Quality Control Laboratory Improvements

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Abstract *— Sanper Pharmaceutical is an inhalation anesthesia manufacturing plant. Its main products are Elim and Marile. The high demand for its products has created the need to make improvements in their processes. As part of this project, the Quality Control (QC) Laboratory Activities should be improved. Currently, the delay in laboratory analyzes hinders the Finished Drug Product release time, increasing the final release cycle's time. Thus, it is difficult to comply with the delivery agreements made with customers. By the end of this project, QC Laboratory will minimize the analyses release time by 20% or more. This will enable the site to be more agile in the delivery of its products. To reduce the QC Laboratory Activities variability, and to align customers' expectations, a Six Sigma methodology is appropriate. DMAIC (define-measure-analyze-improve-control) has been widely used as the method for Six Sigma implementations in Quality Control Laboratory Activities.*

Key Terms *— DMAIC, Finished Drug Product, Quality Control Laboratory Activities, Raw Materials, Release Cycle Time Process.*

PROJECT STATEMENT

Sanper Pharmaceutical is an inhalation anesthesia manufacturing plant. Its main products are Elim and Marile. The high demand for its products in recent years has created the need to make improvements in their processes. As part of this study, the Quality Control Laboratory Activities should be improved.

The Quality Control Laboratory has four different shifts. Each shift has its own job plan structure. This variability between shifts causes an inconsistency in the delivery of results, which affects both internal and external customers. The objective of this project is to improve the Quality Control Laboratory analyses cycle's time, standardize priority management and daily job plan, and align internal goals with clients' needs. The current release process is not standardized and takes too much effort and time to analyze all samples on time. By the end of this project, the Quality Control Laboratory will minimize the chemical analyses release time by 20% or more, which will enable the site to be more agile in the delivery of its products. In addition, Sanper Pharmaceutical will be more robust on its Finished Drug Products release process, making this project one of high priority and visibility.

RESEARCH DESCRIPTION

The importance of this study is to minimize the time required for Chemical Analysis to release the final product to the market. The longer the product release process takes, the longer it will take to reach the customer. This affects the relationship with customers, increases backorders, and minimizes the ability to acquire new markets. In addition, it also affects the relationship with internal customers, Manufacturing, Filling and Packaging, among others. This improvement is aimed at both products: Elim and Marile.

RESEARCH OBJECTIVES

The objectives for this project will be addressed to:

- Improve Quality Control Laboratory analyses cycle's time
- Standardize Priorities Management and daily job plan
- Align internal goals with clients' needs

RESEARCH CONTRIBUTIONS

The main contribution of this study is to improve the chemical analysis process of the Quality Control Laboratory, making it efficient. Internal and external customers would benefit by improving the process; the company in general could benefit from building a good relationship with its customers, and creates direct impact by preventing backorders. The 20% reduction of the analysis time will represent a reduction of approximately one to two days from the process of releasing the final product to the market. The Quality Control Laboratory will also reap benefits, since tasks that have no added value will be evaluated against those that do. This will cause some of these tasks to decrease, freeing the analysts' time to execute chemical tests.

LITERATURE REVIEW

Sanper Pharmaceutical is a global pharmaceutical company. Day by day, Sanper Pharmaceutical markets its products to more than 90 countries. Each country requires different laws and regulations, which Sanper Pharmaceutical is required to comply. Some of these regulations are the Federal Drug Administration (FDA) and Eudralex. The requirements related to laboratory analyses are the following: testing of raw material to be used in the manufacturing process, analysis of intermediate or process samples, studies to bulk products, final drug products, stability samples, and complaint samples, among others. Laboratory tests may include chemical, biological, toxicological, or microbiological tests, among others. In this case, only the chemical laboratory analyses are required.

Sanper Pharmaceutical, has a quality control laboratory, which analyzes all types of samples. Between their two products Elim and Marile, the company packs approximately 600 batches annually, reaching a total of approximately 4,000 monthly samples of all types.

Similar to other laboratories, maintenance activities, completed by the analysts, are required. These are summarized in the preparation of solutions and standards, reagent audits, calibration of equipment, daily equipment verification, weekly and monthly reports, and trend evaluation.

