Using Six Sigma Methodology and Technology to Improve Quality Audit Process Cycle Time

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Abstract *– Currently, at the "Pharmaceutical Company Y", the cycle for launching a product can take an average of 46.7 days. The proposal for this study seeks to reduce this cycle time to 30 days. This project illustrates the improvements that can be achieved when a company understands and applies Six Sigma tools and methodologies to reduce the cycle time between product manufacturing and product approval for shipment. The company must have quality control that ensures that the final product meets the acceptance parameters, but at the same time that the release time is reduced so that the product is shipped in less time. The application of the Six Sigma concepts, the DMAIC methodology and the development of an electronic checklist optimizes the quality audit process and the final approval, provided that the audits are carried out with the manufacturing process in parallel.*

Key Terms *– Cycle Time, DMAIC, Improvements, Lean Manufacturing.*

PROBLEM STATEMENT

Six Sigma principles are frequently used in improvement cycle time. Using the project of White, García, Hernández, and Meza [1] as an example, the principles of Six Sigma and the DMAIC methodology were used as tools for the reduction of the cycle time to increase new business accounts. In a great example, a company needs to minimize cycle time to get its products to customers faster, resulting in increased production. The principles of this methodology are used to analyze and identify areas for improvement during the quality audit process, using work strategies developed to streamline parallel jobs. The approach of the Six Sigma philosophy is focused on the client and the supply of quality products; understanding how the management of an organization operates; and how the time cycle of the audit process is applied. The audit process can be streamlined.

One of the biggest challenges was experienced during the new reality due to the COVID-19 pandemic in the last three years, which motivated many companies to reinvent their processes to streamline and meet the demand for products in the market without affecting their quality. Many companies were affected by their quality requirements, processes, regulations, and internal audit records. For example, the FDA had difficulty reaching many companies and industries. Today, there is a wide range of innovative technologies available to all businesses. It would be helpful to have an electronic application or checklist and some of the required information shared by the FDA or even internal auditors. Some of the critical tasks in the process are auditable, and waiting times would be reduced with these innovations.

One of the main clients that the pharmaceutical industry has, in addition to the bondholders, is the patients. The main objective that the industry has is to provide its patients with the highest quality products. Pharmaceutical companies currently have a high demand for their products, which establishes a work rhythm quantified by the time cycle. Cycle time is a metric and control to measure how long it takes to bring products to market for patients. Cycle time is a very valuable tool that has areas for improvement. Currently, it can take between 45 and 49 days to ship the products, with an average of 46.7 days. By using current innovative technological elements, such as application platforms, programs, or even electronic access checklists, company will be able to reduce the audit cycle time of their products, which means they could be sent in less time. Reducing the quality audit time of a product represents an opportunity to ensure

that patients receive their products in less time, decrease errors, and provide with profitability for an increase in production.

Research Description

This paper will explain the importance of implementing improvements in the cycle time in a quality audit in the pharmaceutical manufacturing. Applying the principles of the Six Sigma methodology in the reduction of the cycle time to speed up the release management of a product for shipment. This type of project is very useful to guarantee a higher rate of customer satisfaction, an increase in sales, and a release of capacity to manufacture other products.

Research Objectives

Using the principles of Six Sigma, it will be possible to reduce the cycle time of a quality audit from 46.7 days to 30 days in a period of 3 months of implementation. The objective of improving the cycle time in the quality audit may be achieved by performing the audit of an extra batch and a half in a period of 3 months compared to the 2 ½ batches that are carried out with the current cycle of 46.7 days.

This will be reflected in the increase in products shipped to the business in less time and improvements in cGMP compliance in manufacturing.

Research Contributions

By applying the principles of the Six Sigma methodology to cycle time in quality audit tasks, it is possible to reduce the approval time of a batch of products. This type of reduction will maximize the performance of the time to put a product on sale, which will also create space for more products to be evaluated and to be able to go on sale. This project will contribute, in addition to reducing time, and reducing the cost by using resources in the approval of a batch and, in turn, will increase the availability of products in the market, allowing increased sales.

