

Improving Product Changeover in Pharmaceutical Manufacturing Through Lean Six Sigma

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Graduate Project EXPO, October 2024*

Abstract — *Pharmaceutical bulk manufacturing is essential for producing important lifesaving drugs, but often faces significant challenges during changeovers that can lead to production delays and increased costs for the company. This study focuses on applying Lean Six Sigma methodologies to streamline complex changeover processes within a pharmaceutical manufacturing facility. With tools such as fishbone diagrams and Pareto analysis, root causes were identified, and solutions were implemented to reduce changeover delays. An Andon board was implemented which reduced operator response times to alarms by 39%, helping to mitigate delays caused by equipment malfunctions. Standardized flowcharts provided consistency which helps in reducing human error and confusion during the process. The 5S initiative reduced wasted time and unnecessary movement during changeovers. The successful application of these methodologies in this study highlights the potential for Lean Six Sigma to drive significant operational improvements in highly regulated environments like pharmaceutical manufacturing.*

Key Terms — *Changeover, Continuous Improvement, DMAIC, Lean Six Sigma, Pharmaceutical Manufacturing.*

INTRODUCTION

Pharmaceutical bulk manufacturing plays a critical role in producing life-saving drugs. Many Bulk Manufacturing Facilities and must implement a changeover between each product campaign to ensure cross contamination does not occur. In many cases, these changeover activities are not as straightforward for operations as producing a batch, which can lead to confusion, repeated efforts, and production delays. Additionally, the amount of documentation required can be daunting and often

leads to omissions that must be corrected before the area can be released to manufacture the next product.

A changeover in pharmaceutical bulk manufacturing facility can involve tasks such as mayor equipment cleaning, swabbing, filter replacements, among other tasks that can consume a large amount of time. The activities often vary depending on which products are going to be manufactured and how similar their raw materials are. When you add the complexities of larger equipment cleaning such as hygienic vessels that often require additional connections and manual manipulations, it becomes apparent how a seemingly simple task becomes a production nightmare. Overall, these activities consume resources, extend production times, and ultimately lead to higher costs without directly contributing to the quality of the final product.

LITERATURE REVIEW

Biopharmaceutical manufacturers face an increasingly competitive environment and stakeholder demands, where staying at their optimal capacity and providing a steady flow of their products is paramount. Because of this, multiproduct facilities have been cropping up, offering significant economic advantages by maximizing resource utilization. A single facility can be equipped to handle the production of various drugs, spreading the fixed costs of equipment, staff, and infrastructure across a wider product range [1]. This translates to lower production costs per drug. Additionally, multiproduct facilities cater to the dynamic nature of the biopharmaceutical industry. They can efficiently switch production between drugs as needed, without the need to invest in entirely new facilities for each product. One setback of multiproduct facility is the downtime that occurs

due to product changeover procedures, an essential practice where the manufacturing area and equipment are cleaned and prepared for the next product campaign and ensures there is no cross-product contamination as we move from one product to the next [1]. These changeover practices are essential for ensuring patient safety and drug effectiveness. By minimizing the risk of contamination between different drugs, changeovers safeguard the purity and potency of each product. Due to the criticality of changeovers, regulatory agencies mandate strict adherence to good manufacturing practices, and documented changeover procedures are a key part of this compliance. But efficiency is also crucial. Long changeovers translate to lost production time, impacting a facility's output and bottom line [2]. Efficient changeovers minimize downtime, allowing for greater production capacity and cost reduction. Efficient changeovers also give manufacturers the flexibility to adapt and produce a wider range of drugs to meet evolving patient needs.

Lean Six Sigma Methodology

Lean Six Sigma is a structured, data-driven methodology that combines the waste reduction principles of Lean with the statistical analysis techniques of Six Sigma to achieve significant process improvements. This approach aims to significantly reduce changeover times, leading to increased production efficiency and customer satisfaction. Six Sigma, on the other hand, brings a data-driven approach to reducing variation and defects. Tools like DMAIC methodology (Define, Measure, Analyze, Improve, Control) [1], can be employed to systematically analyze changeover times, identify root causes of delays, and implement targeted improvements. DMAIC is a structured problem-solving methodology that has become widely used in business, from manufacturing facilities to on-profit organizations all benefit from adopting this strategy as a means for improvement [3]. It is an easily adaptable methodology where each phase leads the team from defining the problem all

the way to ensuring that any implemented solution stays in place.

