Scrap Reduction Evaluation of Filling Equipment and Short-Term Improvement Implementation

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Abstract *— This paper seeks to document an approach to reduce scrap losses using the Lean Six Sigma tools for process improvement in a lean manufacturing environment. The Lean Six Sigma methodology views lean manufacturing, which addresses waste issues, and Six Sigma, with its focus on design, as complementary disciplines aimed at promoting "business and operational excellence". DMAIC (Define, Measure, Analyzed, Improved, and Control) is used for projects aimed at improving an existing business process. Assessments of the manufacturing processes and interviews with key personnel to determine potential opportunities were performed by means of Voice of the Costumer. The project starts with the definition and measure phases, followed by the analysis phase and ends with improve and control phases. Supporting data are presented using Pareto charts to prioritize waste in order to be more focused for improvement. DMAIC methodology was employed to identify the areas in which the product is discarded (waste). Evaluation revealed that the product that remains in the silastic hose and not transferred in the carboy is the major contributor of the product loss at the filling stage. Scrap reduction into filling equipment was successfully employed to improve manufacturing productivity. Twenty five percent (25%) of cost improvement were the immediate benefits attained from implemented process improvements.*

Key Terms *— DMAIC methodology, Lean Six Sigma, Voice of the Costumer (VOC), Waste.*

INTRODUCTION

Biopharmaceutical facility dedicated to the production of therapeutic biological product which involves the following unit operations:

Bulk production – Highly purified and characterized drug substance.

Formulation Process – Drug substance and components are prepared into deliverable product.

Filling Process – Formulated product filled using an automatic filling line into medical device (syringe) or vials.

Inspection Process – Syringes and vials are inspected using a semi-automated inspection system.

Packaging Process – Syringes and vials are packed using an automated inspection system.

Syringe filling process was identified during evaluation to perform scrap reduction as part of the Operational Excellence initiative.

Lean Six Sigma attributes is presented to give a real insight into the leanness level and to further improve it by acting appropriately in the manufacturing system [1]. Lean Six Sigma tools such as the identification of sources of waste and Voice of the Costumer (VOC) facilitated the identification of areas of improvement in the Syringe Filling Process [2]. Waste reduction is consider an effective way to increase profitability. The 8 most common forms of waste are defective production, overproduction, waiting, non-used employee Talent (the 8th form), transportation, inventory, motion and excessive (over) processing [3]. Voice of the Costumer (VOC) refers to the range of results that are acceptable to a costumer, whether in a numeric specification or verbal feedback [4].

Eight (8) sources of waste were identified in the syringe filling process. From the eight (8) waste sources, three (3) were identified as short-term areas of improvement as follow: (1) Transfer Hose Waste (2) Robot Pick-up Failure, and (3) Handling of Units. Even though, Lean Manufacturing can only be achieved through time, and that it is not possible to use it as a panacea to solve short-term problem re-design of establish process cannot be done overnight [1]. Once short-term improvements were implemented a multi-phase project will begin to seek Lean Manufacturing.

SYRINGE FILLING PROCESS OVERVIEW

Transfer to filling

The filling process start with the formulated drug product being sterile-filtered using 0.22 µm filter into a glass carboy which has a deep tube, to minimize foaming, and a 0.22 µm vent filter. The tanks uses filtered air pressure as means to push the product through a silastic hose connected to the 0.22 micron filter and into the carboy. Refer to Figure 1 for aseptic transfer to filling.

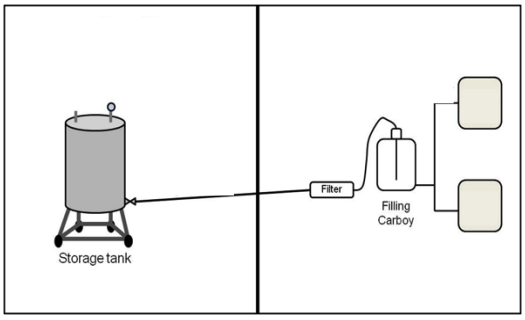


Figure 1
Aseptic Transfer to Filling

Filling Process

The automatic filler machine is a volumetric filler with 10 filling pumps, 10 filling nozzles and 2 quintuplex valves that allow product to be filled under positive head pressure. The filling pumps are piston type pumps of 2cc size. The filler machine fills at a speed (set point) of two hundred (200) syringes per minute (spm) to two hundred fifty (250) spm.

