Process Optimization of Amine Reactions

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Abstract *– Ospira is an inhalation anesthesia manufacturing facility. The main products are Deramine and Dexoflurane. To produce these anesthetics, chemical reactions and distillation processes are required. For Deramine it is necessary to do an Amine Reaction. The importance of this study is to avoid the loss of product during the reaction process. When the product does not recover, it affects the efficiency of the reaction and the company performance. The study goes to the effort in the progress for the manufacture of Deramine. The reaction process must be improved to obtain a better percentage of recovery and avoid product losses. Some customers could benefit if the process is improved, the company in general has a direct impact because it will have a positive cash flow and will not lose. Increasing 2% of the amine recovery percentage will represent a reduction of approximately $20,000 per month. In order to reduce the process variability, to align customer's expectations, and to provide high financial returns; a Six sigma methodology is appropriate. DMAIC (define-measure-analyze-improve-control) has been widely used as the method for six sigma implementations in manufacturing processes.*

Key Terms *— DMAIC, Financial Performance, Reactions, Recovery Percent, Yield.*

PROJECT STATEMENT

Ospira is an inhalation anesthesia manufacturing facility. The main products are Deramine and Dexoflurane. To produce these anesthetics, chemical reactions and distillation processes are required. For Deramine it is necessary to do an Amine Reaction.

The percent recovery and yield percent are directly related to the chemical reactions and its involved efficiency. Percent recovery computes the percentage of an original substance that is recovered after a chemical reaction is completed. These mainly include purification reactions. It also determines their efficiency. All the time, the Amine Reaction process has showed a low percent recovery, obtaining financial losses and affecting the yield percent. Actual recovery percent is 88% and the expected value is 90%.

RESEARCH DESCRIPTION

The importance of this study is to avoid loss of product during the reaction process. When the product is not recovered, it affects the reaction efficiency and the financial and manufacturing metrics. Therefore, this development goes to effort on the progress of Deramine. The reaction process shall be improved to obtain better percent recovery and avoid the product losses.

RESEARCH OBJECTIVES

The objectives for this project will be addressed to:

- Increase the Deramine yield by 2%.
- Increase the recovery of reactions from 88% to 90% to reduce the losses.
- Increase the financial performance of the plant.

RESEARCH CONTRIBUTIONS

The main contribution of this study is to improve the actual process, making it efficient. Some clients could benefit if the process is improved, the company in overall has a direct impact because it will have a positive cash flow and they will not lose money. Increasing 2% of the recovery will represent a reduction of approximately $ 20K per month. Manufacturing Department also will have a positive contribution since improving the process will reach the target of the recovery, complying the customer needs

LITERATURE REVIEW

A chemical reaction is defined as the process, wherein a set of chemical substances react with each other, which leads to their conversion into other different forms. The initial substances used the reaction are collectively called reactants, while the final substances formed after the reaction are known products. In order to determine the efficiency of the process is performed a yield and recovery percent calculation. A percent recovery computes the percentage of an original substance that is recovered after a chemical reaction is completed. Amine Process is an endothermic reaction, which means that absorbs heat from its environment. The product (Demerine) is very volatile and the organic vapors are carrying through a vents condenser system. The formula for Recovery Percent is:

- Recovery Percent = Amount product recovered (kg) amount of crude material used (kg) x 100

The purpose of the Amine Process is to create an inhalant anesthesia called Demerine. Amine Reaction Process has several steps such as reaction, cooking time, condensation, product transfer and neutralization. These steps are fundamental during the manufacturing process. The product loss per each reaction is continuous, in cases exponential. The temperatures, product transfer, condensation, equipment malfunction can affect the low recovery and its represents a negative cash flow for the company and make an inefficient reaction process.

On the other hand, the key business factors for the plant are cost, quality, customer requirements, regulatory compliance, development and participation of personnel. Adherence to the goals set by the key factors is measured through a series of indicators, which are monitored and evaluated on a continuous basis. Puerto Rico is the sole provider for the Demerine worldwide anesthesia market of this product through our distribution centers, international affiliates & Ospira Sales in Puerto Rico. Ospira has remained competitive through the years of being cost effective, providing high quality products and timely deliveries. We have accomplished this by continuously improving our processes and with the active implementation of highly automated control systems.

