Syringe Filling Line Changeover Time Reduction by CIP Recipe Overlap with Product Transfer Recipe

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Abstract *— In a biopharmaceutical company, the syringe filling process is thru one of two filtration trains that must be previously washed with a cleaning in place and sterilized with sterilization in place. Therefore, while one train is transferring and filling product, the other train is preparing it with cleaning and sterilization. It was identified that when lots of 70,000 units or less and lots of Product R were filled, the stipulated changeover time of 4.75 hours was not met. A procedure stipulated that a transfer recipe could not run in parallel with a cleaning in place cycle causing a delay in the lot-to-lot changeover. An analysis by the automation department certified that the system was capable of handling both processes in parallel. The procedures were revised allowing the operator to perform both processes at the same time. After the changes, the stipulated changeover time was fulfilled and an increase of 3.3 million of additional units is projected for this year.*

Key Terms *— Continue Improvement, Efficiency, Productivity, Waiting Time*

INTRODUCTION

This project was carried out in a biopharmaceutical company, specifically in a syringe filling line. The demand of products in this type of industry is high and with this initiative the company can be more efficient, having more time available to be able to manufacture and supply the market.

Syringe Filling Manufacturing Process

The product transfer during the syringe filling process consists of the formulated drug product conveyed through one of two filtration skid trains available, into a Time/Pressure (TP) vessel and in turn to filling needles to charge sixteen syringes at the same time inside an isolator. To proceed with the product transfer, each filtration skid must first be washed using a Clean-In-Place (CIP) process and sterilized using a Steam-In-Place (SIP) process, a procedure that must be repeated in between formulated tanks or lot-to-lot.

Identification of Area of Opportunity

A Standard Operation Procedure (SOP) stablished that the CIP recipe could not be performed during product transfer phase. Due to this fact, two types of lot-to-lot changeover were affected, small lots of 70,000 units or less and Product R lots.

In the case of small lots, the filling process is shorter than the duration of the CIP process in the other train, since it must start after the product transfer phase. Thus, the leftover time of the CIP and the complete duration of the SIP exceeded the appointed target of 4.75 hours for lot-to-lot changeover.

On the other hand, Product R lots have a Dirty Hold Time (DHT) of 5 hours, hence, CIP process had to be ran immediately after that batch ended. Consequently, another delay in changeover of more than 5 hours.

Project Objectives

As part of the continuous improvement, one of the year’s goals for the syringe filling area is to "Sustain and Advance Capacity at Filling to Absorb Incremental Volume/Lots". Following the previous statement, it was identified an area of opportunity where the manufacturing syringe filling line can carry out both processes, the CIP and product transfer recipe in parallel; making possible to

comply with the stipulated changeover time of 4.75 hours. This improvement makes the syringe filling line a more efficient, increasing the number of lots to be fill, and allowing the entrance of even new products into its capacity.

Literature Review

Improvements in the Manufacturing Area is Equal to Efficiency in the Process

The manufacturing area in a company is always looking for improvements to be more efficient and competitive in the market. Efficiency in the manufacturing area is part of the operational excellence department. Programs such as kaizen and the spaghetti diagram show techniques to standardize processes and be more efficient during the manufacturing process [1]. Also, it is important to have knowledge of both, the process that is carried out as well as the details of scheduling and support interventions in manufacturing. To be able to predict how long it would take to produce a large-scale manufacturing product, all possible scenarios must be considered, such as set up times, cycle times, lot sizes, job priorities, cycle changeover times, tools required, and pieces per cycle [2]. It is important to the manufacturing area to identify different types of methodology to carry out a process of time reduction and waste elimination through lean manufacturing.

Waiting Time, a Waste in Manufacturing Process

The most common area of opportunity in the manufacturing area is waiting time. To reduce the waiting time, it is important to identify which tasks can be executed in parallel to be able to save time and be more agile in the process. Lean manufacturing lists the seven waste and one of them is the waiting time, it is important to recognize them, identify them and find a way to eliminate it. Through strategies, such as manufacturing assessment, identifying the capability of the manufacturing process and materials, qualitative and quantitative techniques, and data collection; it is possible to have a led time reduction [3].

