Parts Washer Filling Load Optimization

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Abstract *— Parts washers are used in new manufacturing and remanufacturing processes; they are designed to clean, degrease and dry bulk loads of small or large parts in preparation for assembly, inspection, surface treatment, packaging and distribution. Part washer used to cleaning process of the filling configuration load at Parenteral Vial Area of t he Biopharmaceutical located at Puerto Rico was evaluated for the amount the components in the load. The components were few to the demand of the lots manufacturing for product. An evaluation was performed and the methodology DMAC was choose to analysis the problem found in the filling configuration load in the part washer.* [1]

Key Terms *— DMAIC, Load, PVA, Tweezer*

INTRODUCTION

A global biopharmaceutical company focused on helping to address the unmet medical needs of patients with serious diseases. Manufactures and packages a number of biologic products through its fill and finish facilities. This biopharmaceutical has an opportunity for improvement in the Part washer Configuration filling load, located at Parenteral Vial Area (PVA).

Parts washer are currently qualified for use in the cleaning process of direct/ non-direct product contact parts, related to the A, B and C Drug Product manufacturing process. Each manufacturing lot of Drug Product requires several cleaning processes in the part washer to filling configuration load cycle. The research consists of reducing the number of cycles per lot by adding more load in the filling configuration load. Research Description Based on the current validated configuration load, various cleaning cycles might be required for processing filling components/parts in support to the manufacturing process of A, B, and C. As present condition, Five (5) parts washer filling load cycle runs have to be performed every A manufacturing lot, and three (3) cycles runs every B manufacturing lot.

A (product) filling lot requires nine (9) long tweezers, and B (product) requires six (6). Current filling configuration load for cleaning process has two (2) long tweezers only. Ten (10) additional Long tweezers will be validated for a total of twelve (12) Long tweezers in Filling Configuration load, therefore one (1) parts washer filling load cycle run will be performed to A manufacturing lot.

Research Objectives

The purpose for this research is to include to be included in the validate configuration loads are summarized below Table 1. In the Figure 1 shows the current vs proposed filling load configuration.

Table 1
Filling Configuration Load

Before		**After**	
Maximum amount of component			
Component	**Quantity**	**Component**	**Quantity**
Long Tweezer	**2**	**Long tweezer**	**12**

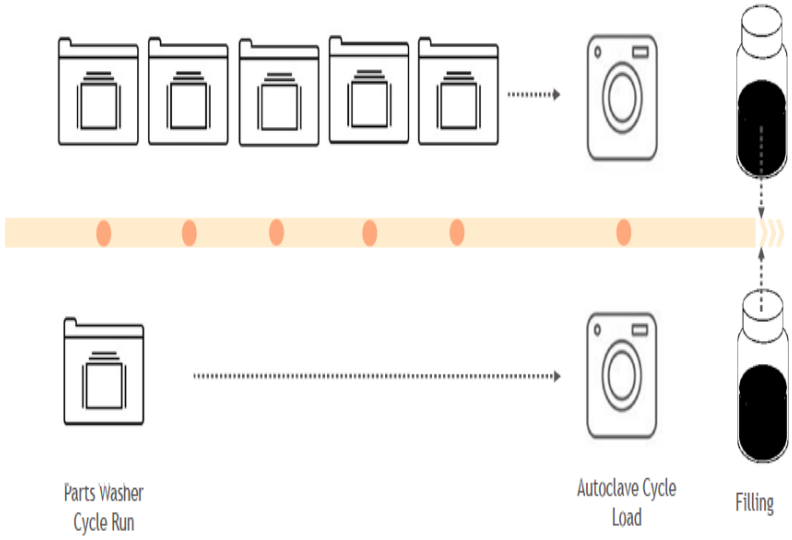

Figure 1
Current vs Proposed Filling Load Configuration Flow

Research Contributions

This improvement being pursued in order to gain operational flexibility in coordinating and consolidate in a holistic way the cleaning logistics of filling parts. The research will provide several benefits to Parenteral Vial Area, such reduced cost of utilities, equipment and labor. In addition, it will reduce the preparation processing time and generation of documentation; therefore, it will reduce the personnel workload and increase the time utilization.