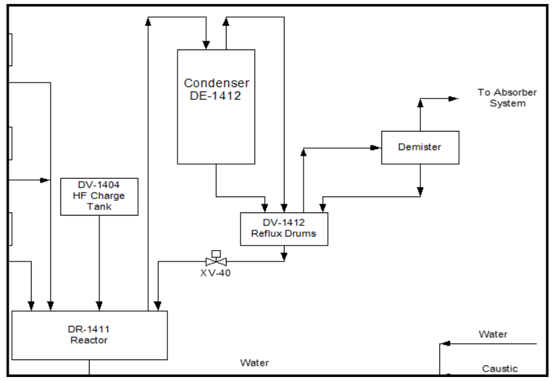


Figure 1
Amine Reaction Process

METHODOLOGY

DMAIC process is a core component of the Six Sigma Methodology. It is used when making improvements to an existing process. DMAIC is an acronym for the 5 key powerful phases: Define, Measure, Analyze, Improve and Control. DMAIC is a Six Sigma methodology which helps in achieving process improvements by reducing variation. Each step in the cyclical DMAIC Process is required to ensure the best possible results.

First one, Define phase has the purpose of the articulate the business problem, goal, potential resources, project scope and high-level project timeline. The information will be captured within project charter document [1] [2].

In the measure phase is to objectively establish current baselines as the basis for improvement. The main objective is to collect data pertinent to the scope of the project. The components of this phase will include creating a process map, collecting baseline data, conducting data analysis, and calculating baseline process sigma with the other steps in the process, the only way to ensure success is to do it systematically; with careful planning. For this reason, a data collection plan is usually the first step in the data collection process. The collection will address to the temperatures, pressure, cooling system, product transfer, and addition rate. All variables (pressure, temperatures, flow rate) are retractable of Delta V Control System [1] [2].

Analyze phase will reveal the root cause of business inefficiencies exposes areas where the implementation of change can provide the most effective results [1] [2].

Then, Improve phase will be completed to create a test run with the change performed. Improvements are ongoing and include feedback analysis and stakeholder participation [1] [2]. As per statistical analysis, the process needs improve because the 88% represents a loss of $400K per year or $38K per month.

Control phase is the last stage of the methodology and is to develop metrics that help monitor and document continued success. Therefore, using Lean Six Sigma tools and methodologies this process can be improved by reducing variations and generate a positive cash flow or complying with the budget established [1].

Results and Discussion

This phase shows the findings of this research using the DMAIC tool.

Define Phase

The percent recovery and yield percent are directly related to the chemical reactions and its involved efficiency. Every year, the Amine Reaction process has showed a low percent recovery, obtaining financial losses and affecting the yield percent. Actual recovery percent is 88%. The reaction process shall be improved to obtain better percent recovery and to avoid the product losses. The objectives for this project will be addressed to assure that the process is able to comply with the standard yield. Increasing the recovery of reactions from 88% to 90% the financial performance of the plant will increase also. Manufacturing Department also will have a positive contribution since improving the process will reach the target of the recovery, complying the customer needs. The following analysis represents the current values of the process.