The operator places a pre-loaded tub of empty syringe barrels arranged in a honeycomb pattern into the filler's indexing conveyor. Tubs are guided to enter the machines lid removal and inspections stations by means of a traffic controller. The robot advances it into position to take the tub and removing the lids. Vision System inspection (camera) that the first lid is completely removed. All inspections of the system are based on contrast. If the inspections are good, a last inspection is triggered by the same camera used for the previous inspections. This time the camera will inspect the presence of one hundred (100) syringes and then moves the tub to the indexing conveyor. The arm grip opens to place the tub on the indexing conveyor once the indexing conveyor flap passes the flap sensor the filling cycle initiates. When the tub is in the home position, the nozzles lower and fill the first row. After the first row is filled, the tray automatically advances and the cycle repeats until all units have been filled. When the last row is filled, the pusher places the filled tub in the transfer plate. A second pusher moves the tub to the stopper placement unit (SPU) in-feed conveyor.

The filled syringes are placed into a rack, topped with a pre-packaged stopper nest and placed inside the SPU vacuum chamber. The SPU robot closes the door and the vacuum draw from the SPU chamber is initiated. Plunger pins come down pushing the plungers into the barrels, forming a seal. The vacuum turns off automatically, and air enters the chamber driving the plungers into the barrels. When the chamber pressure reaches the air pressure outside the chamber, the tubs are unloaded and positioned on the out-feed conveyor.

METHODOLOGY

Six Sigma seeks to improve the quality of process outputs by identifying and removing the causes of defects (errors) and minimizing variability in manufacturing and business processes. DMAIC (Define-Measure-Analyze-Improve-Control) problem-solving methodology was followed to define the problem, implement

solutions associated to underlying causes, and establish best practices to ensure the solutions stay in place **Error! Reference source not found.**.

DEFINITION STATEMENT

The process excellence initiates a waste reduction study to increase profitability. During the VOC manufacturing Subject Matter Expert (SME) identifies and maps the filling process. Potential area for data collection was identified during process mapping. After brainstorming session with SME, causes and effects are represented in terms of lines and symbols in Ishikawa diagram (Figure 2 of Cause & Effect Diagram).

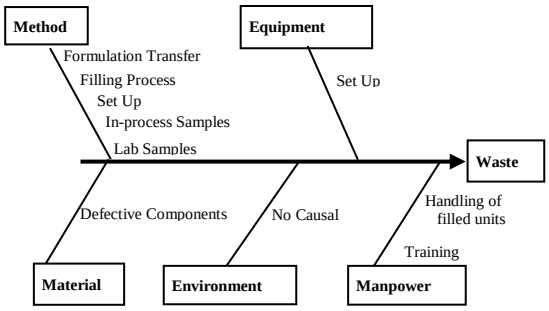


Figure 2
Cause & Effect Diagram

Eight (8) sources of waste were identified in the syringe filling process as follow: (1) Formulation Transfer (2) Set-up, (3) In-process samples, (4), Filling Process (5) Laboratory Samples, (6) Defective Components (7) Training, and (8) Handling of Units. Even though, method was identified as the mayor offender.

During the evaluation of each waste source feasible areas for short-term improvement were identified by the SME. Table 1 summarized short-term improvements by waste source.

