variance (Student T Distribution)	
Variance	1.0%		
Hypothesis Test Results		**Hypothesis Test Results**	
μ	0.50	μ	0.50
σ	0.33%	s	2.86%
$\bar{X}$	50.08%	$\bar{X}$	50.08%
N	5	N	5
z_{exp}	0.541	T_{exp}	0.062981
p_{value}	0.588	p_{value}	0.952803
α	0.05	α	0.05
There is not enough evidence to reject H_0, μ is equal.		There is not enough evidence to reject H_0, μ is equal.	

Figure 3
Hypothesis Test for the Mean Evaluation for 50% Reduction expected

Meanwhile it was obtained that for Y area around $19000 could be generated from the commercialization of products A during 2022 after the implementation of samples reduction during Packaging sampling for Y area samples. Refer to Table 4 above for a detailed information.

The implementation of sample reduction of X and Y samples of Product A and the change of samples orientation on storage will help to avoid the use of an external storage monthly rent. After the project implementation a total of 45 shelves were available for samples storage. Then, since the samples of X area should be stored for 36 months, and the samples of Y area should be stored for 30 months there is a cost saving on external storage avoid of around $3600. Refer to Table 5 below for the cost saving when the external storage is not necessary after implementation of this project.

Standardize was completed offering training to the personnel working on X and Y areas. This process will be successful since only two persons works on the areas to maintain control of these areas. Then, the 5'S method was completed implementing Sustain on X and Y areas. This section will be done executing a checklist form where the samples evaluation will be performed in a monthly basic. The form will be to revise the PDCA Cycle.

CONCLUSION

Last and not less important is the Act Phase of the Deming Cycle. This last phase is to decide if the solution applied is effective or not. If the implementation does not work, then the lesson learn should be evaluated before starts the Deming Cycle all over again.

The execution of lean techniques for cost improvement in a Quality Area of a small regulated company established in Puerto Rico was concluded. The project charter, SIPOC and process flow chart tools helped to find out the overview of the project for improvement. Although the 5'S methodology was a guide to execute the cost improvement of this project with the lean technique Deming Cycle (PDCA). The project milestones were accomplished. The project was concluded within 12 weeks and with a cost saving of $85784.82. Also, it was found a reduction of around 50% of the sampling for Product A, B, C, and D on X area as well as the Product A on Y area. A Hypothesis Test for the Mean was developed and with alpha 5% it was concluded that the reduction was completed with a 50% Reduction as expected. Additionally, the sample storage of 88 shelves was organized generating 45 shelves available for samples storage offering a 51% for storage of Product A. Refer to Figure 2 on next page for a summary of the reduction and cost saving per product and to Figure 3 for Hypothesis Test for the Mean Results.

REFERENCES

[1] M. Fritz, "Data Integrity and Warning Letters", NSF International, Ann Arbor, MI, USA, 2020. https://d2evkimvhatqav.cloudfront.net/documents/ph_data_integrity_warning_letters_white_paper.pdf?mtime=20200623104054&focal=none

[2] Food and Drug Administration. (2018, Dec.). Data Integrity and Compliance with Drug cGMP: Questions and Answers – Guidance for Industry. [Online] https://www.fda.gov/media/119267/download

[3] M. Neumeyer, "Data Integrity: 2020 FDA Data Integrity Observations in Review", American Pharmaceutical Review, https://www.americanpharmaceuticalreview.com/Featured-Articles/565600-Data-Integrity-2020-FDA-Data-Integrity-Observations-in-Review/, (accessed March 14, 2022).

[4] S.J. Schniepp, "ALCOA+ and Data Integrity", Pharmaceutical Technology, 43, 10, (October, 2019), 77. https://www.pharmtech.com/view/alcoa-and-data-integrity