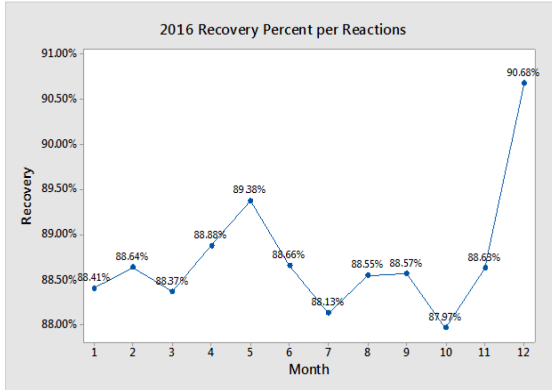


Figure 2
Recovery Percent

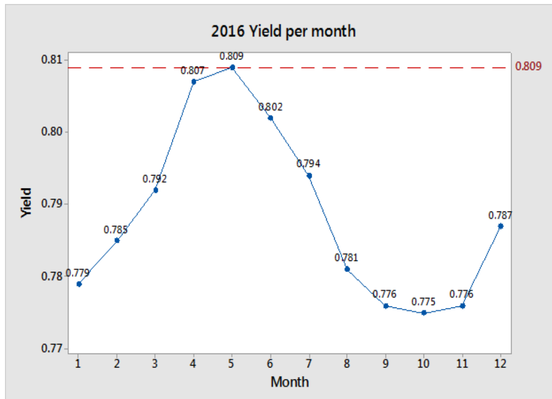


Figure 3
Amine Yield

Analysis represents the Amine Yield per month. Amine yield is correlated to recovery percent since if the recovery percent decreases, the yield will decrease. Amine yield meets the standard (0.809) only one month (May). The remaining months does not comply the standard yield.

When the recovery percentage is approximately 88%, the average in losses are -$38,285 per month. During the year, each month had a negative variance and this fact affects the performance of the plant.

Measure Phase

The main objective is to collect data pertinent to the scope of the project. The components of this phase will include creating a process map, collecting baseline data, conducting data analysis, the only way to ensure success is to do it systematically; with careful planning. The collection will address to the temperatures, pressure, cooling system, product transfer and addition rate. The measure will be address to those reactions with more recovery vs reactions with less recovery. The comparison will show the good reactions (high recovery) vs bad reactions (lowest recovery).

The data collected for the process were temperature, pressure, cooling through condensers, raw material addition among others. The data was collected for both reactors where anesthesia is made. The measure was performed taking points of temperature, pressure, cooling flow, addition rate, among others each 30 minutes.

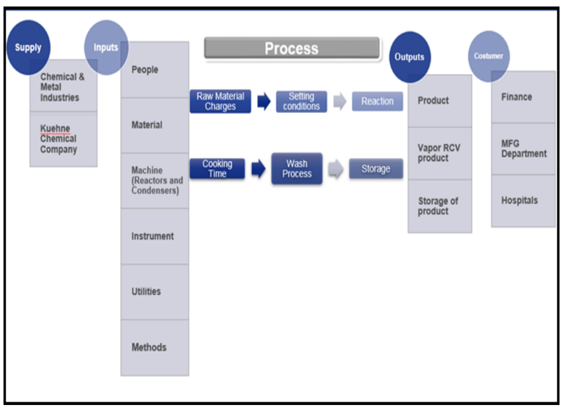


Figure 4

SIPOC Diagram

On the other hand, a SIPOC diagram was used to identify all relevant elements of a process improvement project before work begins. It helps define a complex project that may not be well scoped.

Process Map involved is the Supply to made the anesthesia, Operators (people), Material (purity of compound), Reactors and condensers (Machine), temperatures, pressure (Instrumentation), Cooling (Utilities) and Gas Chromatography Analysis (Methods). The main steps of the process (setting conditions, reaction time, cooking time). The Amine product is the output, while Finance and Manufacturing are the costumers.

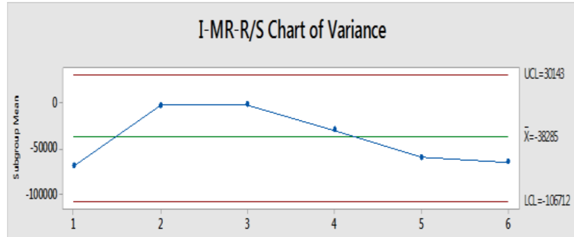


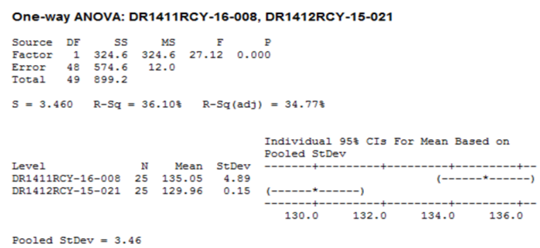
Figure 5

I-MR Chart Diagram

The data collected of total losses of the process was plotted using an I-MR Range chart. The average in losses are -$38,285 per month. Even though, UCL was $30,143 and the LCL was -$106,712.