Currently, an increase in manufacturing processes has been observed. This has led to an increase in activities and analyses in the Quality Control Laboratory. In addition, as part of an improvement project, there has been a decrease of quality in the Finished Drug Product release time. As a result, waiting for laboratory analyses has become a stopper to the process of Finished Drug Product release to the market.

Puerto Rico is the sole manufacturer of Elim and Marile in the worldwide anesthesia market through our distribution centers, international affiliates, and Sanper Pharmaceutical Sales in Puerto Rico. Sanper Pharmaceutical has remained competitive through the years by being cost-effective, providing high quality products, and delivering in a timely manner. They have accomplished this by continuously improving their processes and with the active implementation of highly automated control systems. This project is focused in maintaining that standing by reducing analyses process time to contribute with the improvement of Finished Drug Product release to our customers.

METHODOLOGY

Six Sigma is the methodology used in improvement projects. Its main component is the DMAIC discipline, which is an acronym for Define, Measure, Analyze, Improve, and Control. These are the five basic stages that guarantee that the results obtained will be satisfactory.

During the Define phase, the project charter (Figure 1) is developed. This includes identifying the project's problem, purpose, and benefits, as well as its timeline. In addition, we will discuss aspects such as Voice of the Customer, Critical to Quality Parameters (CTQs), and SIPOC map [1].

The measurement phase consists of collecting data from the process that helps establish a baseline, a starting point. During this phase, the

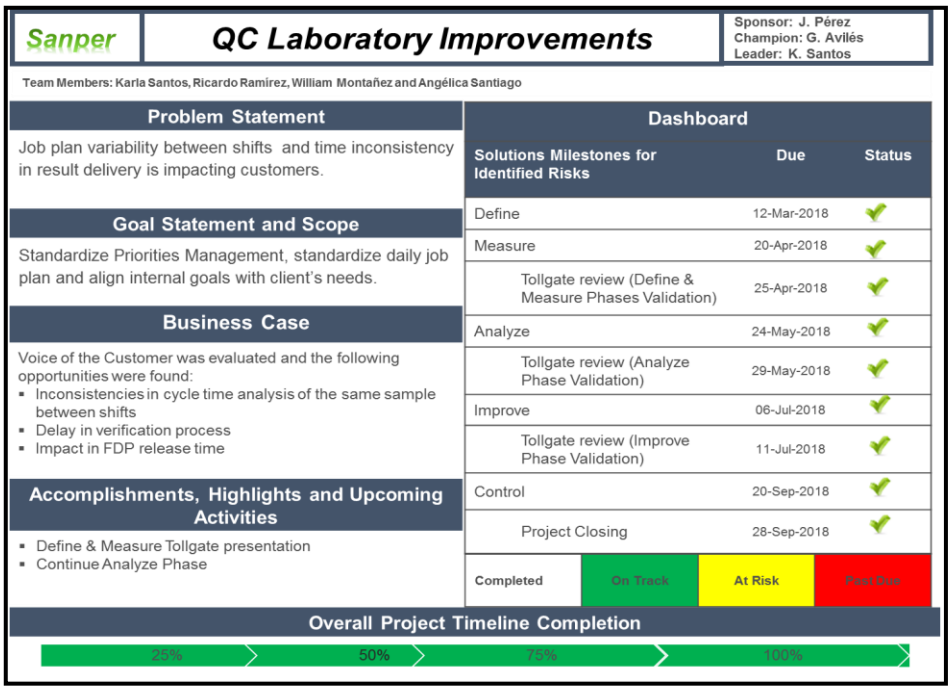

Figure 1
Project Charter

tools to be considered are the process map, Value Stream Map (VSM), and Failure Modes and Effects Analysis (FMEA), among others. As part of this phase, data of Quality Control Laboratory analyses release time was collected. Those data were compared with the time required by the internal and external customers. The results confirmed the need of improvement in Quality Control Laboratory Activities. [1]

