Yield Improvement for Anesthesia Product at Filling & Packaging Line

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Abstract *— In the manufacturing process of anesthesia, the yield for Fluxane product, manufactured at ANESTHER Healthcare, is consistently performing lower than target (2.785 bottles/kg) from tank F-SV-001 in comparison to tank F-SV-002. Based on a 12-months data review, the yield is not met for 77% of the manufactured lots, resulting in an annual loss of $115,000. The DMAIC methodology was used to determine the possible causes for the low product yield results in BDP tank F-SV-001. The following causes were identified: (1) the venting system of the tank F-SV-001 was not working efficiently due to pressure valve malfunction, causing evaporation of the product; (2) calibration classification was not appropriate for load cells causing tolerance errors; and (3) lack of a standardized yield reporting method. During control phase, yield data was collected for one (1) month and results were equal to or greater than 2.785. The objective of increasing product yield in tank F-SV-001 to approximately 2.785 bottles/kg was achieved.*

Key Terms *— Anesthesia, DMAIC, Process Yield, Six Sigma.*

INTRODUCTION

In the pharmaceutical industry, the productivity of a manufacturing process is measured as a ratio between the number of finished goods produced (outputs) against the resources needed -such as time, materials, energy, and labor- to produce those goods (inputs). Product yield is used as an indicator of the productivity of a process. ANESTHER Healthcare is a world global manufacturer of anesthesia, distributing their product in around 70% of the countries around the world. Its portfolio includes injectables and inhaled anesthesia. One of their lead products, Fluxane, is a non-flammable liquid administered through inhalation using a vaporizer machine. It is manufactured by means of a series of chemical reactions, distillation and purification steps, and finally, filled and packed at packaging Line 1 into 240mL glass bottles presentations.

The Filler Machine at Line 1 is dedicated to the filling of Fluxane product, which is feed from two (2) storage tanks: F-SV-001 and F-SV-002, located at the Vessel Room in the Packaging area. The product yield from storage tank F-SV-001 is consistently performing lower than the target 2.785 bottles/kg. Based on a 12-months data review (01-Jun-2018 to 31-May-2019), a 77% of the time, the yield is not met, with a mean of 2.772. A low yield results in an annual loss of 6,989 bottles of Fluxane, at a cost of $115,000, and consequently, the site does not meet the customer demands based on the bottles produced.

Research Objectives

Increase product yield in bulk drug product (BDP) storage tank F-SV-001 from 2.772 bottles/kg to approximately 2.785 bottles/kg or by 5,940 bottles equivalent to 85% annual increase by December 2019.

Research Contributions

An increase in product yield will provide the following benefits:

- Achieve a state of control for BDP tank F-SV-001 filling process.
- Save cost to maintain competitiveness.
- Increase packaging line productivity and capacity.
- Meet customer’s demands on time.

BACKGROUND INFORMATION

In recent years, manufacturing industries have engaged in continuous process improvements initiatives to maintain a competitive business advantage and satisfy customer demands. As a result, the Six Sigma methodology has been increasingly adopted as an innovative approach to business performance improvement, focusing primarily on quality. The philosophy of Six Sigma is based on the implementation of the continuous improvement strategic approach of Total Quality Management or TQM, which involves quality awareness at every step of production with a focus on the customer. Therefore, a Six Sigma process targets a 99.99927% defect free manufacturing [1].

Six Sigma

A Six Sigma process aims to reduce the number of mistakes or defects in a process to as low as 3.4 occasions per million opportunities [2]. In statistical terms, sigma is a measure of "variation about the average" which indicates to what extent the process varies from perfection. Six Sigma is used in the manufacturing sector to improve process capability, efficiency, reduce waste or non-value added activities, reduce quality costs and, consequently, improve profitability [1,2]. As defects and mistakes are reduced and wastes are eliminated from the process, customer satisfaction is maximized, and financial benefits are obtained (cost reduction).