Table 1
Short-term Improvements by Waste Source

Process Step	Short Term Improvement
Formulation Transfer	Shorten the transfer silastic hose Silastic hose pressure blow
Set-up	None identified
In-process Samples	None identified
Filling	Improvement in robot pick-up
Laboratory Samples	None Identified
Handling Units	On the job training and awareness

MEASURE PHASE

Data collection was performed from July to September for all manufactured products for Syringe Waste Reduction Initiative (Graph 1). Data collection was perform using Guide provide in Figure 4. Only one (1) manufacture product was selected to initiate the Syringe Waste Reduction Initiative (Graph 2). The selection was performed using the quantity of production (base line), available data and major profitability in short-term period. Data was collected from formulation transfer and syringe filling process to assess the better approach for waste reduction. Data gather from one (1) manufacture product as part of the Syringe Waste Reduction Initiative is presented in Graph 2.

Data gather from short-term improvements defined in Table 1 is presented in Graph 3 and discuss as part of this evaluation.

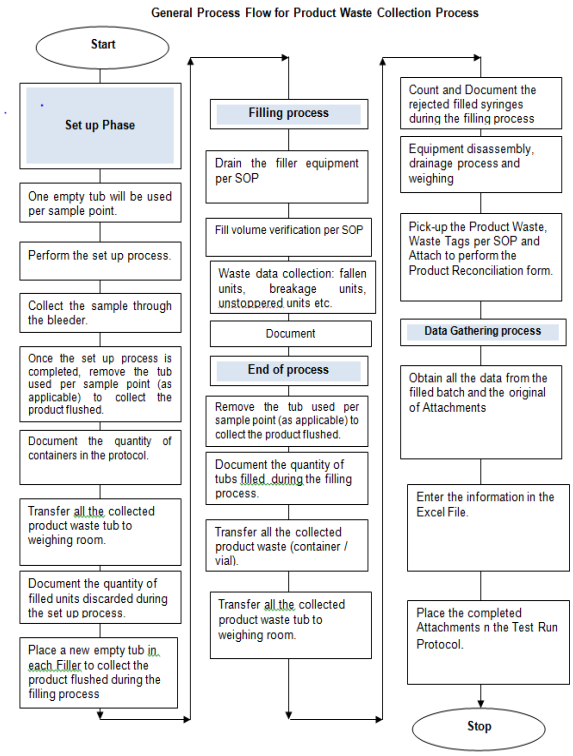
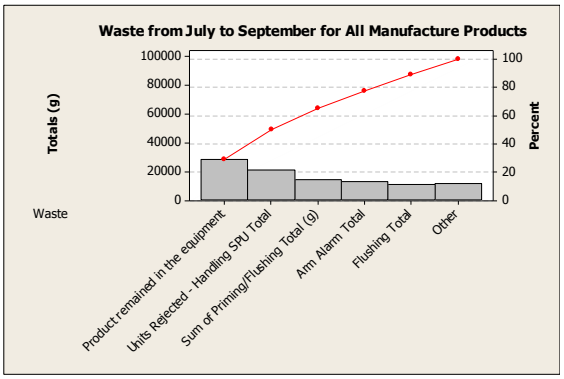


Figure 3
General Process Flow for Product Waste Collection Process

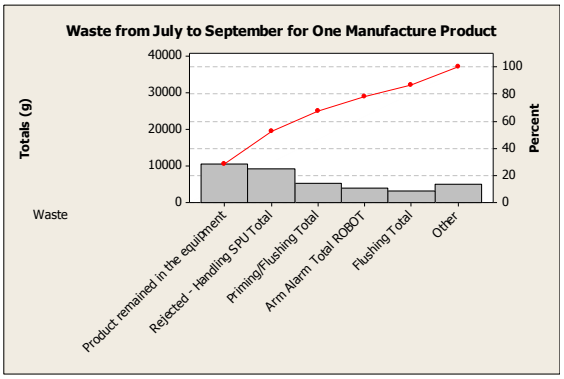
ANALYZE PHASE

Graph 1 identified potential waste for all manufacture products from selected time period defined (July to September). Even though more data need to be gather for all other manufacture product since baseline can be define.