Within Lean Six Sigma there are many tools can be used to drive process improvement, reduce waste, and meet customer demands. One of the main goals of Lean Six Sigma is to eliminate waste within a process that gets in the way of productivity and affects customer satisfaction. These wastes are classified as the following:

- Defects-This involves any errors or mistakes in products of services that will require rework or scrapping.
- Overproduction-Producing more than is needed or before it is needed.
- Waiting- When resources such as operators, technicians, and machines waste time waiting for the previous step to finish in order to continue the process.
- Transportation- This waste includes the movement of people, tools, materials, equipment or products more than what is necessary. Excessive movement can lead to a number of negative situations, such as defects on the way from point A to point B, unnecessary work and poor resource utilization.
- Inventory- This is one of the most difficult wastes for many companies to understand, as it goes against traditional accounting methodology of seeing inventory as an asset rather than a waste. However, lean states that having more inventory than necessary leads to increased inventory cost.
- Motion- Unnecessary movements incurred by people, such as walking excessively to gather tools and materials.
- Extra processing- Any activity in the process that does not add value for the customer.
- Unused Talent- Not using people's skills and knowledge to their full potential.
- Identifying and eliminating these wastes can significantly improve efficiency and productivity in any organization.

Statistical analyses are an important aspect of any Lean Six Sigma approach as it helps pinpoint

areas with high variability, allowing manufacturers to focus on standardizing procedures and minimizing inconsistencies that lead to longer processes and poor resource utilization. One of the pillars of Lean Six Sigma is flow optimization, where we ensure tasks and products move through the process in a smooth manner that minimizes bottlenecks and delays. It aims to create a continuous flow that optimizes capacity and leads to process improvement, which many cases translates to savings for the company.

Lean Six Sigma in Pharmaceutical Manufacturing

Streamlining product changeovers in biopharmaceutical manufacturing can help reduce downtime while also ensuring regulations are met and minimal documentation errors are encountered. In this sense, pharmaceutical manufacturing changeover can benefit greatly from combining Lean and Six Sigma methodologies. Research shows that Lean manufacturing and Six Sigma are the most widely used methodologies to implement continuous improvement on industries [4], integrating these methodologies into their culture as an organization. In Lean Six Sigma, things that don't meet customer's needs are either defects or waste [2]. Lean principles focus on eliminating waste and optimizing the flow of materials and information. Here, tools like Value Stream Mapping (VSM) can be used to identify and eliminate non-value-added activities during changeovers, such as excessive cleaning steps or waiting for tools [5].

Previous research has also shown how Lean improves sustainability by enhancing working conditions and promoting kaizen and kanban systems, prioritizing the employee's safety as well as promoting process improvement [5]. This can be very beneficial in changeover procedures, where equipment preparations and cleaning are non-routine tasks that vary greatly depending on the next product campaign and usually have room for improvement. Non-optimized changeover procedures can generate significant waste in productive manufacturing time, which may increase one or more of the seven types

of waste: transport, inventory, motion, waiting, overproduction, over-processing and defects [6]. These types of waste are described by lean as follows: By implementing Lean Six Sigma methodologies while a keen eye on their regulatory and validation requirements, biopharmaceutical companies can achieve significant reductions in changeover times, enhancing overall production efficiency and maintaining compliance. By combining Lean Six Sigma's structured approach with a suite of continuous improvement tools, this approach helps organizations achieve significant reductions in changeover times, leading to increased production output, improved resource utilization, and ultimately, enhanced customer satisfaction.

Compliance in Pharmaceutical Manufacturing

Regulations in pharmaceutical manufacturing are a double-edged sword when it comes to efficiency. On one hand, they impose strict protocols and meticulous documentation, which can be time-consuming and add extra steps to the production process. For instance, Good Manufacturing Practices (GMP) requires extensive validation procedures and detailed records for every step of production. Current requirements by many regulatory agencies aim a reducing operator bias and ensuring data integrity, which leads to stricter and longer documentation. This adds resources to the process and can slow things down compared to less regulated industries. Additionally, many activities that would be considered waste in other types of industry cannot be eliminated from pharmaceutical processes because they are performed to ensure compliance with GMP, such as identifications, records, segregations, checks, and inspections [4]. However, these regulations are ultimately in place to ensure patient safety and drug efficacy. Stringent quality control measures prevent contamination and ensure the drugs are pure and potent. This translates to fewer product recalls and rework, which can significantly disrupt production and cost companies dearly. In the long run, robust regulations can lead to long-term efficiency by minimizing errors and the