The Six Sigma methodology uses a variety of techniques and tools that are focused on producing defect-free products. The most common is the DMAIC, which is explained next.

DMAIC Methodology

The DMAIC methodology consists of the following phases: define, measure, analyze, improve and control. As observed in Figure 1, this methodology is a standardized approach consisting of a series of sequential stages used to determine the causes of a problem and implement improvement opportunities.

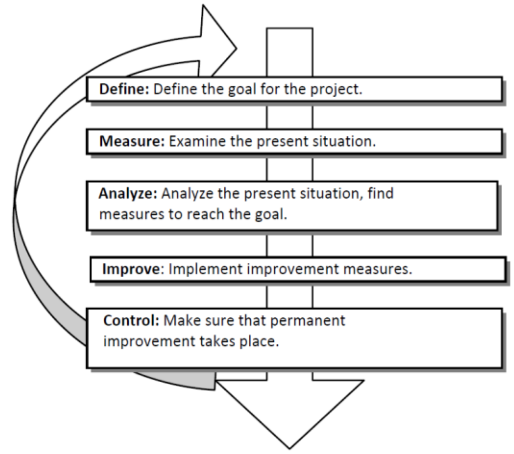

Figure 1
DMAIC Methodology [3]

The purpose of each phase and applicable tools is detailed below.

- **Define:** The purpose is to determine objectives and scope of the project and establish a business case based on the customer and organization's requirements. This phase involves the development of a project charter which sets forth the commitment between the project leader, project team, advisor and stakeholders (internal and external). The problem statement is established and must be defined in a clear and concise manner. Some useful tools to aid in the development of a robust problem statement and objectives includes the SIPOC diagram (stands for Supplier, Input, Process, Output, and Customer), voice of the customer (VOC), stakeholder analysis, and Critical to Quality (CTQ) tree.
- **Measure:** This phase includes a map of the process, operational definitions, establish a measuring system and perform data collection for the purpose of establishing a baseline. Some tools include process mapping and pareto charts.
- **Analyze:** This phase focus on identifying root cause or potential causes of defects and identifying opportunities to eliminate the recurrence or occurrence of the problem. The tools include cause and effect diagrams, why

analysis, pareto analysis of causes, failure mode and effect analysis (FMEA).

- **Improve:** Once the most probable causes of the problem (or the vitals X's) are identified, the next step is to implement actions identified to eliminate the problem and/or improve the process. This phase involves planning and management.
- **Control:** This is the last phase of the DMAIC. On previous phases, the problem was stated, the most probable causes were identified, and improvement measures were implemented. Therefore, the sustainability of the changes needs to be monitored and evaluated for effectiveness.

Process Yield

The process yield, also known as first-time yield (FTY), is defined as the percentage of units coming out of a process free of defects. It is calculated as the number of good "acceptable" units coming out of a process divided by the number of total units going into the process [4]. For the purpose of the manufacturing process outlined in this project, the yield is defined as the ratio between the quantity of good units (Quarantine bottles and QA Samples) and the Net Weight in the storage tank (F-SV-001 or F-SV-002). It is calculated as follows (1):

$$Yield = \frac{Quarantine\ (bottles) + QA\ Samples\ (bottles)}{Net\ Weight\ (kg)} \tag{1}$$

Quarantine = the number of acceptable units (bottles) produced

QA Samples = includes acceptable units (bottles) that are sampled for the Reserve Sample Program and for stability studies (as applicable)

Net Weight = the difference between the storage tank load cell reading at the end of the bulk and at the beginning (prior to start filling)

The process yields results, and the cost of poor quality (rejects and reworks) are an indication of performance measures for the manufacturing of a product that signals the causes of variation of the process [2].

METHODOLOGY

The DMAIC methodology was used to determine the possible causes for the low product yield results in BDP tank F-SV-001 (less than 2.785 bottles/kg in average).