Revenue Through Customer Satisfaction

One of the factors to maintain competitiveness in the market is that companies reduce operational costs and meet customer needs and requirements. To maintain competitiveness, the technique of balancing the 5M's (man, machine, material, method, and management) may be used [4]. Whenever a change is made or one of the M's is intervened [4], it is important to calculate what the benefit and projection would be. These projections and analysis require the implementation of standardized methods to be able to carry out a systematized process. Improvement requires changes and changes require training; this ensure that manufacturing process complies with the quality requirements [5].

Analysis Approach

A data collection and analysis were performed with a multidisciplinary team to understand the batch size impact in the lot-to-lot changeover (ChO). Process Map of current state was completed for Small and Product R Lots. As mentioned, lots of 70,000 units or less and Product R lots exceeded the stipulated changeover time of 4.75 hours. Figure 1 shows data from the third quarter of 2021 where the exceeded changeover time of the two types of lots can be observed.

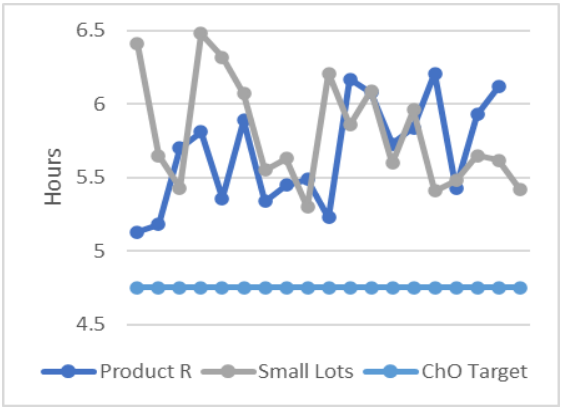

Figure 1
Product R and Small Lot 2021 Third Quarter Lot-to-Lot Changeover

Problem Solving Methodology

DMAIC (Define, Measure, Analyze, Improve, Control) methodology was used to develop and implement this project, as follow:

- Define – The SOP for the CIP and SIP process established that the product transfer recipe cannot be performed in parallel with a CIP recipe. This has an area of opportunity to decrease or eliminate the downtime between lots of 70,000 units or less, since the process must wait for the completion of the SIP recipe in the other train for the processed of a new batch. The CIP would be running throughout the duration of the current lot. Product R lots have a DHT of 5 hours; thus, the CIP recipe must be performed before the start of a new product transfer recipe. In these cases, the target time of 4.75 hours for a lot-to-lot changeover cannot be reached, unless the CIP recipe run in parallel with the product transfer recipe.
- Measure – Data analysis confirmed that Product R lots and lots of 70,000 units or less exceeded the stipulated 4.75 hours of changeover target. The total lots of Product R and lots of 70,000 units or less were more than 160 lots for 2021 representing the 35% of total manufactured lots. This represents that 35% of the operation exceeded the stipulated changeover time.
- Analyze – After an assessment of the automation engineer team, it was certified that the filling systems are capable to run both processes (the CIP recipe and the product transfer recipe) in parallel. A process map was developed where, if both recipes run in parallel, there would not be downtime and the production and capacity of the filling line could be increased. A water run to simulate both process in parallel was performed and there were no issues. Everything went as expected without any event or malfunction of automatic valves or loss of pressure in the test that is done in the piping system after the manipulations made by the manufacturing operators.
- Improve – The SOP was modified to allow the CIP process to be performed during the product transfer recipe. This was implemented after completing the actualization of the Job Hazard Analysis and Risk Assessment Worksheet documents, as required by the environmental health and safety department. Manufacturing associates were notified and trained for the change in the SOP, the process operation steps and on the capability of the system.
- Control – The syringe filling system has process and engineering controls like the post fill pressure hold test and the pressure hold test before the start of the CIP recipe. This guarantees that there will not be a CIP leak in the Isolator. The Risk Assessment Worksheet was reviewed, and no major safety risk were found for having both processes running in parallel. Lot-to-lot changeovers are being monitored as part of the overall equipment efficiency (OEE) tool. The standard work for the small lots and Product R lots were updated based on the revised process.