LITERATURE REVIEW

This type of study and improvement could be extended to other operations within manufacturing to reduce lead time and maximize productivity. The focus of this work is to reduce wasted time and organize the process to be one of multiple parallel tasks during the quality audit of batch production. Quality audit is a review to assess conformance to the requirements of a quality management system based on the international standard ISO 9001. There are different types of quality audits depending on what is audited, who is audited, and where. where the audit is performed. For the purposes of this project, the researcher will focus on the types of quality audits that apply to the manufacturing sector under investigation.

Types of quality audit

- Process audit: verifies that an organization's processes achieve compliance with the requirements of ISO 9001.
- Product audit: checks the quality of the product or service to determine if it meets the specifications or needs of the client.
- System Audit: seeks to provide objective, proving evidence that the elements of the system and the documents have been developed and implemented in accordance with the requirements of the standard.

The phases for the development of the different types of quality audit for any type of audit require following a process that is carried out, basically, in five stages:

- Planning and preparation
- Execution of the audit
- Informs presentation
- Closing of the audit
- Tracking

Elimination of lost time from the batch audit process is due to process optimization. Directing the quality assurance (QA) representative to do their work in parallel with manufacturing promotes faster auditing within manufacturing to get approved for shipment in less time. The quality audit process will be improved through the application of DMAIC

principles, process mapping, and the development of an electronic checklist. Align the processes with the objectives of this project by correctly applying the Six Sigma tools will be followed. Next, the Six Sigma principles that are suggested to be applied in this research:

- Always focus on the customer.
- Understand how a process occurs.
- Audit parallel to manufacturing so that the process flows smoothly.
- Reduce waste and focus on value.

Some of the benefits include faster time to market and, if other cost factors are controlled, an opportunity for higher profitability. Reducing cycle time also helps a company become more competitive against other companies offering similar products to the same customer base. When proposing to use the methodology called Six Sigma, it must be understood that it is a set of techniques and tools used for process improvement, developed by the American engineer Bill Smith while he was working at Motorola in 1986. Created as a statistical analysis tool to help Define problems systematically. Providing tools to measure and analyze influencing factors, identify potential solutions, and help maintain and sustain results.

The DMAIC method is generally used to advance an existing process and as mentioned by Shahar and Mohd, where they mention that the DMAIC method integrates the foundations of the Six Sigma methodology and is beneficial and successful in the cycle time improvement, explaining that "Each of the tools used to record and visualize the system. Even with different functions, the main objective is the same which is to identify the main problems to be addressed" [2].

Using Six Sigma techniques, we will be able to identify problem areas that affect the general expectation of quality of a service and/or product from the customer's point of view. Each step of the DMAIC methodology has the appropriate tools available. The benefits of cycle time reduction include faster time to market and an opportunity to increase profitability, which also helps a business become more competitive against other businesses. Cycle time in Six Sigma is the time from the beginning to the end of a process, known as a STEP.

Process mapping is a technique used in the Six Sigma project to visualize the steps involved in a certain activity or process. Six Sigma process mapping is a flowchart that illustrates all the inputs and outputs of an event, process, or activity in a systematic, easy-to-read format. It's important because it helps communicate and guides to specific areas of focus. For this reason, it is an adequate tool for the work that is proposed.

By making these improvements to the data measurement, analysis, and visualization process, the overall process will be compared to the process before the improvements, with the process optimized. This will result in the identification of areas that need improvement and a better understanding of the batch release report, where the process can be minimized from 46.7 days to 30 days. In the end, this will translate into a reduction in time and an increase in capital for the company, causing the final product to go to market and the customer to have greater satisfaction by having a greater availability of their product when they need it.