Analyze Phase

Analyze phase will reveal the root cause of business inefficiencies exposes areas where the implementation of change can provide the most effective results. One way ANOVA was used to observe the difference (visually) of the pressure, temperatures, and cooling flow rate during the reaction period.



```
One-way ANOVA: DR1411RCY-16-008, DR1412RCY-15-021

Source  DF     SS     MS      F      P
Factor   1  324.6  324.6  27.12  0.000
Error   48  574.6   12.0
Total   49  899.2

S = 3.460   R-Sq = 36.10%   R-Sq(adj) = 34.77%

                                   Individual 95% CIs For Mean Based on
                                   Pooled StDev
Level              N    Mean  StDev  -------+---------+---------+---------+--
DR1411RCY-16-008  25  135.05   4.89                          (------*------)
DR1412RCY-15-021  25  129.96   0.15  (------*------)
                                     -------+---------+---------+---------+--
                                          130.0     132.0     134.0     136.0

Pooled StDev = 3.46
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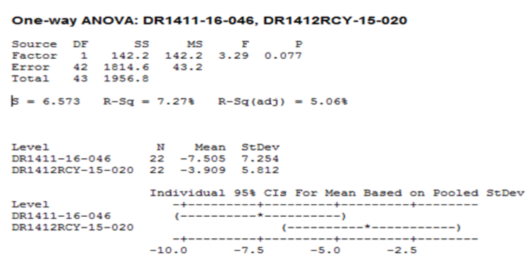
Figure 6

Comparing Cooling Flow Rate (gpm)



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One-way ANOVA: DR1411-16-046, DR1412RCY-15-020

Source  DF      SS     MS     F      P
Factor   1   142.2  142.2  3.29  0.077
Error   42  1814.6   43.2
Total   43  1956.8

S = 6.573   R-Sq = 7.27%   R-Sq(adj) = 5.06%


Level              N    Mean  StDev
DR1411-16-046     22  -7.505  7.254
DR1412RCY-15-020  22  -3.909  5.812

                  Individual 95% CIs For Mean Based on Pooled StDev
Level               -+---------+---------+---------+--------
DR1411-16-046       (----------*----------)
DR1412RCY-15-020                 (----------*-----------)
                    -+---------+---------+---------+--------
                  -10.0      -7.5      -5.0      -2.5

Pooled StDev = 6.573
```

Figure 7

Comparing Condensed Organic Temperature

As mentioned earlier, the analysis was conducted to compare the reactions resulted with high recovery versus batches with lowest recovery. Figure 6 and 7 showed that the reactions with high recovery had more cooling flow rate (cold oil in gpm) and the condensed organic temperature was more cold.

```
One-way ANOVA: DR1411-16-022, DR1414-15-014

Source  DF      SS     MS     F      P
Factor   1   0.802  0.802  2.46  0.122
Error   56  18.238  0.326
Total   57  19.040

S = 0.5707   R-Sq = 4.21%   R-Sq(adj) = 2.50%


Level           N    Mean   StDev
DR1411-16-022  29  4.4145  0.4814
DR1414-15-014  29  4.6497  0.6478

               Individual 95% CIs For Mean Based on Pooled StDev
Level           +---------+---------+---------+---------
DR1411-16-022   (----------*---------)
DR1414-15-014               (---------*----------)
                +---------+---------+---------+---------
               4.20      4.40      4.60      4.80

Pooled StDev = 0.5707
```

Figure 8
Comparing Pressure

After measuring the data for the reaction process for a period of 2 months, the goal in the analyze phase is to identify the possible root causes of low recovery and yield that can affect the performance of reactions. The analysis showed the following:

Reactions with High Recovery

- There are no pressure problems.
- Condensed organic temperature is low.
- Cooling Media was consistent (135 gpm).