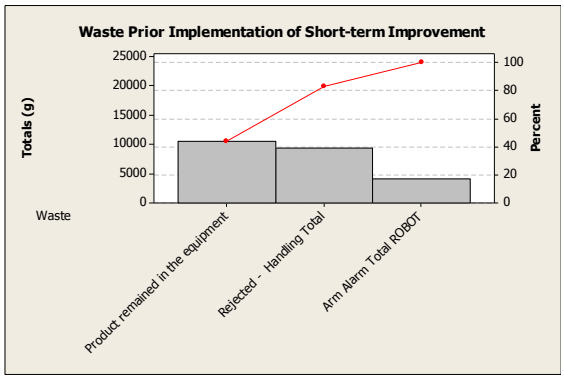
Graph 1
Waste from July to September for All Manufacture Product

Graph 2 identified potential waste of the baseline for short term improvements definition.



Graph 2
Waste from July to September for 1 Manufacture Product

Filling process evaluation identified areas of improvement as follow: (1) Transfer Equipment Waste (2) Handling of Units, and (3) Robot Pick-up Failure. Data from long-term improvements and other manufacture products were removed for comparison purpose after improvements. Graph 3 identified potential waste of the baseline for short term improvements defined.



Graph 3
Waste Prior Implementation

A functionality exercise was executed to evaluated areas identified in which the product is discarded. Functionality exercise revealed that the product that remains in the hose and not transferred in the carboy is the major contributor of the product loss at the filling stage. Functionality activities included: assembly, manipulation, and hoses length determination. In addition, a silastic hose pressure blow experiment were performed at the end of the filling process in order to assess the suitability of transferring drug product from the portable storage tank to the filling carboy by applying clean air pressure. Table 2 shows actual parameters prior to implementation.

Table 2
Short-term Improvements Parameters

Short Term Improvement	Parameter
Shorten the transfer silastic hose	40 ft. (2x20 foot)

As a result of the functionality test results, the following are recommended:

- Use a 35 feet long, (1 x 20 feet and 1 x 15 feet) pre-molded silastic hose length.
- Use a cap color code system in order to identify the 15 feet and 20 feet long pre-molded silastic hose length (Figure 3).
- Update Standard Operation Procedure's applicable.

The silastic hose pressure blow experiment was performed at the end of the filling process in order to assess the suitability of transferring drug product from the portable storage tank to the filling carboy

by applying pressure starting at 1 psig up to 10 psig, in 1 psig step increments. During the experiment, the remnant product was not transferred at the tested pressures. In order to perform the pressure blow transfer of the remnant in the transfer line it would be necessary to apply pressures higher than 10 psig.

Improvement in the robot pick-up mechanism (grippers) was evaluated and a like-for-like replacement was feasible. On-the-job training and awareness was initiated once the Syringe Waste Reduction Initiative began.

IMPROVEMENT PHASE

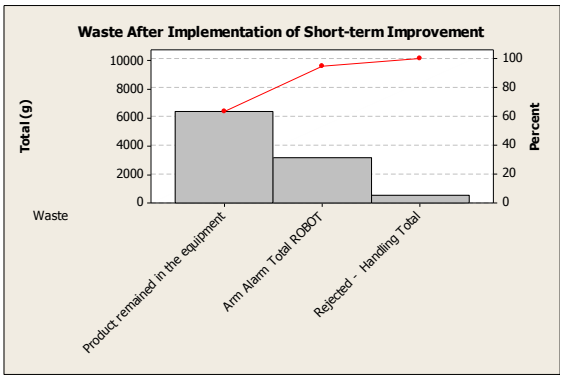
Short-term improvements were initiated in July with the beginning of the data collection. On-the-job training and awareness was initiated once the Syringe Waste Reduction Initiative began.

Product filing was verified with Regulatory Department for process parameters or specific definition in the filing for the improvements. Regulatory evaluation was completed and approved with no regulatory complication for short-terms improvements. In mid-September reducing the length in the transfer silastic tubing, and the like-for-like replacement for robot grippers were completed.

Figure 3 shows the implementation of the silastic hose with the cap color code system.

Figure 3
Silastic Hose with Color Cap

Graph 4 represent data gather of twenty five (25) batches after implementation of short-term improvements manufacture from mid-September until October.