METHODOLOGY AND FINDINGS

This design project has both observational and experimental elements using the Six Sigma methodology; the proposed activities developed were totally based on the execution procedure and application of the methodology. The objective of this work is to reduce wasted time and organize the process so that it is executed together with the various tasks carried out during manufacturing parallel to the quality audit of a batch production. As is mentioned Ray and Das “The selection of right projects in a Six Sigma program is a major concern for early success and long-term acceptance within any organization” [3].

The research consists of applying DMAIC techniques and tools to reduce the approval and approval time in the final stage of approval of shipments based on the five main stages of DMAIC.

Define- This project took as its inspiration model the manufacturing line of parenteral products of a pharmaceutical company in PR. The parenteral line of the pharmaceutical company manufactures vial supply products, that is, known in the industry as "Fill and Finish," where the product is formulated at its final concentration and is adjusted to doses in vials, which are the ones that reach our customers. At different stages of the product's manufacturing, there are areas which depend on quality audits. The areas that represent a greater consumption of audit time by quality personnel (QA) are weighing, formulation, filling, lyophilization, sealing, inspection, and packaging, resulting in these manufacturing areas as internal clients of the operations and the service of the quality audits that decide with their functions the approval of the shipment. Patients who are affected by diseases, such as but not limited to Crohn's disease, are direct customers of this product.

In Table 1 the final times that were used for 10 commercial batches were compiled, where the current cycle time could be seen reflected during the batch audit before being approved for shipment. Using this reference data, a series of questions were developed to give direction to the project to be proposed. Refer in Table 2.

Table 1

Original study date

Quality Audit before implementation of improvements			
Batch	Starting Date	Ending Date	Total time (days)
1	03/10/22	04/25	46
2	03/13/22	04/29	47
3	03/16/22	04/30	47
4	03/19/22	05/06	48
5	03/22/22	05/10	49
6	03/26/22	05/10	45
7	04/01/22	05/17	46
8	04/03/22	05/21	48
9	04/08/22	05/23	45
10	04/10/22	05/26	46
		Average	46.7

The data collected was the baseline of the improvement of the time cycle. They are key to determining and justifying if a project is aligning with the company's strategy, which will be explained in more detail in the second phase of this methodology.

Table 2

Voice of the Customer (VOC)

Questions that seek to define the objectivity of the current process.	
Answer on a scale of 1 to 5, with 1 being completely disagree, 2 disagree, 3 neutral, 4 agree, and 5 completely agree.	
Do you think the current batch approval cycle time for shipment represents the effort of streamlining processes in manufacturing?	
With the current market demand, does the current wait time for shipment meet the customer's needs?	
Do you think that the waiting time for product shipment approval is a reason that affects the quality of life of our customers?	
Do you think that incorporating the final quality audit together with manufacturing can speed up and reduce the time in which a batch is approved?	

From March 10 to May 26, 2022, the approval time cycle of 10 batches was recorded, where 100% exceeded the suggested objective, resulting in a delay for the product to reach the hands of patients.

Measure- As a data collection plan that is proposed to be implemented, a process map was made to understand the distribution of work time according to the stages of actual manufacturing, as shown in Figure 1. This helps to identify the best way to measure the process for efficiently using resources to achieve parallel work of manufacturing operations alongside audits. Table 1, used to define the objectives of this project, plays a crucial role in quantifying the performance of the final audit based on the data collected.

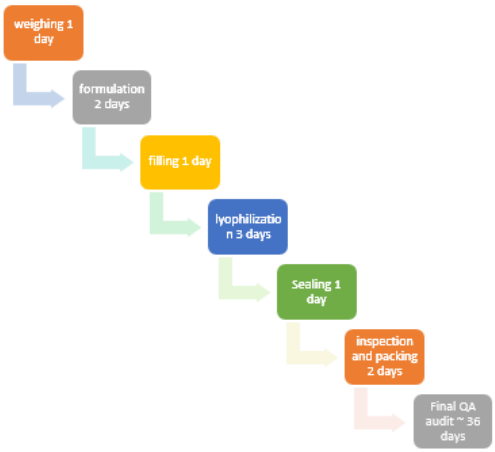

Figure 1

Process Map

The data is compiled, considering when the first operation of a batch begins and when it is declared ready to be shipped by the quality audit. As was done in Table 3, where the time elapsed per batch can be quantified to be approved to go to market.