In the Define phase, the business case and problem statement is established. The scope, goals and stakeholders (internal and external) requirements are identified and clearly stated. This phase addressed the current and proposed states. This is the most important phase of the project since a clear and concise problem makes it possible for it to be solved appropriately. The following tools will be used to define the problem statement, scope of the project and objectives: SIPOC diagram, Is/Is Not and Stakeholder Analysis.

The Measure phase sets the process baseline and an understanding of the current process. A data collection plan will be established in order to validate and set an adequate measurement system for the process. The data of the process will be collected to define a baseline, and further determine the process capability. Process mapping and basic statistics will be used as data measurement tools.

In the Analyze phase, a root cause analysis will be performed, which includes, brainstorming, fishbone and 5 whys to determine the root cause or most probable cause for the low yield results in BDP tank F-SV-001. The critical X's of the process are determined and evaluated.

Once the root cause(s) is determined, the Improve phase will address this cause(s) and identify actions to eliminate it (them). The tools to be used includes, but are not limited to, brainstorming for identification of solutions and kaizen events to introduce rapid change.

In the last phase, Control, the improved process will be monitored for one (1) month after the implementation of the corrective and/or preventive actions. Product yield will be measured after the improvements and compared with the objectives and baseline. To measure the effectiveness of the changes implemented, the project should render an increase in product yield for bulk drug product (BDP) tank F-SV-001 from 2.772 bottles/kg to approximately 2.785 bottles/kg or by 5,940 bottles (85% annual increase) by the end of the year.

RESULTS AND DISCUSSION

The results of the different stages of the DMAIC methodology are detailed next.

Define

A historical discrepancy exists between two similar Fluxane Bulk Drug Product (BDP) Tank Yields. The yield target is 2.785 bottles/kg: Tank F-SV-001 is performing at a mean of 2.772 bottles/kg based on 12 months data review and Tank F-SV-002 is performing at a mean of 2.786 bottles/kg during the same review period.

A SIPOC diagram of the process is illustrated in Figure 2.

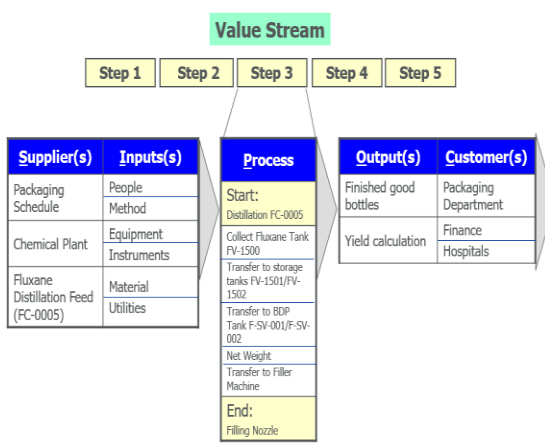

Figure 2
SIPOC Diagram

The scope of the project is the product transfer of Fluxane BDP storage tank F-SV-001 from the chemical plant (drug product formulation) to the Filler machine reservoir. The Is/ Is Not tool was used to define the problem (refer to Table 1).

A stakeholder analysis was performed to evaluate the degree of impact of the project in the affected areas (refer to Table 3).

Table 1
Problem Statement - Is/ Is Not

	Is	Is not
What	The yield of Fluxane Product BDP Tank F-SV-001 is below the target of 2.785.	The yield of BDP Tank F-SV-002, or other finished product.
Where	Distillation Column FC-0005; Storage Tanks FV1500, FV-1501, FV-1502; Transfer lines FE-0000026 and FD-0000027	Distillation Column FC-0006; Storage Tanks BDP F-SV-002; Tanks, reactors and transfer lines associated with other bulk products; Transfer lines FE-0000028 and FD-0000029
When	June 2018 to May 2019	Prior to June 2018 nor after May 2019
Extent	Process from Distillation Column to the Filler Machine Nozzle in Line 1	API Intermediates Processes, Filling Process, Labelling and/or Packaging.