The Analyze stage focuses on the data gathered in the Measure phase of DMAIC to identify the cause of product defects. In order to obtain the best results, it cannot be a conjecture or assumption. It should be an analysis based on complete data gathered. Therefore, for this phase, Six Sigma provides the following tools to identify the root cause(s): Cause and Effect Diagram, Statistical Analyses, and Process Map Analysis, among others. [1]

Based on the root cause(s) resulted during the Analyze phase, a brainstorming among the project's team can be performed to identify possible solutions or improvements to the process. The selected solution(s) will be implemented. As part of this phase, the project tools used can be Standard Work and Cell Designs. [1]

The last step is the Control phase. This phase helps to monitor how the implemented improvements are working. It can be done using statistical analyses. In addition, as part of this phase, it will identify different types of controls for the improvements implemented. [1]

RESULTS AND DISCUSSION

This phase shows the findings of this research using the DMAIC tool.

Define Phase

The Quality Control Laboratory has four different shifts. Each shift has its own job plan structure. This variability between shifts causes an inconsistency in the delivery of results, which affects both internal and external customers. The objective of this project is to improve the Quality Control Laboratory analyses cycle's time, standardize priority management and daily job plan, and align internal goals with clients' needs. The

current release process is not standardized, and it takes too much effort and time to analyze all samples on time. By the end of this project, the Quality Control Laboratory will minimize the chemical analysis release time by 20% or more, which will enable the site to be more cost-effective, more agile in the delivery of its products. In addition, Sanper Pharmaceutical will be more robust on its Finished Drug Products release process, making this project one of high priority and visibility.

The first step of the project was the development of the project charter. This tool helped in the definition of the Problem Statement, Project Scope, and Business Case. Also, it can be used to organize the different phases of DMAIC methodology in the project.

A SIPOC diagram (Figure 2) was used to identify all relevant elements of a process improvement project before work begins. It helps define a complex project that may not be well scoped.

As part of Define phase, and in order to have the complete process scenario, a Voice of the Customer (VOC) was performed.

Following is a summary of the results of the VOC:

- Variability between shifts in reporting time for the same samples.
- Raw Materials cycle time not aligned with customers' needs. Release time for bulks and Finished Drug Products is not aligned with new area goal and special requirements.
- Change in Job Plans and priorities among QC Lab shifts.
- Instrument Verifications that expire at 00:00 stop the flow of results from 00:00 to about 02:00
- Internal Goals vs Real Goals are not aligned.
- Special Tasks require time away from normal lab operations. [2]

Measure Phase

During this phase, the important points to take into consideration are data collection and measurement of the analysis times of both products, understanding the processes of the Quality Control Laboratory, and the evaluation of value added activities versus non-value added activities.