LITERATURE REVIEW

Pharmaceutical parts Washer provides efficient cleaning of various materials and components utilized in the biotechnology and pharmaceutical manufacturing process industries, such as glassware, vessels, filling line components, and exchange parts. The Programmable Logic Control system (PLC) provides up to eleven adjustable cycles. Pharmaceutical Part Washers are designed, manufactured, validated, and documented according to the latest global practices and standards to facilitate customer compliance with current Good Manufacturing Practices (cGMP).

Parts washer has specific characteristics which demonstrate the efficiency of the machine are as follows, Monitoring of Total Organic Carbon (TOC) and Spray Arm rotation provides a higher level of cleaning assurance; Productivity, high performance drying system helps improve overall washing cycle times and Cost Savings, reduced water consumption results into lower operation costs.

General cleaning principles in regulated industry are governed by Good Manufacturing Practice (GMP). Cleaning process equipment has been part of the GMP for pharmaceutical manufacturing for many years. Good cleaning practices are necessary to keep the safety and efficacy of the drugs products. An inadequate cleaning include cross contamination for both materials and microorganisms and the presence of endotoxins during the manufacturer of parenteral. [2]

The cleaning process definition is performed to determine the validation efforts required due to a change that may impact the validated state of the cleaning process (e.g. introducing a new active ingredient and/or drug product into the manufacturing site).

The cleaning process must include the following:

- Product characteristics (e.g. solubility, miscibility, minimum therapeutic dose,

maximum daily dose, minimum batch size, toxicity, and where applicable cleaning agent compatibility) of the active pharmaceutical ingredient, cleaning agent, excipients and other materials of concern. [3]

- The cleaning agent selected must be scientifically justified to be effective for the formulation (e.g. lab/full scale cleanability studies, pH solubility evaluations, etc.).
- Product characteristics review must also take into consideration if there are known concerns for toxic degradation product. Where such instances occur, procedures should be developed to reduce these residues to acceptable levels. Acceptable levels would be determined based on toxicology of the degradation product.

The cleaning validation apply to critical cleaning processes. The critical processes are those handles product-contact surfaces of equipment, machines as well as utensils. The cleaning methods are divided in: Clean in Place (CIP) and Clean out of place (COP). Clean-in-place (CIP) is a method of cleaning the interior surfaces of pipes, vessels, process equipment, filters and associated fittings, without disassembly.

Cleaning Out of Place is defined as a method of cleaning equipment items by removing them from their operational area and taking them to a designated cleaning station for cleaning. It requires take to pieces an apparatus, washing it in a central washing area using an automated system, and checking it at reassembly. In the pharmaceutical industry, there are different types of cleaning processes, which will be used for this research is cleaning of items in part washer.

The cleaning process is regulated for the Food and Drug Administration (FDA) cleaning validation guidelines. Validation of Cleaning Processes (7/93) "This guide is designed to establish inspection consistency and uniformity by discussing practices that have been found acceptable (or unacceptable). Simultaneously, one must recognize that for cleaning validation, as with validation of other processes, there may be more than one way to validate a process. In the end, the test of any validation process is whether scientific data shows that the system consistently does as expected and produces a result that consistently meets predetermined specifications"[4].

PROJECT METHODOLOGY

Current validated configuration load in the Part Washer at Parenteral Vial Area were qualified for use in the cleaning process. This configuration load for cleaning includes the following components. Refer to Table 2.

Table 2
Current Configuration

Configuration Load	Maximum amount of Component
Filling	**Two (2) Long Tweezers**

The propose of this project is to include additional amount components to the current miscellaneous parts configuration loads. The proposed amount of additional components to be include in the validated configuration load are the Table 3.

Table 3
After Project Configuration Load

Configuration Load Maximum amount of Components	Additional Components to be included
Filling Twelve (12) Long Tweezers	**Ten (10) Long Tweezers**

As part of Parts Washer Filling Load Optimization Project methodology includes documents development and verification in order to complete and document the additional components to be included in the validated configuration load complying with Good Manufacturing Practice and Validations Requirements.