Measure

A process map was performed to establish the sequence of steps for the process within the scope of this project (Figure 3). The process includes the final steps of the synthesis of the anesthesia and ends with the starting point for filling the anesthesia product into bottles.

The data of yield was collected for the period June 2018 to May 2019 (12-month period). The data collection plan was for Fluxane product at storage tank F-SV-001 (refer to Table 4).

The following lots, shown in Table 2, were investigated as outliers and found to have an assignable cause associated with the low yield results obtained. Therefore, these lots were not included in the data analysis.

Table 2
Yield Results F-SV-001 from June 2018 to May 2019

Lot	Filling Date	Yield/ Lot	Investigation Results
F-19-002	26-Jan-2019	2.722	Impacted by Validation PQ for new filler machine. High incidence of rejects.
F-19-004	29-Jan-2019	2.728	High incidence of filling rejects; adjustments to filler machine were performed.
F-19-059	06-May-2019	2.702	High incidence of filling rejects; pressure of filler reservoir increased.
F-19-071	21-May-2019	2.636	Water content observed in the filler reservoir (383 bottles rejected).

Table 3

Stakeholder Analysis

Stakeholder Name/Group	Degree of Influence on Project (H/M/L)	Degree of Impact to Stakeholder (H/M/L)	Engaged Already? (Y/N)	Criticality to Project? (H/M/L)	Potential Barriers
Engineering/ Utilities Manager	H	H	N	H	Calibration verifications/ capital request lead times if any
Chemical Plant Field Operators	M	H	N	H	N/A
Chemical Plant Console Operators	M	M	N	M	N/A
Chemical Plant Mgr/Supervisors	H	L	N	M	N/A
Chemical Plant/ Packaging Line 1 Process Engineers	H	H	Y	H	Project vs. Day job priorities
Packaging Mgr/Supervisor	H	M	Y	H	N/A
Line 1 Packaging Operators	L	H	N	M	N/A
QC Lab	L	L	N	L	N/A
Finance	H	L	Y	H	N/A
General Manager	H	L	Y	H	N/A