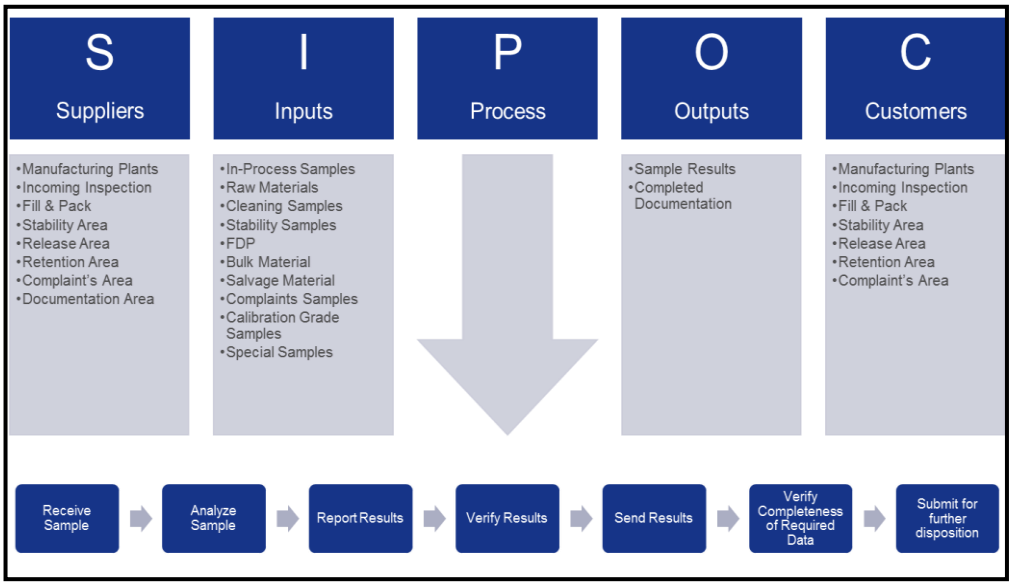

Figure 2
SIPOC

To work with our first point, we evaluated the data obtained from the LIMS electronic system. These reports provided the exact time between the date and time that each sample arrived at the laboratory and the date and time when the release process was completed

Figure 3 presented the Raw Material and Bulks analysis that need improvements to comply with the Finished Drug Product Release Cycle Time (Ideal Scenario).

The Bulk Analysis Process was studied using a Value Stream Map (Figure 4). Its development provided the time required, step by step, for the analysis of Elim and Marline Bulks, respectively. In addition, the waiting time between each step could be identified. [2]

					Current Scenario		Ideal Scenario	
Product	Minimum	Maximum	Average	Median	Internal Goal	QC vs. Goal	Goal	QC vs. Goal
Amine	4.1	11.4	9.2	11.4	5.0	6.4	2.0	9.4
Bottles	0.3	6.1	6.1	6.1	5.0	1.1	2.0	4.1
Cabosil	0.4	6.9	3.5	4.7	5.0	-0.3	2.0	2.7
Caps	0.2	9.6	3.4	3.9	5.0	-1.1	2.0	1.9
Hexafluoroisopropanol	1.4	7.9	3.9	3.5	5.0	-1.5	2.0	1.5
Sevomethyl Ether	0.2	4.1	2.3	2.4	5.0	-2.6	2.0	0.4
Elim Bulks	1.5	9.5	5.3	5.7	5.0	0.7	3.0	2.7
Marile Bulks	1.3	8.7	5.0	5.0	5.0	0.0	3.0	2.0