need for corrective actions. In a regulated environment, the DMAIC methodology implementation becomes even more important as there is only one opportunity to improve, and it must be “right the first time” as any error will result in a corrective and preventative action report being raised [7]. One of the aspects that hinders quick process improvement in a highly regulated industry is the required time investment of the validation process. This extra burden of regulation and resource consumption can create barriers that must be considered when designing a Lean Six Sigma Project in a pharmaceutical manufacturing environment. Seeing these barriers, we find that the key for pharmaceutical manufacturers lies in striking a balance. By implementing efficient compliance strategies, such as automation and digital record-keeping, they can streamline the adherence to regulations without sacrificing production speed. Additionally, reducing waste in the areas that don't impact GMP standards offers significant process improvement in their procedures.

METHODOLOGY

Excessive changeover times can significantly hinder production efficiency and responsiveness. This study employed a Lean Six Sigma (LSS) approach to improve process changeover within a pharmaceutical manufacturing environment. The DMAIC cycle, which defines the five core phases of LSS projects – Define, Measure, Analyze, Improve, and Control – provided the framework for this improvement initiative [7]. By focusing on waste reduction and process improvement, this approach aims to minimize changeover times, leading to increased production capacity and customer satisfaction.

Define Phase

The Define phase of the DMAIC methodology centers around defining the project scope, expectations and goals. The goals of this project were defined to be:

- Identify and quantify the current state of changeover times within a specific pharmaceutical manufacturing process.
- Implement effective solutions based on Lean principles to significantly reduce changeover times.

A SIPOC diagram was developed to highlight information that is critical to the project success. With this SIPOC diagram, identify key inputs, outputs, activities and boundaries.

Measure Phase

The measure phase involves gathering and measuring the current state of the process to establish a baseline for our project improvements. To properly understand changeover processes, observations and group discussions were conducted. This way, we obtained first-hand and descriptive information while also involving the manufacturing operators and technicians who will benefit the most from the implementations. This also provides an opportunity for manufacturing personnel to express any areas for improvement they have come across. Stratification factors were identified in order to help guide the discussions in a way that generated a deeper understanding of the problem. Another important baseline to establish is the movement the operator must make in the workplace to complete each step in the process. For this purpose, a spaghetti diagram is used to map the process including time and distance incurred to complete the task.

Analyze Phase

This step focuses on identifying root causes and key inputs for the process important. The information gathered throughout the data collection will be analyzed with a pareto chart to identify the major causes for changeover delays. This pareto chart can help us determine which issues show the highest frequency so that we know what to focus on improving using the pareto principle discussed earlier. These are the causes that will make the most impact on changeover efficiency. A root cause analysis for the major changeover delays will be conducted using the fishbone diagram method.

Additionally, a t-test will be performed to determine the statistical significance of any measurable improvements during the project. In Lean Six Sigma, a t-test is a statistical hypothesis test used to determine if there is a significant difference between the meanings of two groups. [3] Other statistical analyses will be conducted depending on the data collected in the previous step.

Improve Phase

In this phase, improvements are made, and tools are implemented. It is important that before any tool is implemented, a proper risk assessment has been conducted and operator feedback has been considered. The improve phase can include workplace organization to deliver higher performance and safety with minimal monetary input. In here we may see many of the wastes mentioned above, such as motion, transportation and waiting. The 5S methodology, designed after the principles of good housekeeping, is a systematic way to improve the workplace that promotes employee engagement [3]. This methodology reduces setup time and ensures all necessary tools and materials are readily available for changeovers. The 5S methodology is divided into 5 steps:

- Sort - Identify all unnecessary items from the workspace such as only the tools needed are kept in the work area.
- Set in order - Arrange the necessary items in a way that promotes easy access and use.
- Shine - Clean the workspace to maintain a neat and tidy environment.
- Standardize - Establish the standards for maintaining and organizing the workspace
- Sustain - Make a habit of maintaining the established procedure for the workplace

The result of a well-executed 5S is a clean and organized space where everything is in its place and there is a place for everything. In terms of a multiproduct pharmaceutical company, having a designated area for all changeover equipment can help personnel easily find their tools and begin work faster and more efficiently. There is less wasted time

and less frustration from traveling from one area to another gathering all materials and everyone knows exactly what tools they need.