RESULTS

Figure 2 shows the direct results of the implementation of this initiative. The ChO of four out of five lots of Product R were below the target time of 4.75 hours and the three small lots were also below the target ChO time.

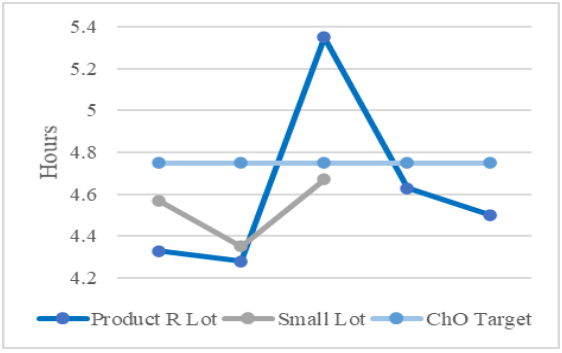

Figure 2
Product R and Small Lot ChO After Implementation

During the ChO of the third batch of Product R, an additional troubleshooting was being carried out with one of the filling equipment, this caused the ChO time to be exceeded.

Projection Project Impact to the Manufacturing Process

Table 1 shows an analysis from the industrial engineering department of the projected benefits for this current year 2022, after the implementation of this project. This information highlights the additional 217 hours per year that would be able to manufacture and the amount of 3.3 million of additional units that could be adsorbed.

Table 1
Projections of Project Benefit for Syringe Filling Line

Lots	ChO average per lot hrs.	Benefit Hours per Year	Units that could be absorb
Product R	4.07	217	3.3 million
Small Lots	3.46		

The syringe line is running at more than 95% capacity and with the implementation of this project it was granted a flexibility of an increase in production. Impacting the manufacturing process in Reliability, Efficiency, Agility and Differentiation as follow:

- Reliability – Improved and standardized lot-to-lot changeover by reaching the stipulated 4.75 hours. The recommendation to run the product transfer recipe and the CIP recipe in parallel was evaluated by a multidisciplinary team and a water run simulation was performed to certify the capability of the filling system.
- Efficiency – Increase quantity of lots number per campaign; an equivalent of 5 small lots (≤70,000 units) or 2 big lots (≥100,000 unit). Overall capacity gain of 217 hours equivalent to 9 days/year for filling commercial process (26% utilization). An absorption of 3.3 million additional units. As per the industrial engineering analysis.
- Agility – Reduce downtime during the aseptic processing of the isolator. The operation SOP was reviewed, and the staff was trained in the changes and standardization of the process. Risk Assessment Worksheet was updated, no major safety risk was identified for having both processes running in parallel
- Differentiation – Expand the implementation of this project to the vial filling line. Increasing in volume of both filling lines increases the production capacity of the site.

CONCLUSION

The implementation of this project allows all lots manufactured in the syringe filling line to comply with the stipulated changeover time of 4.75 hours. One of the goals of the production department was to absorb an increase in lots and volume of units filled, and as Figure 2 shows, this can be achieved by having the product transfer recipe in parallel with the CIP recipe. According to the analysis of the industrial engineering department, the syringe filling system is capable to adsorb an increase of 3.3 million of additional units, since this initiative has a flexibility of 26% utilization, which is equivalent to 217 hours per year.

Recommendation for Future Work

The process engineering department are engaged with the continues improvement program developing new ideas to be more efficient, reduce downtime and eliminate other process waste. Identification of other project to increase capacity in the manufacturing filling lines are under evaluation with process development scientist, manufacturing team and management. Therefore, the vial filling line is being evaluated since the filling process is like the syringe line and could benefit from the implementation of this project.

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