Figure 3
Data Collection

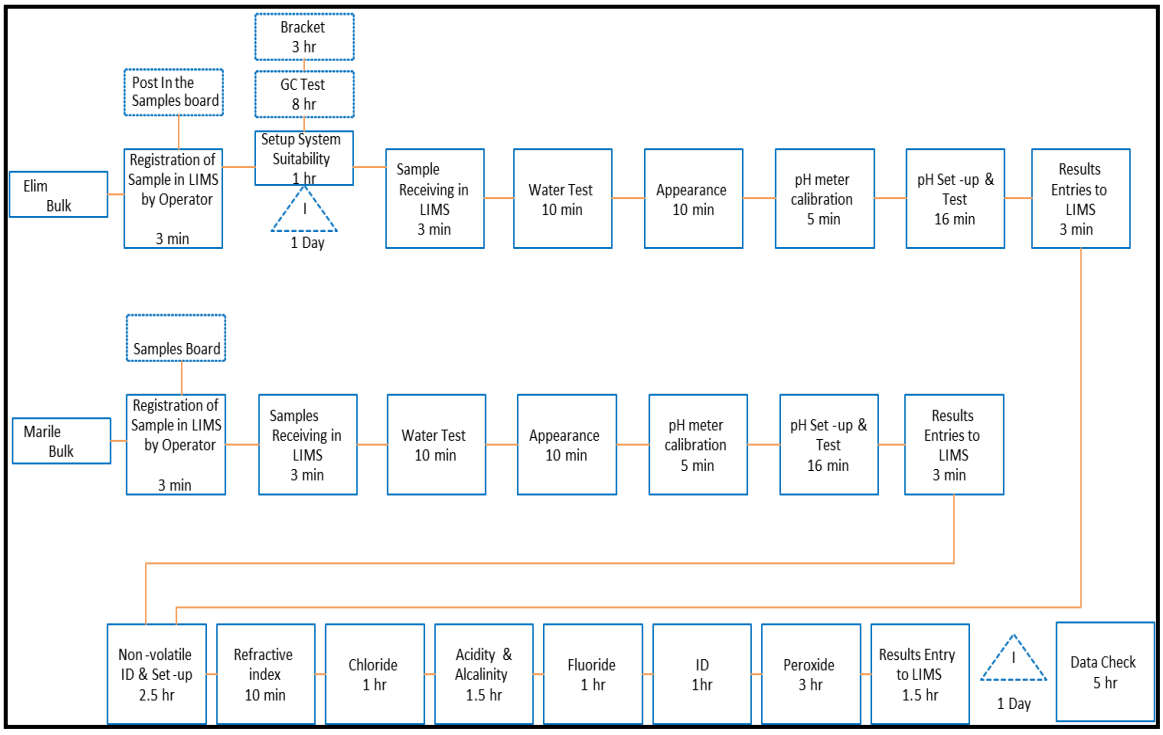

Figure 4
Value Sream Map

A total of 75 activities, additional to sample analyses, were identified in the Quality Control Laboratory. In summary, the tasks were related to trend analysis, logbook audits, and different types of reports. All of them were assessed and divided into value-added activities and non-value-added activities (Figure 5).

Analyze Phase

The Analyze phase will evaluate the possible solution(s) for the Problem Statement.

First, after the evaluation of data collected from the LIMS electronic system, we identified that the most impacted analyses were the ones for Raw Materials and Bulks for Elim and Marile Products.

The Value Stream Map developed in the Measure Phase helped in the understanding that the current analysis process can reduce the delivery time of the Quality Control Laboratory analysis results. One of the causes identified by which laboratory analysis has become a stopper for the Finished Drug Product release cycle process is the organization and distribution of laboratory activities on a day-to-day basis.

After evaluating the Value-Added and Non-Value-Added activities, the following points were identified as major offenders:

- A total of 16 reports are made without apparent functionality.
- After each analyst audits their logbook, it is audited again, for a total of 28 audits.

The dynamic was very interesting, because it is possible to think that all those activities were necessary to keep the laboratory working, when they really are not, since they do not add value to the process or to the products' quality. [4]

Improve Phase

The Implementation phase is based on providing improvements to the root causes identified in the Analysis phase.

QC Lab Operation - Special Tasks			
Daily / Weekly / Biweekly / Quarterly / When Required			
1. FV-1344 Monitoring	2. Accountability Board Update	3. Daily Work Plan Update	4. 6S & Lean Audit
5. DVS Binders Replacement	6. DVS Binder Audit	6. Lab Metrics Board Update	7. REES verification
8. SSS & WSS / SS Due Date Audit	10. PMOs		
Monthly			
1. Reagents & Solvents Inventory	2. Halocarbon BDS Notebook Audit	3. GC / HPLC Columns Installed Report	4. Barometer Binder Audit
5. ITP Report	6. OOS Report	7. REES Notebook Audit	8. NaOH Notebook Audit
9. FV-1344 Cycle Time Report	10. Amine Notebook Audit	11. Special & Inventory Notebook Audit	12. Safety Talk
13. Fume Hoods Report	14. Outgoing Notebook Audit	15. Controlled Reagents Report	16. Laboratory Safety Inspection
17. pH meter Binder Audit	18. GC History Log Audit	19. N2 Notebook Audit	20. TFE Recycle Notebook Audit
21. IR PC Binder Audit	22. Wet History Log Audit	23. R-22 Notebook Audit	24. TFE Recycled Notebook Audit
25. UV Verification Binder Audit	26. Balance Binder Audit	27. Sevo Water Notebook Audit	28. Gas Inventory
29. Buffers Audit	30. Plant II Notebook Audit	31. Sevo pH Notebook Audit	32. Fire extinguisher & Shower Inspection
33. DES FDP Notebook Audit	34. Sevo BDS/BDP Notebook Audit	35. Sevo Stability Notebook Audit	36. Sample Count Report
37. Plant I Notebook Audit	38. Sevo Reduced Testing Notebook Audit	39. ISO Water Notebook Audit	40. Cpd-229 Notebook Audit
41. Reference Standards Inventory	42. Complaint Cycle Time Report	43. Wash Room Housekeeping	44. GC / HPLC Columns Inventory
45. GC Sample Tray PM	46. ISO FDP Notebook Audit	47. Stability Report	48. Solution Notebook Audit
49. ISO BDS Notebook Audit	50. Des BDS Notebook Audit	51. Therminol Notebook Audit	52. Quality Talks
53. ISO BDP Notebook Audit	54. SME Notebook Audit	55. Bromophenol Notebook Audit	56. ACE
57. ISO Raw Material Notebook Audit	58. CSE Notebook Audit	59. ISO Stability Notebook Audit	60. Acetone Notebook Audit
61. FDP Cycle Time Report	62. Sevo FDP Notebook Audit	63. DES Stability Notebook Audit	64. Score Card Report
65. Solution Due Date Audit			