An Andon board is a visual management tool used in manufacturing to display the status of production lines or workstations. It is part of the Andon system, which provides real-time alerts about issues in the production process. The term “Andon” comes from the Japanese word for a paper lantern, reflecting its purpose of providing visible alerts [3]. Andon boards highlight problems that may require immediate action and can help the manufacturing floor stay informed on what is going on with their equipment. It is important that the outcome of the improvements is measured via a form or check sheet to compare the results vs the baseline gathered earlier.

Control Phase

The control phase is one of the most important steps in this methodology as it ensures that the gains are sustained, and the process doesn't fall back to its previous state. Metrics for changeover efficiency can be implemented and measured periodically to ensure goals are met and kept. Procedure improvements to include operator responsibilities in keeping the workspace organized and visual tools inside said procedures will help maintain any 5S initiative in the long run. Training process owners on how to use and update Andon boards also ensures these improvements are sustained and maintained.

RESULTS AND DISCUSSION

The objective of this research is to improve process changeovers by implementing Lean Six Sigma methodology and tools on the production floor. The first step is to map out the process through a SIPOC diagram as shown in Figure 1. This helps us understand and visualize the scope of the process and the departments involved. The general changeover process begins with the empty tanks being cleaned as per normal procedures. Next, mechanics place major changeover equipment and operators proceed to perform the major cleaning

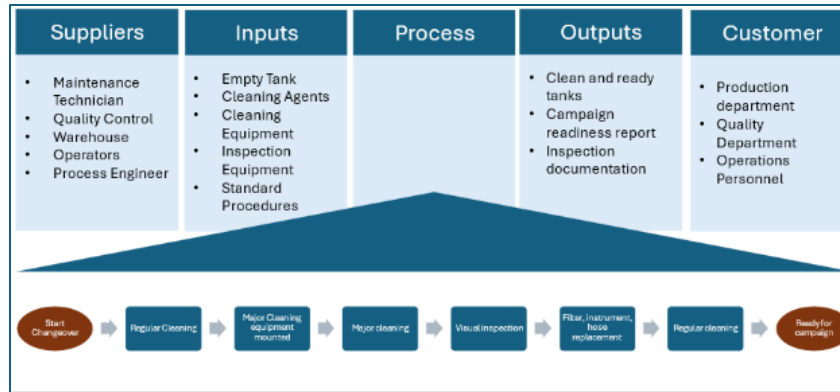


Figure 1
SIPOC Diagram of the Changeover Process

with cleaning agents. A visual inspection is done on various points in the tanks and pipelines. If the tank fails the inspection, the major cleaning is repeated. Once the inspection is passed, equipment such as instruments, probes, filters and hoses are replaced to avoid any cross contamination. Finally, a regular cleaning is done of the system and the equipment is ready for a new production campaign. From this Diagram we can have a better view of where potential bottlenecks may be present, such as in the major cleaning step and the instrument and filter replacement, which are manual operations as opposed to the cleanings which are automated.

Using the data gathered during interviews and brainstorming a fishbone diagram was developed to identify possible causes for long changeover or changeover delays. The Diagram can be seen in Figure 2, with causes categorized as environment, employee, equipment, method and machine. This diagram was used to narrow down our focus and as a basis for the rest of the project analysis. From this fishbone diagram, a few patterns can be seen, such as the problems with Procedures that lead to lack of understanding what tasks need to be done by the employee. This can lead to problems during the process that will most likely cause delays in changeover. Likewise, seeing that the tools are not available or are scattered across the production buildings can likely be a major cause for delays.

Next, defects data was gathered from the changeovers in 2024, focusing on schedule delays and problems reported by production, of which there

was a total of 41 reported problems that caused mayor delays. Problems were categorized using the fishbone diagram as a guide. This data was quantified into frequencies and analyzed using the pareto method, which is premised on the idea that 80% of problems are traced to 20% of the causes. This means that not all inputs have the same impact on a given output. This tool helps direct focus on those outputs that make the highest impact for the company. Figure 3 Shows the resulting pareto diagram, where we can see the major culprits in changeover delays.