Note: H= High, M=Medium, L=Low

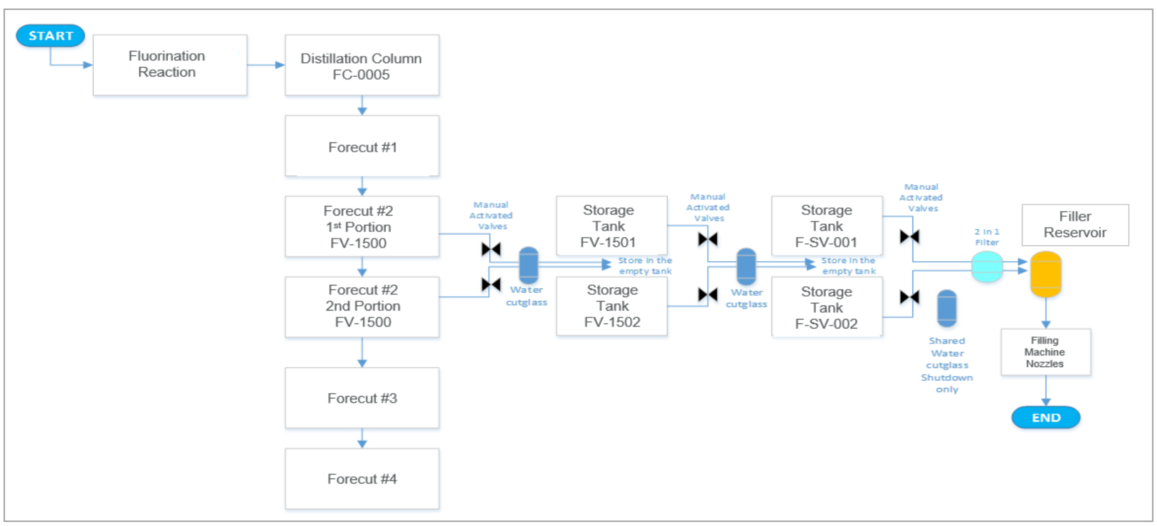

Figure 3

Process Map

Table 4
Yield Results F-SV-001 from June 2018 to May 2019

Month	Lot	Yield/Lot	Month	Lot	Yield/Lot	Month	Lot	Yield/Lot	Month	Lot	Yield/Lot
Jun-18	F-18-087	2.772	Sep-18	F-18-137	2.788	Nov-18	F-18-185	2.776	Mar-19	F-19-029	2.762
	F-18-089	2.780		F-18-139	2.784		F-18-187	2.788		F-19-031	2.774
	F-18-091	2.768		F-18-141	2.785		F-18-189	2.784		F-19-033	2.755
	F-18-093	2.783		F-18-143	2.783		F-18-191	2.781		F-19-035	2.752
	F-18-095	2.779		F-18-145	2.784	Dec-18	F-18-193	2.790		F-19-037	2.767
	F-18-097	2.782		F-18-146	2.797		F-18-195	2.784		F-19-039	2.765
	F-18-099	2.774		F-18-147	2.780		F-18-197	2.794		F-19-041	2.747
	F-18-101	2.788	Oct-18	F-18-149	2.773		F-18-199	2.783	Apr-19	F-19-043	2.765
	F-18-103	2.786		F-18-151	2.773		F-18-201	2.764		F-19-045	2.753
	F-18-105	2.785		F-18-153	2.780		F-18-203	2.792		F-19-047	2.778
Jul-18	F-18-107	2.782		F-18-155	2.791		F-18-205	2.784		F-19-049	2.777
	F-18-109	2.759		F-18-157	2.791	Jan-19	F-19-002	2.722		F-19-051	2.767
	F-18-111	2.778		F-18-159	2.790		F-19-004	2.728		F-19-054	2.773
	F-18-13	2.781		F-18-161	2.786	Feb-19	F-19-006	2.764		F-19-056	2.763
	F-18-115	2.744		F-18-163	2.787		F-19-008	2.756		F-19-057	2.766
	F-18-117	2.740		F-18-165	2.785		F-19-010	2.784	May-19	F-19-059	2.702
Aug-18	F-18-118	2.769		F-18-167	2.773		F-19-011	2.771		F-19-061	2.767
	F-18-120	2.767		F-18-169	2.787		F-19-013	2.771		F-19-063	2.742
	F-18-123	2.782		F-18-171	2.786		F-19-015	2.772		F-19-065	2.704
	F-18-125	2.788	Nov-18	F-18-173	2.777		F-19-017	2.770		F-19-067	2.772
	F-18-127	2.787		F-18-175	2.794		F-19-019	2.776		F-19-069	2.765
	F-18-129	2.791		F-18-177	2.774		F-19-021	2.785		F-19-071	2.636
	F-18-131	2.781		F-18-179	2.788	Mar-19	F-19-023	2.785		F-19-073	2.770
	F-18-133	2.789		F-18-181	2.772		F-19-025	2.765		F-19-075	2.777
Sep-18	F-18-135	2.782		F-18-183	2.777		F-19-027	2.769	**AVERAGE**		2.772