Table 3

Original study date

Quality Audit before implementation of improvements			
Batch	Starting Date	Ending Date	Total time (days)
1	03/10/22	04/25	46
2	03/13/22	04/29	47
3	03/16/22	04/30	47
4	03/19/22	05/06	48
5	03/22/22	05/10	49
6	03/26/22	05/10	45
7	04/01/22	05/17	46
8	04/03/22	05/21	48
9	04/08/22	05/23	45
10	04/10/22	05/26	46
		Average	46.7

With the objective of looking for the current time cycle of a product to be released towards the shipment of the product, taking as research data the dates of 10 batches between March and May. Where in the 10 batches used, the time cycle to process the batches was over 45 days. As can be seen in Figure 3, where the average of the 10 samples is 46.7, and 46 audit days is the most repeated value within the population. The lowest value within the samples was 45 days and the highest was 49 days. In addition to taking into account that the mean is 46.7, the standard deviation of this process is 1.337 in a population of 10. When analyzing the variation of the values in the process, the data obtained show that the distribution of the data does not fit in the expected between the values is intended for the process to be.

Descriptive Statistics: Total time (days)

Statistics

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Q1	Median	Q3	Maximum
Total time (days)	10	0	46.700	0.423	1.337	45.000	45.750	46.500	48.000	49.000

Statistics

Variable	CoefVar
Total time (days)	2.86

Figure 2

Descriptive Statistics of Total time(days)

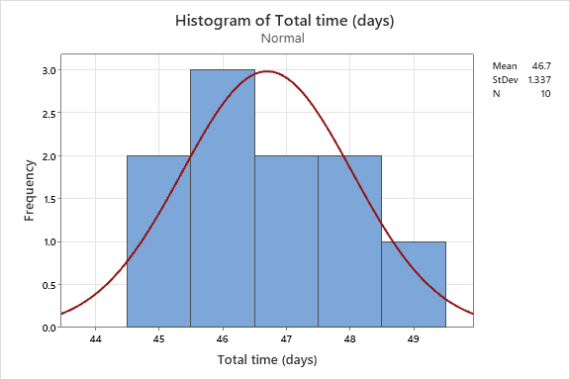

Figure 3

Histogram of Total time(days)

It is evident that most of the batches have a frequency of being released when reaching 46 days of process audit, as shown on the histogram graph, showing the behavior of values inclined to the left of the graph.

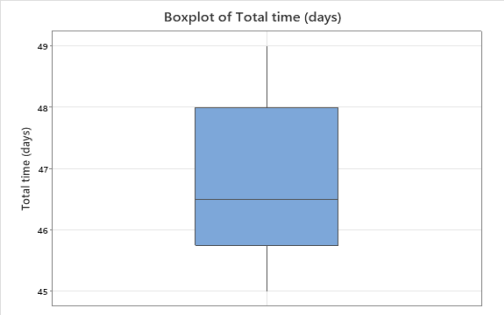

Figure 4

Boxplot of Total time (days)

Analyzing Figure 4, boxplot shows the median of the process is 46.7, but wishing the data there is some values that showed 45 days of process and other that showed 49 days. Most of the values stayed higher the median between 47 and 48 days. Just a fewer sample were below the median.

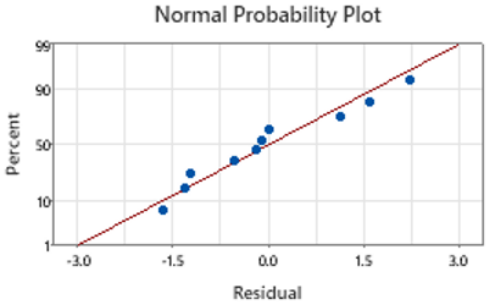

Figure 5

Probability Plot of Quality Audit

Since Figure 3 shows that the distribution of the values does not deviate from the normal distribution, it is clear from Figure 5 that it is a typical for the batches that were successfully audited in their entirety to be sent close to the average.