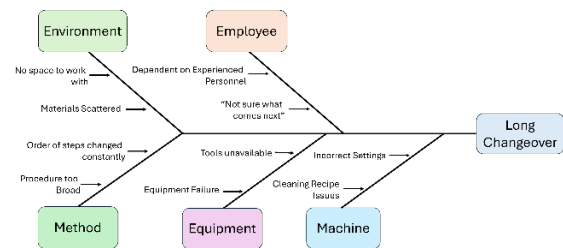


Figure 2
Fishbone Diagram

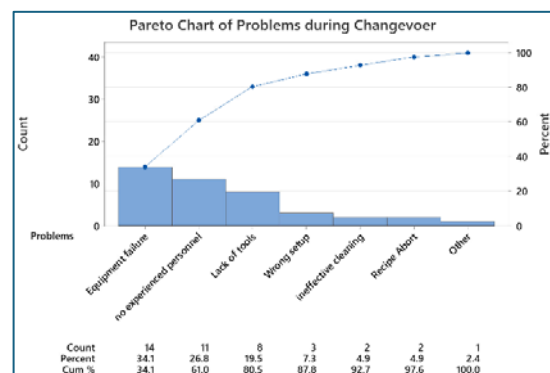


Figure 3
Pareto Chart of Problems during Changeover

From the Pareto Diagram we can see that there are three problems that make up 80% of the causes for the changeover delays. We focused on solving these problems as they yield the highest impact for changeover improvement. During interview and brainstorming sessions, production personnel expressed how problems with the production line and failure of different equipment caused many headaches and delays. This was often because problems with segments or equipment were only noticed after they had reached a critical state, this was in part due to the extensive amount of parameters and equipment that the building has. To tackle this issue an Andon board was developed to help production personnel quickly identify and solve problems before they can cause significant delays.

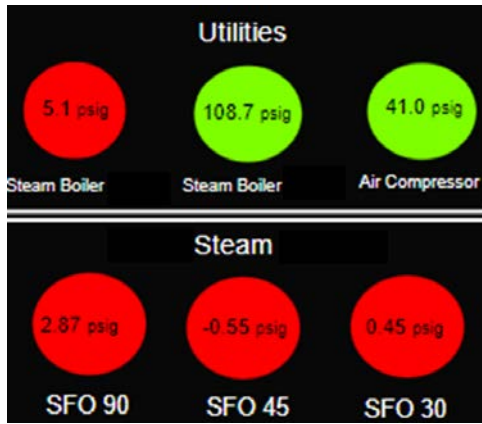


Figure 4

Section of Equipment Status Board Developed for the Area

Figure 4 shows an excerpt of the board, where we see different equipment separated by areas, and color-coded light that indicates the state of the equipment. Here, we use green as “good”, yellow as a warning that it is near the upper or lower limit for the parameter, and red as almost out of parameter and needs immediate action. This helps personnel have an “at a glance” view of their equipment and be able to react quickly to issues. The information from the Andon board is extracted directly from their automation and control software, which makes the data accurate and contemporary and requires little intervention from personnel to operate. For example, Steam is an important component during changeovers as it is used in the equipment Cleaning

in place (CIP) system. Having an issue with steam pressure will result in inadequate cleaning, and thus a re-cleaning must be done. In this sense, having a quick reference such as the steam header section can help operators determine if a cleaning must be halted, or if special troubleshooting must be done to a cleaning due to loss of steam. This board is useful in a variety of scenarios that make it a valuable Lean tool for any company.

After this Equipment Status Board was implemented, there was a reduction in operator response time to alarms in the equipment. A t-Test was performed to verify if the perceived improvements are statistically significant and to verify the magnitude of difference between the response rate before vs after the Status Board implementation. For this test, the historical values for the equipment alarms were compiled randomly, showing the time from when the alarm first appeared until the condition was corrected (i.e. when the operator responded to the alarm). The average response time went from 51.8 minutes to 32.1 minutes, which is a 38% decrease. Figure 5 and Figure 6 show the t-Test results, where we can see that the observed difference in means is statistically significant, and furthermore shows that the Andon Board has successfully helped reduce operator response time to alarms which in turn reduces delays due to equipment failure not being resolved promptly. Figure 6 shows the boxplot of the response time before and after the Andon board implementation. This shows there is less spread of the data after the Board, meaning there is less variability now versus before as well as a smaller average response time.