Reactions with Low Recovery

- Pressure variations.
- Condensed organic temperature is almost positive (there was no sufficient condensed organic).
- Cooling Media less than 135 gpm.

As presented on the measure phase, the pressure of the system, cooling through condenser and the condensed organic temperature have been showed more variation. However, comparing the temperature in reactors were behaved similarly. Reactions with more efficiency has demonstrated that with more cooling through the condenser the recovery increases. During Amine reaction process it is required to maintain good cooling media because the boiling point of Amine is 23.5 C; possibly means that the product is losing during reaction or cooking time, affecting the low recovery.

Also, reactions with high recovery showed low temperatures of condensed organic because the material was recovered through condenser. The cooling for the system is Cold Oil and it is provided at -32 C. Manufacturing process have a process to recover the organic vapors (Amine vapors) but it is required enough cooling and more capacity of the condensers. Therefore, based on the data gathered and the investigation performed; the most probable cause is Equipment and Utilities.

Improve Phase

The objective in the improvement phase is to bring proposed solutions and implement them to solve each problem.

a. As present condensers behaviors, we need approximate 125% more area in order to cool everything (peak gas solution rate). Condenser with more area and cooling will increase the recovery since the organic vapors will not loss.
b. If instead of -32 C Cold Oil Supply temperature is -37 C, these 5 C of change in cold oil temperature affects positively the condensers performance. The temperatures of condensed organic temperature can reach -3 to -14 C.
c. Reevaluate the cooling set point (135 gpm) of condensers. If we have more flow of cold oil, the organic vapors can be converted to liquid easily. See diagram below.
d. Perform a pressure test through all system to assure the integrity of the lines and equipment.

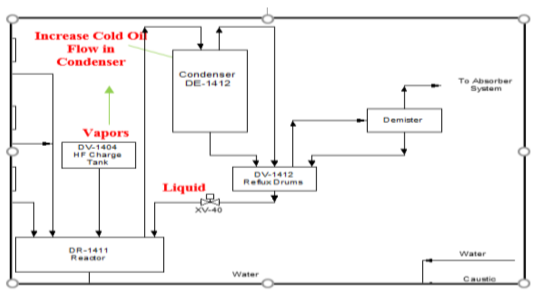

Figure 9
Condenser Diagram

After modifications in the Amine Reaction Process, the yield has increased from 0.788 (annual average) to 0.806. Using the baseline 0.809 for the yield, the percent increased by 3%. Although, the value of 0.809 could not be reached consecutively. To reach the target of 0.809

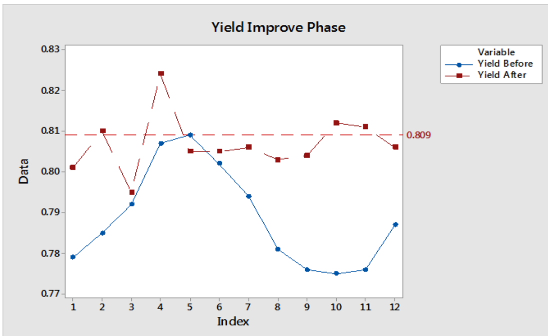

Figure 10
Yield Increased

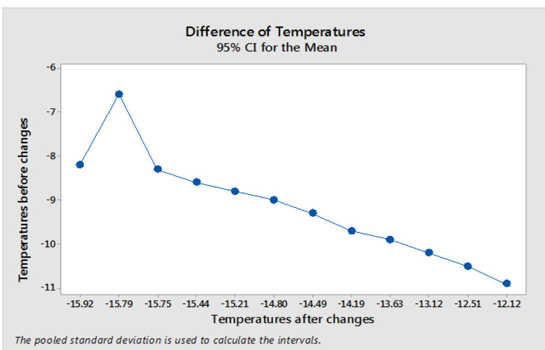

Figure 11
Difference of Temperatures

As observed above, the effect of decreasing the temperature of the cold oil supply is cooler through the condensers. The lowest temperature after the change was -15.92 °C, while the lowest temperature before the change was -11 °C. In addition, the cooling flow medium was increased from 135 to 185 gpm. If the cooling temperature is low and the oil flow is higher, organic vapors can be converted into liquid more effectively.