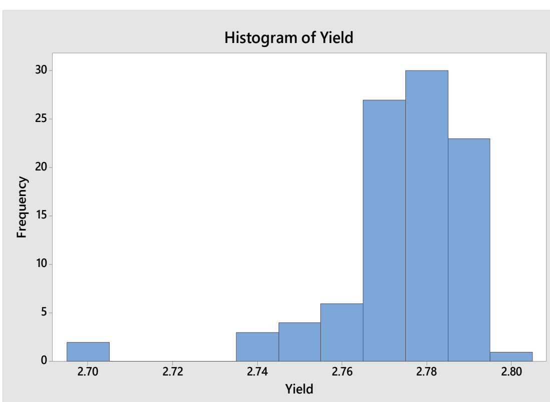

Figure 4
Histogram of Yield in Tank F-SV-001

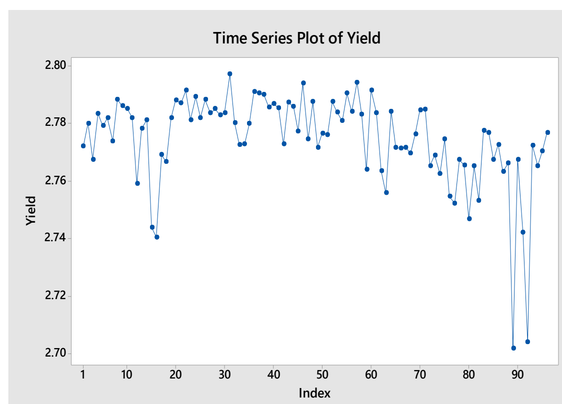

Figure 5
Time Series Plot of Yield in Tank F-SV-001

The 12-months yield data was analyzed using Minitab version 17 software. Figures 4 and 5 shows a histogram and time series plot, respectively. Based on Figure 4, the data does not follow a normal distribution (unimodal, left-skewed). The data suggests high variability and fluctuations in the yield results obtained from tank F-SV-001, as observed in Figure 5.

Analyze

A fishbone (root cause) analysis was performed to determine the direct and/or most probable cause of the low yield results obtained in tank F-SV-001 (Figure 6). The Five-Whys tool was used to evaluate the possible causes for the low yield in storage bulk tank F-SV-001 (refer to Tables 5, 6, and 7).

Table 5
Five-Whys for Machine Element

Problem Cause:	
Pressure variations have a direct impact to Net Weight therefore it impacts yield calculation	
Why	Tank pressure higher than set point.
Why	Filler Machine reservoir adjustment (machine pressure increments) increases Tank F-SV-001 pressure.
Why	Venting system not working efficiently at the established setpoint.
Why	Inadequate pumping system also adds bubbles increasing pressure buildup and product evaporation.
Why	The tank and release label reflect a net weight greater than actual, resulting in low yield actuals.

Table 6
Five-Whys for Method Element

Problem Cause:	
Calibration Classification impacts type of calibration & actions/ PMs required	
Why	The tank reflects a net weight greater than actual, reflected in low yield.
Why	Load cells error is cumulative.
Why	Load cells are not left at 0 error if as found within tolerance.
Why	Calibration classification of tank F-SV-001 is not critical.
Why	The equipment is not considered a critical quality attribute (CQA).

Table 7
Five-Whys for Human Element

Problem Cause:	
Reducing errors in yield reporting method will improve yield accuracy	
Why	Net weight included in the yield calculation is different than net weight use for bulk reconciliation.
Why	The yield reporting method for Line 1 is different from Line 2.
Why	Data is entered in Plan Attainment Excel sheet by different group leaders and/or backups (as applicable).
Why	Lack of instructions for yield calculation and data reporting method.
Why	No standard work in place; each person may report differently. No verification from a second person.

Temperature and pressure data in tank F-SV-001 was collected for each lot evaluated. Based on data analysis, a correlation was identified between yield and tank pressure in F-SV-001. An increase in tank pressure was observed for lots F-19-059 to F-19-075 (2.45 psiag to 4.50 psiag in average). Consequently, low yield results were obtained consistently, as shown in Figures 7 and 8. The pressure in tank F-SV-001 (3.12 psiag) was higher in comparison to tank F-SV-002 (2.72 psiag) for the period between March 2019 and May 2019.