Figure 5
Value Added Tasks vs. Non-Value Added

Throughout the project, we have demonstrated that the organization and distribution of laboratory activities are possible root causes for the delay in laboratory results. For this reason, a Core Group (Figure 6) was designed. This group of analysts is in charge of working on Raw Material, Bulks, and Finished Drug Products. The analysts who stay in the regular shifts (Figure 7) are in charge of the in-process samples and tasks of laboratory maintenance. [3]

After implementation of the Core Group, Raw Material lots, and Bulks of Elim and Marile, products were analyzed. A significant reduction in the time required for laboratory analysis was observed. The difference observed was from 1.0 day to 4.0 days less in the execution and release of laboratory analysis (Figure 8). [3]

	Position	Responsibilities
Core Group (Day)	Group Leader	- Personnel Deployment, support SOP revisions, support Investigations, Tier attendance, C/R
	All Group Responsibilities	- BDS, BDP, FDP, Stability of all 3 Products - Raw Materials - Working Standard and Solution preparation - System Suitability / Cleaning / Special Samples - C/R - Safety Inspection / Safety Talk / Quality Talk - Personnel Development - Calibration Program Support - SOP Revision / Investigations / Instrument Troubleshooting - Cross training / New Hire Training

Figure 6
Core Group Responsibilities

	Position	Responsibilities
Shifts A, B, C & D	Supervisor	- Primary Responsibilities: Personnel Deployment, Verification: In-process samples, FV-1344, FDP (all three products), Equipment Daily Verifications
	2 Analysts: In-process Area	- Primary Responsibilities: In-Process Samples, Equipment Daily Verifications
	1 Analyst: Wet Area	- Primary Responsibilities: FV-1344, Previous Shift Documents Verification, Equipment Daily Verifications, BDP (appearance, pH, water

Figure 7
Regular Shift Responsibilities

As a result, the need of our internal and external customer will be met, thus providing the results on time.

Products	Lots Before Implementation (Days)	Lots After Implementation (Days)	Difference
Amine	4.9	1.7	3.2
Bottles	5.5	1.5	4.0
Cabosil	2.1	0.6	1.5
Caps	3.1	2.1	1.0
Hexafluoroisopropanol	1.7	0.7	1.0
Sevomethyl Ether	3.0	1.1	1.9
Elim Bulks	5.0	2.9	2.1
Marile Bulks	5.0	2.6	2.4

Figure 8
Raw Materials and Bulks QC Lab Release Time (Days)

All laboratory activities were evaluated. Those that were non-value-added to the process, product, or regulatory aspect were eliminated. Opportunities were identified, through electronic reports, to cover different reports in one. As a result, 59% of the tasks were eliminated, all of them non-value-added activities (Figure 9). [4]

Additional improvements related to lack in communication were implemented. Following is a list of them:

- Include a Procurement Supply Chain Department Representative in the Daily Work Plan (DWP) email for Raw Materials status.
- Explanation of the other Areas Status Report (Raw Material, Product Release and Packaging Schedule) by the Owner and the expected response time from the Quality Control Laboratory.
- Include laboratory personnel in the Raw Material Status Report.