Based on the Proposed Project any documents needs to be revised including Standard Operating Procedures (SOP's). For this change no modification to the validated cleaning process, recipe and no changes to the drug product manufacturing process. This implementation will

have no impact to the validated state of manufacturing process.

This change will require to cleaning verification study (Confirmation run) to confirm the additional components in the configuration load at Part Washer comply with requirements stablished and obtain successful results in the Cleaning process study to can consider the load validated.

During the first phase of the project, an evaluation was made and it was determined to use the DMAIC methodology for the development of analysis and results. This statistic-based tool will give us a quality strategy for gathering information and comparing improvements based on the project's strategy of adding components in the load configuration to help reduce costs, equipment and labor. Also, it will reduce the preparation processing time and generation of documentation. [5].

The DMAIC methodology is composed of the following steps:

- Define: Objective or scope of the Project.
- Measure: Having established some metrics to follow that help us to know the situation in which as maximum amount components in the configuration just be two components that are causing manufacturing time problems, we want to solve it, we must measure these parameters and establish a follow-up that allows us to analyze the situation later.
- Analyze: With the data that we have collected we will do an analysis of them, to try to find out the reasons why something is failing and we will apply the strategy of adding the components as a corrective action to be able to correct the problem and improve the cleaning process in manufacturing.
- Improve: All analyzes developed will be applied to improve the problem and solve it.
- Control: In the final project phase after completing all the improvements, the implementation will take place. [5]

A Project schedule was performed to show the due date of the project. Refer to Table 4.

Table 4
Project Schedule

TIMELINE	
Phase	**Planned Completion Data**
Kickoff meeting	**08-10-20**
Data Collection,Documents	**08-17-20**
Define	**09-01-20**
Measure	**09-09-20**
Analyze	**09-17-20**
Improve	**09-22-20**
Control	**10-02-19**
Confirmation Run	**10-13-20**
Close documentation/Implementation	**10-21-20**

RESULTS AND DISCUSSION

The DMAIC methodology was performed the following steps were analyzed.

Define

Project Charter shows our preliminary understanding of roles and responsibilities, the objective of the project, and will be give the authority to do our job. See the Table 5. [6]

Measure

Current Filling Configuration load will be compared with New Filling Configuration load determine the improvement between two loads. Filling Configuration load are used in the part washer to cleaning process and then this part are used to complete required components for lots manufacturing. The Table 6 shows the comparison load.

In the Pareto Diagram we can visualize as Current Filling load has run cycle time more long (8 hrs) for 5 cycles compared with the New Filling load that the run cycle time of 4 hrs less (2 hr). This indicate that the current load is impacting cost of utilities, equipment, labor and lots manufacturing amount. In addition, the percent of run time is of 80% more long time during cycle for the Current filling load, this does not effective to the operator and the organization. Refer to Table 7 for data collection to Pareto Diagram and Figure 2.