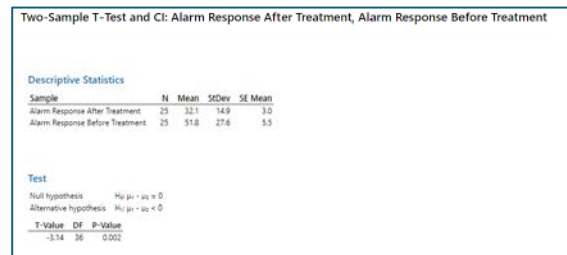


Figure 5

t-Test Results for Alarm Response Time

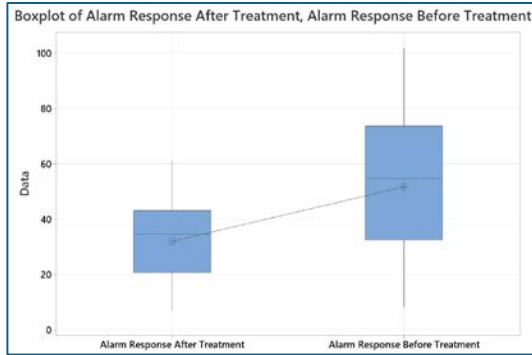


Figure 6
Boxplot of Response time Before and After Implementation of Andon Board

Looking back at the Pareto Diagram, we see that the problem with the second highest instances was no experienced personnel on shift, which caused delays in getting work done. This problem is further analyzed using the fishbone diagram in Figure 2, where we see that work depends on the more experienced personnel, mainly due to procedures that were too broad and newer employees not knowing how to specifically tackle the tasks involved. Additionally, experienced personnel knew by memory how each piece of equipment must be prepared for a new campaign. Not having these personnel on hand meant that newer employees did not know what to do, delaying the process. This lack of procedure specificity ranged from procedures being too broad and thus operators did not know what type of changeover applied to certain equipment to not knowing which cleaning parameters applied in the Cleaning in Place recipe. They also mentioned how with every changeover, it seemed like the steps were always in different order, which made it difficult for operators to keep track of what had been done and what needed to be done. It was identified through our analysis that many of the tasks are not explicitly stated in the Operating Procedures or that it does not show the order of specific tasks. This makes the operators feel lost when executing a PCO and often leads to wasted time trying to get clear instructions. A flowchart diagram was developed for each equipment to facilitate the process steps for everyone. This ensures consistency and standardization of the

changeover process for each equipment. An example of this flowchart can be seen in Figure 7, where we see how the diagram “guides” you through the process, minimizing human error due to lack of knowledge of what needs to be done. As an example, some operators retold a near miss they had in their operations where they had forgotten to change the process hose for a specific tank, because they did not know if it was necessary. Thankfully, it was captured before they had to use the equipment. This near miss was captured in the flowchart in the decision section where it asks if there was a change of protein. If the answer is yes, then the flexible hose must be changed. If not, then no change is necessary for the hose. This alone cleared many questions for personnel and helped them better understand the different elements of the changeover and when to apply them.

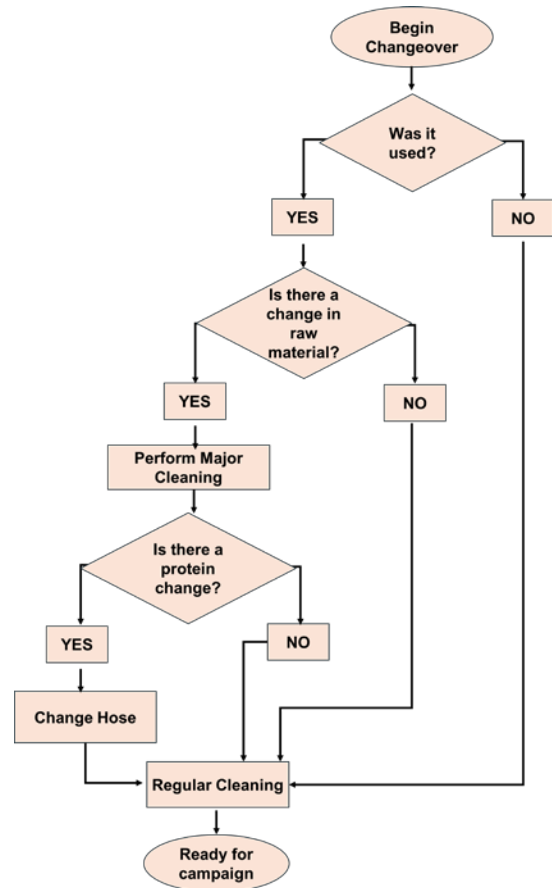


Figure 7
Example of Flowcharts Added to Standard Operating Procedures

The third most reoccurring problem is lack of tool availability. Changeovers occur once to six times a year in this company, however there is no designated area for changeover equipment. There are certain tools and equipment such as valves, hoses and pumps that are required during changeover. However, operators express frustration when looking for these tools, not knowing where they are stored and even having to move all over the building to find this equipment. To analyze this problem a spaghetti diagram was made for the task of finding all changeover tools. Figure 8 shows the current flow of materials for changeover procedures and the proposed new flow to minimize unnecessary movement and waste.