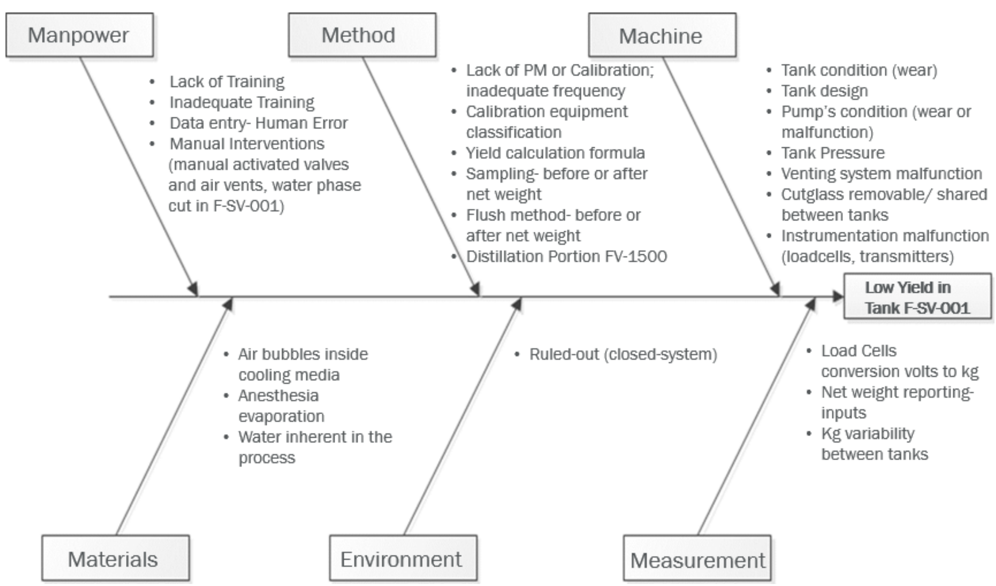

Figure 6
Fishbone Analysis for Low Yield in Tank F-SV-001

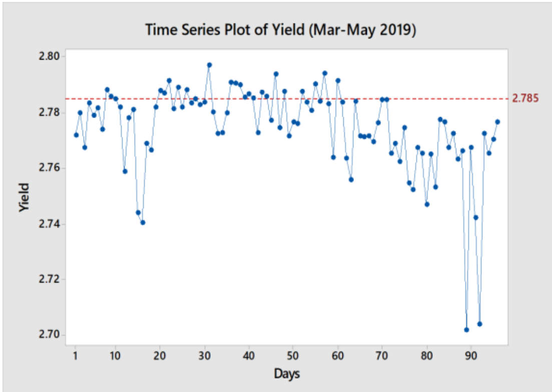

Figure 7
Time Series Plot of Yield (Mar-May 2019)

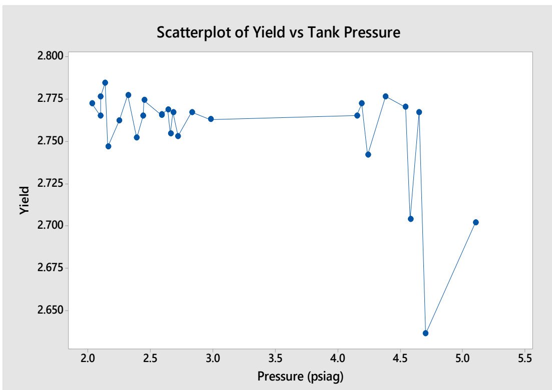

Figure 8
Scatterplot of Yield vs. Tank Pressure

The pressure venting valve of storage tank F-SV-001 was evaluated during manufacturing shutdown period. The valve was found damaged and consequently, it was not sealing properly causing product to evaporate. Since the net weight data used for yield calculation is obtained from the tank release label, product evaporation is not considered and results in a misleading yield result.