Table 5
Project Charter

<table>
<tr><th colspan="3">PROJECT CHARTER</th></tr>
<tr><th>PROBLEM STATEMENT</th><th colspan="2">BUSINESS CASE</th></tr>
<tr><td>Present Condition
Five (5) parts washer filling configuration load cycle runs have to be performed every A manufacturing lot, and three (3) cycles runs every B manufacturing lot.
A (product) filling lot requires nine (9) long tweezers, and B (product) requires six (6).
Current filling configuration load for cleaning process has two (2) long tweezers only.</td><td colspan="2">The change will provide several benefits to Parenteral Vial Area, such reduced cost of utilities, equipment and labor. In addition, it will reduce the preparation processing time and generation of documentation; therefore, it will reduce the personnel workload and increase the time utilization.
The consequences of not doing this project would be that the industry will lose money and time when the runs last a longer time due to the number of cycles it has for each filling confirmation load for each lot.</td></tr>
<tr><th>GOAL STATEMENT</th><th colspan="2">TIMELINE</th></tr>
<tr><td rowspan="6">Obtain at least ten (10) additional Long tweezers for a total of twelve (12) Long tweezers in Filling Configuration load</td><td>Phase</td><td>Planned Completion Data</td></tr>
<tr><td>Define</td><td>09-01-20</td></tr>
<tr><td>Measure</td><td>09-09-20</td></tr>
<tr><td>Analyze</td><td>09-17-20</td></tr>
<tr><td>Improve</td><td>09-22-20</td></tr>
<tr><td>Control</td><td>10-02-20</td></tr>
<tr><th>SCOPE</th><th colspan="2">TEAM MEMBERS</th></tr>
<tr><td>Scope
• validate ten (10) long tweezers in filling configuration load for a total of twelve (12) long tweezers to obtain one (1) parts washer filling load cycle run to a (product) manufacturing lot.
• Evaluation and assessment of new configuration load.
Cleaning verification study (confirmation run)
• SOP standard operating procedure revision
Out of scope
Unexpected situations encountered during the development of the project that impacted the deadlines.</td><td colspan="2">Team Members
Sr. Process Validation Scientist
Engineering
SME (Subject Matter Expert)
Quality Assurance QA
Manufacturing Supervisor or designee</td></tr>
</table>

Table 6
Loads Comparison

Current Filling Configuration load	New Filling Configuration load
For Filling configuration load has two (2) long tweezers for cycle run. For A (product) filling lot require nine (9) long tweezers = 5 cycles = 7hr 35 min For B (product) filling lot require six (6) long tweezers = 3 cycles=4hr 41 min Filling load part washer time= 1hr 47 min	For filling configuration load Ten (10) additional long tweezer are included. For a total of twenty long tweezers for cycle run. For A (product) filling lot require (9) long tweezers = 1 cycles=1hr 47 min For B (product) filling lot require six (6) long tweezers = 1 cycles=1hr 47 min Filling load part washer time= 1hr 47 min

Table 7
Data Collection Plan to perform Pareto Diagram

Loads	Run cycle time (hr)
Current Filling load (5cycles)	8
New Filling load (1 cycle)	2

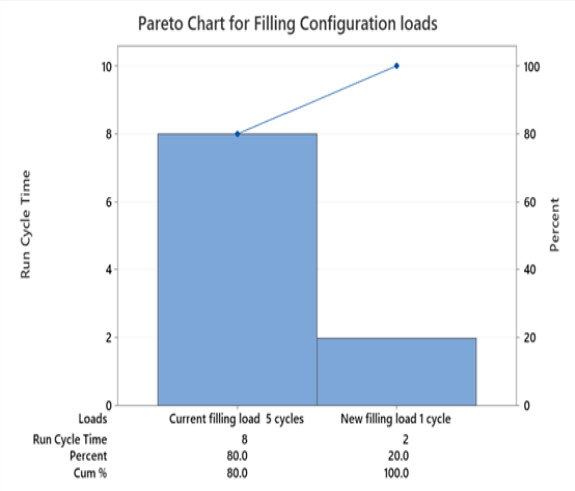

Figure 2
Pareto Diagram

Analyze

The analysis of the load was based in that two (2) long tweezers only in the filling configuration load for cycle, was evaluated and identified as the

primary root cause. The following cause and effect Diagram on Figure 3 shows the analysis.

After developing and analyzing the cause and effect diagram, we can determine that the Filling Configuration load (2 long tweezers) has many causes and situations that could improve with the implementation of this project.

Additional components to this load will be an effective and reasonable way to obtain the amount items enough to complete the lots manufacturing with all the necessary features to guarantee an improvement to the manufactory area and obtain a successful production.