The objective of this project is to reduce the time cycle for the approval of a lot for shipment. It is sought as an improvement of the time cycle to identify and eliminate the waste of time that can be seen related to the tasks of manufacturing and product release. Analyzing the efficiency of the data obtained versus the desired data in the objective, having an efficiency of:

Efficiency= (New cycle time / average cycle time actual) * 100%

E= (30 days/46.7 days) * 100%

E=64%

Low efficiency's outcome makes it easier to see where this process needs to be improved. This will speed up the product's release to the market and ensure that patients receive it.

Analysis- In the development of the analysis, the Pareto Chart (Figure 6) was used to find out which was the time that had the greatest incidence of being repeated to use it as an improvement item. The most typical number of days a batch gets to market among processed batches, as shown in Figure 4, is 46 days. This indicates that the current audit cycle time norm is about 46 days, and any batch surpassing that amount may indicate issues with production and documentation.

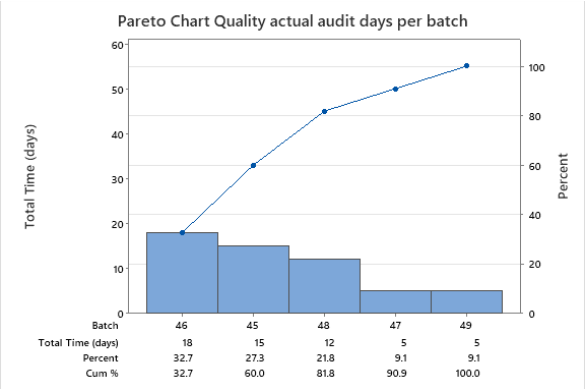

Figure 6

Pareto Chart

A run chart (Figure 6) was made to study the impact of the current time cycles, where 5 points out of the 10 samples used in this study are above the current cycle average. This visual evidence supports the urgency to improve the cycle times during the quality audit to release a lot. It does not show that there is a dramatic improvement in the way operations are currently carried out.

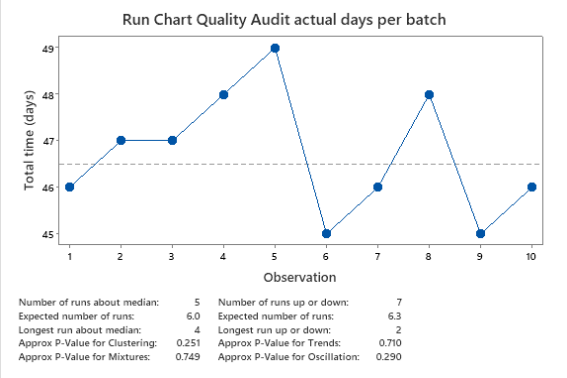

Figure 7

Run Chart

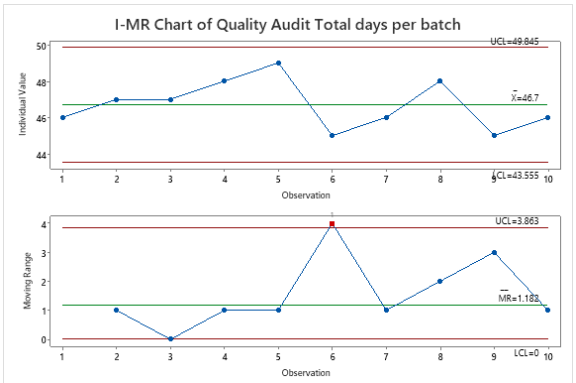

Figure 8

I-MR Chart of Quality Audit days

In the run chart of Figure 7, which represents the order in which the data was collected according to the dates of the batches when they were completed, it helps to recognize the behavior of the data through its p-values. When analyzing the data from the run graph, the following values are obtained: Clustering has a P-value of 0.251, Mixtures has a P-value of 0.749, Trends has a P-value of 0.710, and Oscillation has a P-value of 0.290. The same when compared against the value $\alpha = 0.05$, it cannot be concluded that they have a greater tendency for any behavior. This is because the values in those behaviors are closer together than trends or mixes. Therefore, it would be more appropriate to conclude that they maintain random variation patterns and that the process needs improvement. This values do not have a pattern displayed to confirm their behavior, resulting in random variation patterns.