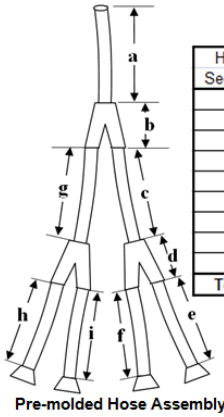
Graph 4
Waste After Implementation

As part of the Syringe Waste Reduction Initiative short-term improvements will be implemented in the remaining manufacture products once the base of at least 10 batches is reach. Regulatory evaluation was requested with no further complication to implement in all other products. Long term improvements definition project was initiated. Some of the projects in the pipeline for waste reduction are summarized in Table 3.

Table 3
Long-term Improvements

Process Step	Long Term Improvement
Set-up	• Minimize air bubble formation in filling lines. • Shorter silastic hose configuration using connector fittings.
In-process Samples	None identified
Filling	• Minimize formation of air bubble on the product filling lines during filling operation. • Use of hose holders as an additional to provide a hose angle for an easy product transfer. • Modification of the nozzle to include bubble traps
Laboratory Samples	None Identified

Figure 4 shows test run result and potential reduction for silastic hose configuration using connector fittings. This improvement represents an additional 44% hose reduction additional to the demonstrated during the short-term improvements.



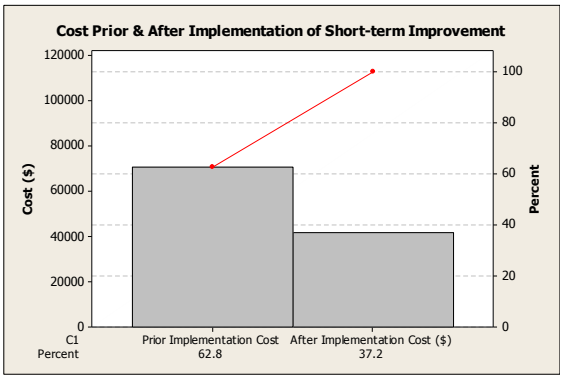
Pre-molded Hose Length Reduction

Hose Section	Inches (before cut)	Inches (after cut)	% Reduction
a	47	4.25	91%
b	2	2	0%
c	29	19.25	34%
d	2	2	0%
e	26	20.75	20%
f	26	20	23%
g	29	14	52%
h	26	20.25	22%
i	26	20.75	20%
Total	213	123.25	42%

Figure 4
Pre Molded Hose Length Reduction

CONTROL PHASE

Based on the functionality test results for the shortness of the silastic hose and the color code caps, the standard operating procedure was revised to illustrate the measure and location of each silastic hose with it respective color caps to standardize equipment assembly. Manufacturing Batch Records and procedures were revised to include new length, modify the assembly instruction prior to start the set-up and re-enforce current process controls with an on-the-job training including instructions for handling of filled units during the filling process. Profitability of the improvements was review in October after of two (2) of implementation. Graph 5 shows comparative quantitative data.



Graph 5
Profit from Waste reduction

CONCLUSION

Six Sigma seeks to improve the quality of process outputs by identifying and removing the causes of defects (errors) and minimizing variability in manufacturing and business processes. Its problem-solving methodology (DMAIC) was followed to define the problem, implement solutions associated to underlying causes, and establish best practices to ensure the solutions stay in place [3].

Waste reduction short-term improvements were identified and accomplishing using the Lean Six Sigma DMAIC methodology in a way that is systematic, sustainable, confirmed with data, and in alignment with customer and stakeholder quality expectations. Results confirmed adequacy of recommended process improvements and evaluated data. Equipment modification and on-the-job training reduced the waste generated during the syringe filling process of one manufacture product. Increasing flow rate during line flushing reduced actual flush time. Equivalence test supported the reduction of the spray gun verification. Benefits from implementation of all process improvements include a 25% overall in operational cost from $70,871.19 to $41,909.44 for a single product with short-term improvements.

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