Control Phase

The last phase of Six Sigma's DMAIC model is the Control phase. The focus of this stage is to make sure that the action item created in the Improve phase is well implemented and maintained. Several tools were used in this stage to make sure that variables are within limits. One key to achieve continuous improvement is to standardize the process. In order to accomplish this, work instructions tools were implemented:

- A Standard Worksheet was generated for Core Team and Shift Teams.

Direct Activities			
Weekly / Biweekly / Quarterly / When Required			
1. Receive MBR Checklists	2. Instrument Calibrations	3. Weekend Meeting	4. Gas Cylinder Replacement
5. Solutions Standardizations	6. Preparation of solutions for other areas	7. OOS / Atypical / OOT Investigation	8. Nonconformance Investigation
9. SOP Revision	10. Test Method Revision	11. Personnel Annual Qualification	12. Training
13. Glassware cleaning (weekend/night shift)	14. Manufacturing Equipment Cleaning Release (weekend/night shift)	15. Assemble volumetric funnel separators	
Daily			
1. ISOtrain	2. DVS (21 GCs) (6 Balances)	3. Other Verifications (6 Instruments)	4. System Suitability
5. WSS / SSS Preparation	6. Sample Analysis	7. Sample data Verification	8. Previous Shift document Verification
9. Verify completeness of Data	10. Receive Controlled Forms	11. Solution Preparation	12. Disposal of Samples
13. Email verification	14. Tier meeting attendance	15. Shift Turnover	16. Waste Cans Material Disposition

Figure 9
Value-Added Activities

- To be more effective in the analysis and disposition of the Raw Materials and Primary Packaging Components, a Schedule for their receiving was established. They will be received from Monday to Wednesday every week. The analysis and disposition will be completed from Tuesday to Friday evey week.
- A visual aid was designed to establish a Visual Control of the Manufacturing Process with the priority of all samples under normal process conditions. It includes a scale of priorities from 1 to 5.
- Everyone involved in the process received proper training, including Laboratory personnel and all internal customers.

CONCLUSION

The main objectives of this project were:

- Improving the Quality Control Laboratory analysis cycle's time
- Standardizing priority management and daily job plan
- Aligning internal goals with clients' needs

To work with the first objective, a new organization of work shifts was designed. With this new structure, work responsibilities were aligned. In this way, each group will prioritize the tasks as per the needs of the client, as previously established. With the rearrangement of the shifts, we obtain a decrease in release time of raw materials up to 27% and up to 48% in the Marile Bulks product. These results significantly exceed the initial expectation of a 20% reduction.

The second objective was the standardization of priority management and the daily job plan. A series of meetings with internal clients were carried out. Thus, it was determined what will be the time limit required for the release of each product and/or Raw Material. In addition, an agreement was reached with the Supply Chain area, in which the Raw Material will be received from Monday to Wednesday and analyzed and dispatched from Tuesday to Friday of each week. In addition, to work with the process samples, a Visual Control was designed to prioritize them, in normal process conditions, on a scale from 1 to 5. To maintain a standardized work shift, a Standard Worksheet was designed for rotating shifts and another one, for the Core Group. In this way, everyone will work in the same way, no matter which group is working.

As part of the analysis phase, we identified that the established goal for some products and/or Raw Materials were not aligned to the current processes. Using the historical data and the time required for each analysis, a reasonable target was established for each product and/or Raw Material.

All laboratory activities were evaluated. Those that were non-value-added to the process, product, or regulatory aspect were eliminated. Opportunities were identified, through electronic reports, to cover different reports in one. Thus, 59% of the tasks were eliminated, all of them Non-Value-added activities.

Finally, although during the execution of the project the financial aspect was not considered, we were aware that it was positively affected. The importance of this study was to minimize the time required for Chemical Analysis to release the final product to the market. The longer the process of releasing the product, the longer it will take to reach the customer. This affects the relationship with customers, increases pending orders, and minimizes the possibility of acquiring new markets. In summary, the more satisfied customers are, the more sales the company will generate.

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