Analyzing Figures 8 and 9, it is clear to see that the current process of bringing a product to market is not under control. The variability and little consistency show that this process has room for improvement, and it is necessary to adjust the company's process that does not go in parallel with manufacturing, so that it quickly reaches the hands of those who need it most, the patients. Both figures show how the data is outside the expected ranges, according to the proposal of this 30-day project. These graphs support the room for improvement that this process could have.

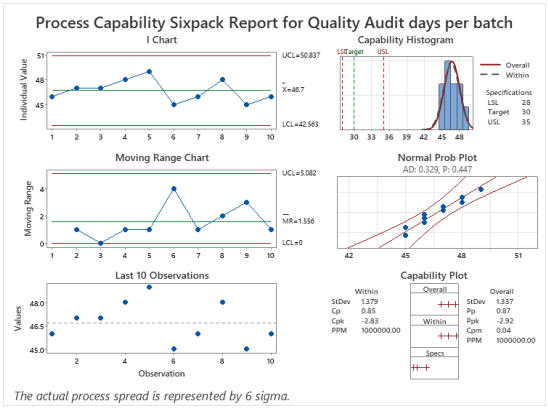

Figure 9

Process Capability Six pack

When process capability is analyzed according to Figure 8, Cpk is used to assess the potential capability of a process based on the data used and its location within the process spread to determine if the process needs improvement. The value of Cpk in this analysis has a value of -2.83. Industries usually use the value of Cpk = 1.33 as a reference. The value obtained in this analysis is lower, which is an indication that the process needs improvements. When comparing the Cp that has a value of 0.85 > Cpk=-2.83, it is an indication that the process is not centered and needs to reduce variation and/or move its location. Likewise, taking into account the value of Ppk, which is -2.92, it is a lower value than that used in industries. Another indication that the process is not centered: when observing and analyzing the histogram, it is completely outside the expected

ranges. Visually, it is understandable that the process does not comply. The potential capacity result of this process does not meet the customer's requirements.

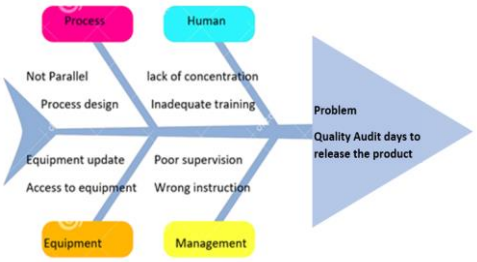

Figure 10

Fishbone Diagram, Cause and Effect

The fishbone diagram is used as a tool to collect feedback on the possible causes of the current problem of such a long product release process. This diagram shows how these causes are influential in the cycle of time that a quality audit lasts. A 5 Why's was developed to analyze the reasons for the causes that promote the problem.

Table 4

5 Whys

The product takes time to reach the market, which has an impact on the patient's availability.
Why?
Because the quality audit release is a lengthy process.
Why?
The design of the process could be improved since most of the audit is carried out at the end of the production of the batch.
Why?
The quality audit process takes more than 30 days, which is the new goal.
Why?
The final audit is not executed in parallel to the manufacturing process; it is necessary to wait for the process to be finished before the audit is carried out.
Why?
Because there is no electronic system that allows auditing the batch live to close the phase of that audit with the process.