As shown in the figure 12, the Amine Recovery Percent is around 90% and there no significant variances comparing with last performance mentioned in Define phase. Otherwise, as limitations the replacement of Condensers could not be performed since the replacement cost are expensive. The improvement in the condensers will maintain the organic vapors in the reaction loop.

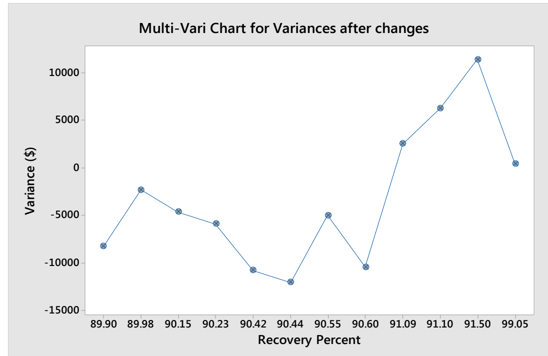

Figure 12
Multi-Vari Chart for Variance and Recovery Percent after Changes

Control Phase

The last phase of Six Sigma's DMAIC model is the Control phase. The focus of this stage is to make sure that the action item created in the Improve phase is well-implemented and maintained. Several tools were used in this stage to make sure that variables are within its limits. One key to achieve continuous improvement is to standardize the process. In order to accomplish this, work instructions tools were implemented:

- Manufacturing Batch Records were revised to include new setpoint of Cold Oil flow by 185 gpm instead of 135 gpm.
- Utilities Department fixed the Cold Oil temperature by -37 C.
- Everyone involved in the process received proper training and that effective communication occurred.
- Process monitoring is important to identify opportunities for continuous improvement, to confirm the new process, and measure achievement.
- A total of 30 Reaction lots were monitored after new process implementation. The I-MR chart below shows that average in variances is $-3205, with this result the process has been recovered $35,080 per month. See the graph below.

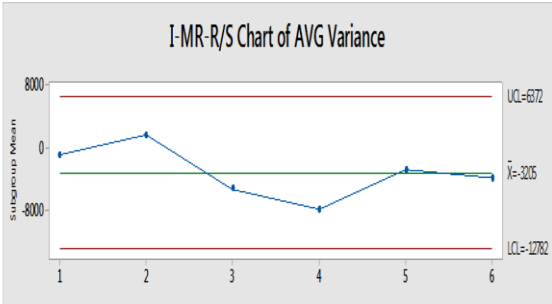

Figure 13
I-MR Chart for the Variance Average ($)

Conclusion

Six Sigma looks at all work as a series of processes with inherent variations, which can cause inefficiency. Focusing in our processes with greatest impact on business performance, the methodology involves statistical analysis to quantify repeated common cause variations, which can then be reduced by the Six Sigma team. Six Sigma becomes a continuous process for process improvement and cost reduction flowing throughout the company.

According to the data collected, the Amine process was able to increase the recovery percentage by 2% and the Deramine yield by 3%. These factors have a greater impact in financial terms. At the end of the project, all the objectives were achieved, exceeding the loss reduction by $ 35K per month and the performance by 1% of the established target. The yield of Deramine could not be constant in its objective (0.809), but this value was reached in 3 times. As mentioned in the previous phase, the replacement of Condensers could not be installed because it is expensive. It is necessary to have a 125% more area to cool everything (maximum rate of gas solution) to increase the yield constantly.

The major contribution of this study was the optimization of Amine process, making it efficient. Manufacturing Department has a positive contribution since the targets have been met successfully. Thus, a DMAIC developed the capability of reducing problems or issues effecting customer expectations on key business processes.

Acknowledgments

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