Cause and Effect Diagram

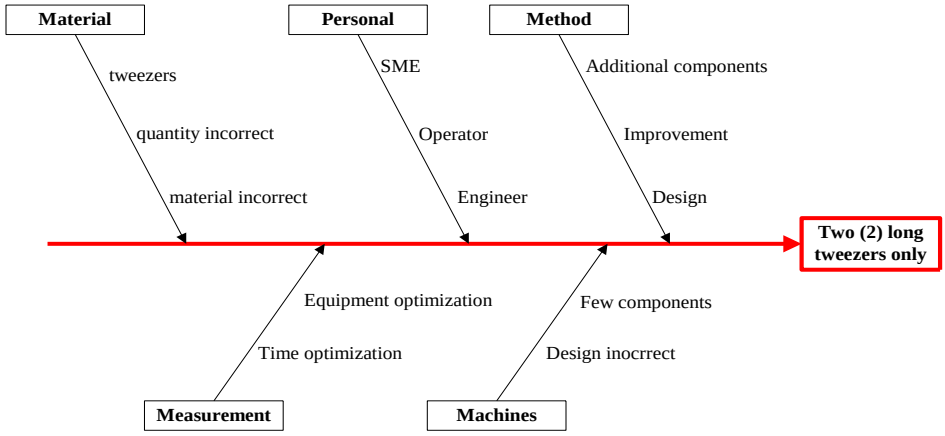

Figure 3
Cause and Effect Diagram

Improve

The improvement plan include additional amount components to the Current parts Filling Configuration load, in order to complete the required components for lots manufacturing, reducing multiple cleaning cycles performed. As part of Analysis will be perform a cost analysis to compare the cost with Current Configuration load.

As part of improvement the benefits established show in the Figure 4.

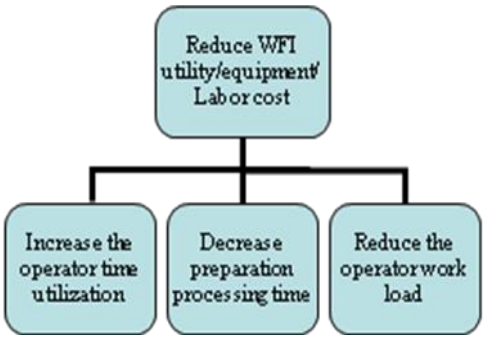

Figure 4
Benefits of Optimizing Parts Washer Filling Load

Table 8
Costs Analysis

TOTAL COST ($/YEAR)		
	Current Cost	**Propose Cost**
	$100,711	$37,422
	$40,723	$9,293
	$94,764	$21,624
Total	$236,198	$68,339
Diff.	$167,859	

In Table 8 shows the cost analysis for year. Based in the cost analysis that the difference between current Cost vs proposed cost was a total of 167,859 in the expense of operator, equipment and lot impact. It is estimated that it is a reasonable change for the improvement that will be obtained

when the 10 tweezers will be added to filling configuration load at part washer as result a better production will be obtained in less time and obtain the components necessary for lots manufacturing.

Control

As part of the implementation of project a cleaning verification study (confirmation run) was performed including the 10 long tweezer additional using the same recipe of the current filling configuration load in the part washer machine. All Results were satisfactory and its was confirmed that the New Filling configuration load comply with the requirements stablished for Good Manufacturing Practice and it's validated. Interim report was completed and this load is release to manufacturing use.

After developing all the DMAIC analysis for this project; as part of the improvement and the implementation, the following documentation will be revised:

- Standard Operating Procedures (SOP'S)

CONCLUSION

As part of analysis of the Project, the Six Sigma DMAIC methodology was chosen for the development and improvement of the problem detected in the Parenteral Vial Area in the Part Washer loads. This methodology helped to determine the root cause of the problem and reach an effective solution by improving the tweezer cleaning process load in the Part Washer.

Upon detecting the cause of the problem which was two (2) long tweezers only in filling configuration load for each cycle. Ten (10) long tweezers additional were included in the load and a confirmation run was performed to verify of load consistently comply with the requirements stablished.

The run was completed and the results were satisfactory. The New filling configuration load was implement and release for manufacturing use. All Standard Operating Procedures (SOP's) that were impacted for this project will be revised.

With the implementation of this project and the improvements obtained in the filling configuration load in the part washer located Parenteral Vial Area, the biopharmaceutical industry will obtain a total annual cost savings of $ 167,859.

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