Improve- Improvement- As part of the improvement design in this project, the nature of the business was taken into consideration. When working with a parenteral product, it must be taken into account that its processes are continuous; one stage ends to continue the other. Part of the problem that arises in this pharmaceutical company is the amount of wasted time that is lost waiting for the process to finish to be audited. One of the ideas for improving cycle time in the final audit of a product is parallel execution. This means that within the stage of a process, for it to be completed, it must be audited in detail as part of the regular process. A new process map was developed to illustrate how the process should flow, along with the quality audit visible in Figure 11.

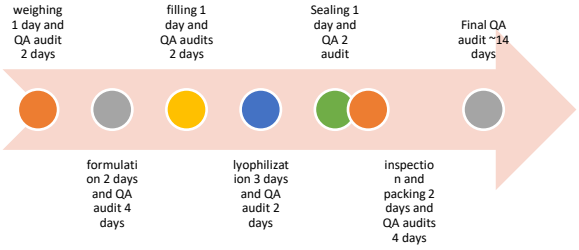

Figure 11

Process Map of Manufacture Activities with QA Audit in Parallel

As it can be seen in Figure 11, approving each phase of the process while it is being carried out helps to reduce the time spent when a batch is audited and approved for shipment. This translates into the prompt availability of the product in the market accessible to the customer. It is not only beneficial for the customer who receives his product when he needs it, but it is also beneficial for the cGMP compliance of the processes since, in the event of any type of situation that may affect the product or the operation, he has early visibility and the situation can be worked. Part of the improvements promoted in this project is the development of a checklist that could be filled in while working in parallel with the process, as can be seen in Figure 11.

Checklist: Quality Assurance Audit Process		
1. Identification of the audit		
Area:	Start time and date:	
Audit type: □ Process □ Final	Time and date of completion:	
Product:		
2. Auditor		
Name:	Tel. Email-	
3. Checklist		
	Yes	No
1) Does the process meet quality standards?		
2) Were any discrepancies observed in the process?		
3) The production time is within the acceptable range?		
4) Is the documentation complete?		
5) Are there pending corrections?		
6) Did any quality or safety event occur?		
7) Was the machinery in compliance with its calibrations?		
8) The materials used in the batch were within the use date?		
9) Does the lot meet the expected appearance?		
10) Was there any delay?		
11) Were the documents and procedures effective?		
Comments:		
Complete by:		
Approved by:		

Table 5

Quality Checklist

As part of the improvements was the realization of an electronic checklist as part of the audit during manufacturing. This sheet was made to expedite the release of the lot once the audit was completed. The trained staff perform audit activities online and in person to reduce the time lost between auditing a batch when it is finished and releasing it. Following the recommendation from ISO 9001 the quality audit checklist needs to meet those requirements.

Control- To ensure that the new conditions in which the process has been placed are within the established parameters, the electronic checklist must be included as part of the official documentation. Quality personnel will need to be trained in the use of this new tool and procedures will need to be developed that explain its use and approach. After implementing these changes in the logistics of the work and applying the concept of parallel execution, together with the use of an official checklist, it will be possible to observe that the time cycle for the approval of a batch can be carried out in 30 days. The new flow work implies concentrating 14 days during the different stages of the process to audit it exhaustively, allowing an additional 16 days for any type of review and correction that must be carried out.

CONCLUSION

The implementation of the Six Sigma methodology in the quality audit process allows the creation of a standardized work tool and achieves the elimination of various activities that do not add value to the process. Understanding how to apply the principles of this methodology is of great value to achieve the reduction of the cycle time, which, as mentioned by Taifa and Vhora [4], "is one of the viable parameters which needs to be optimized as much as possible whenever the manufacturing industry is trying to improve efficiency, cost base and customer responsiveness."

Understanding these ideas helps achieve consistency and reduce batch release delays. Knowing the workflow helps to find the tasks that do not add value and delay the batch release. The elimination of this wasted time and the parallel execution is due to process optimization. Directing QAs to do their work in parallel with manufacturing to streamline their process results in fewer days being taken to approve a lot for shipment. Applying the principles of DMAIC, process mapping, and the development of an electronic checklist can enable us to align the processes with the objectives of this project.

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