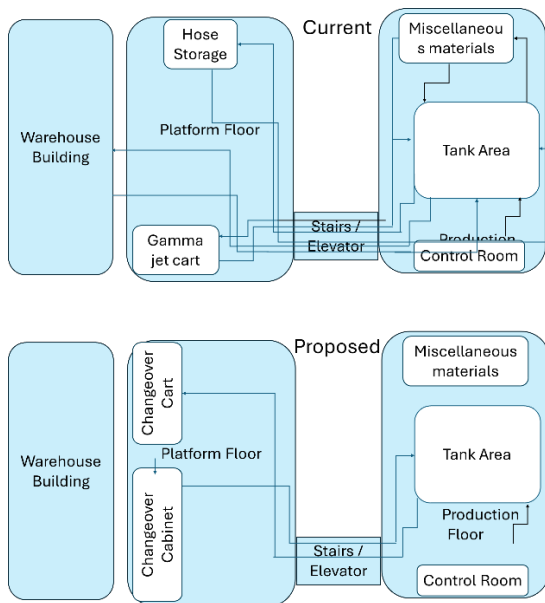


Figure 8
Current versus Proposed Flow of Material for Changeover

From this figure, we can see the long distances and wasted time that are part of this task. Additionally, we see the waste of excessive movement from personnel. For this reason, a 5S was conducted, with an area in one of the platforms designated for changeover equipment. First, unnecessary items were removed from the area, next items were arranged in a way for easy access. A cabinet was placed to organize equipment such as smaller hoses and funnels necessary for the process. A cart was designated for changeover purposes with larger items and placed in the area for easy access

and transportation of materials. The platform chosen for this is located between production floors making the movement minimal, as you only must move either up or down one floor with the equipment. The second image in Figure 8 shows a diagram of the new flow with the designated changeover area in place, which is neater and involves much less travel between areas to gather all materials. This also helps reduce delays in finding and gathering materials and in wasted talent from employees that could be put to better use on other steps of the changeover but are instead stuck all shift looking for the equipment.

For these three tools, we have deliverables in terms of the final “control” phase of the DMAIC Methodology used. For the Andon Board, the technical specialist in the area will be given full control with documentation on how to update and maintain the tool. The information is gathered from automated systems, so the intervention is minimal. The flowcharts created for each equipment cleaning sequence will be included in the applicable standard Operating Procedures. Finally, the 5S initiative will have a checklist with monthly inspections and a designated champion per shift in charge of maintaining the area. These efforts will ensure the improvements are maintained and the gains are sustained in the process.

CONCLUSIONS

The objective of this project was to use Lean Six Sigma Methodologies for changeover procedure improvement within a pharmaceutical manufacturing facility. The tools developed in this project serve as aids to improve changeover by reducing defects, waste, and time. The Andon board developed to help gain better visibility for equipment status is an important addition for the production personnel. With this tool any personnel can verify the status of critical equipment and fix any problems before it becomes a major issue for the floor. There was a notable reduction in alarm response time by 39%, which in turn will reduce delays due to equipment failure in changeover procedures. This board can be expanded beyond changeovers to

production as well. Standard Operating Procedures were revised and updated with the inclusion of flowcharts to clarify the sequence of cleaning to be executed. These flowcharts are a simple yet effective way to ensure standardization across all shifts and personnel regardless of their experience. These flowcharts also help reduce time looking for which are the next steps to proceed with the changeover and helps guide them through the process for each specific equipment. A designated changeover equipment area was set up as part of a 5S with checklists to ensure the area stays neat and tidy. This 5S helps reduce time for the operator looking the right tools as well as unnecessary movement and transportation across various production floors. The involvement of production personnel is paramount to ensure these initiatives are sustained. Their input is valuable when conducting improvements in the workplace and workflow. Future projects can be focused on measuring the impact of these tools and further improving other campaign procedures. There should also be future projects focused on expanding the DMAIC methodology into other areas of production.

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