Improve

Based on the investigation results, the following corrective and preventive actions were identified. A new preventive maintenance (PM) record was issued to include in the job plan instructions to check pressure valves in tanks F-SV-001 and F-SV-002 in a six-month basis. The tank F-SV-001 was calibrated with satisfactory results. The calibration classification for the load cells of the tank were re-classified as a critical instrument to assure the error reading is left in zero after calibration. In addition, for a period of six months, the calibration frequency of the tank was increased to a monthly basis instead of three months for monitoring. As a preventive action, the tank pump was replaced from Wilden type to a Centrifuge type in order to improve product transfer from the storage tank to the filler machine reservoir. A permanent, dedicated cut-glass for water removal was installed in both tanks, F-SV-001 and F-SV-002. This action was intended to minimize the loss of product as a result of changing the cut-glass between storage tanks.

A standardized yield reporting method was developed in an electronic database to reduce data entry errors. A standard work was implemented, and training was provided to personnel.

Control

Product yield data was collected for Fluxane product, tank F-SV-001 for one (1) month after the implementation of the corrective and preventive actions. Table 8 summarizes the results obtained.

Based on the 1-month data review, yield was not met for bulk lot F-19-125 (yield= 2.724). However, an assignable cause was identified during the manufacturing of lot F-19-125. There was a high incidence of rejects (467 units) resulting from an equipment malfunction. The equipment was verified, and corrections/ corrective actions were implemented. Therefore, the result for lot F-19-125 is considered an outlier.

From a total of 15 bulk lots manufactured from storage vessel F-SV-001 during a 1-month period, the target yield of 2.785 was met for 14 lots (refer to Figure 9). The average yield result for the 14 lots (that is eliminating the outlier) was 2.788 (above target).

Table 8
Yield Results F-SV-001 from 19-Aug-2019 to 20-Sep-2019

Lot	Yield/Lot (Target: 2.785)
F-19-105	2.785
F-19-107	2.786
F-19-109	2.788
F-19-111	2.790

F-19-113	2.789
F-19-115	2.790
F-19-117	2.790
F-19-119	2.785
F-19-121	2.787
F-19-123	2.788
F-19-125	2.724
F-19-127	2.789
F-19-129	2.786
F-19-131	2.786
F-19-133	2.794
AVERAGE	2.784

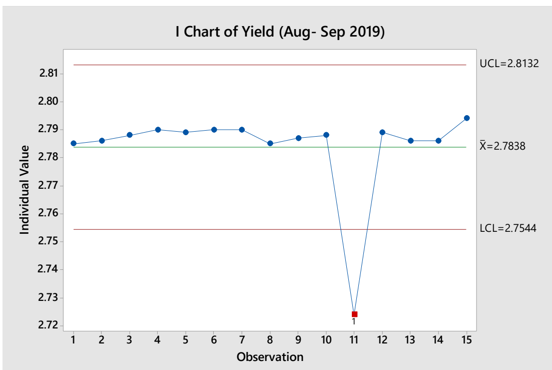

Figure 9
Control Chart of Yield (Aug-Sep 2019)

CONCLUSION

The objective of the project was to increase product yield in bulk drug product (BDP) storage tank F-SV-001 from 2.772 bottles/kg to approximately 2.785 bottles/kg or by 5,940 bottles equivalent to 85% annual increase by December 2019. Based on the data collected and investigation results, improvements on the equipment (tank F-SV-001) and yield calculation method were implemented. One-month yield data was monitored and evaluated after implementation of actions, and results demonstrated that the increase in product yield for BDP tank F-SV-001 was achieved. The bulk lots monitored resulted in a yield equal to or greater than 2.785 (target). Also, a reduction in data variability was observed. The increase in product yield results in a financial benefit of approximately $207,900 by the end of the year.

It is recommended to continue the monitoring of process yield up to December 2019. Also, the impact of multiple lot presentations for a bulk in yield results should be investigated in order to identify opportunities that will assure a product yield within or above target.

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