Optimize Batch Transfer between Processing Tanks

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Abstract *— Estimates indicate that Diabetes will increase affecting the population worldwide in the future. To mitigate current and future demand, Barceloneta's Factory 2 needs to improve the MK-0431 manufacturing process. Several stages in the manufacturing process have been identified for improvement. This project focuses in the optimization of the batch transfer between vessels. Six Sigma tools and methodologies (Define, Measure, Analyze, Improve and Control) were utilized to identify the problem and improve the process. As a result we were able to optimize the batch transfer process, reducing the cycle time of the vessel and helping the MK-0431's train ability to increase its manufacturing capacity.*

Key Terms *— Cycle Time, DMAIC, Prioritization Matrix, Process Baseline.*

INTRODUCTION

Did you know that 8.3% of the population in the United States has diabetes? This is roughly 25.8 million patients that struggle with this condition everyday and these numbers continue to increase every year. Diabetes is a chronic disease where the body cannot process glucose correctly due to an irregularity in insulin supply. Medical researchers have discovered two types of Diabetes categorized as Type 1 and Type 2. Type 1 Diabetes is when the body does not produce any insulin and Type 2 Diabetes is when the body does not produce enough insulin or utilizes it correctly.

Global demand for diabetes medication has increased exponentially in the past few years. Due to this factor MK-0431 has incremented its production to not only meet this demand but to optimize its' process for any increase in future demand. Factory 2 located in Barceloneta, PR manufactures Sitagliptin Phosphate Crude and Pure, the active ingredient for Januvia and Janumet which treats Type 2 Diabetes. The MK-0431 Sitagliptin Phosphate process was mapped and verified to help improve the manufacturing process cycle time to meet consumer's demand.

MK-0431's current process cycle time was 28hrs. During the initial process analysis it was noticed inconsistent batch transfer times between VR-227 and TA-291. During ideal batch transfers the measured transfer time was four and a half hours without any visible incident. On other occasions the batch transfer seems to be more problematic requiring replacing filters located between the vessels several times within the same batch. Ultimately this contributed to longer transfer times.

Define

To help improve production and supply consumer's demand for Sitagliptin Phosphate, Barceloneta's Factory 2 management asked to improve the batch's transfer time between VR-227 and TA-291. Some of the project parameters were that any process improvement should keep a safe production and keep utilizing current good manufacturing practices. They also required that any process improvement should be long term and not revert back into its original way. The batch's yield and quality should not be affected and it shouldn't add any additional cost into the process.

The MK-0431 Sitagliptin Phosphate Crude process is divided into 6 process stages. The first stage in the process is creating an Enamine Amide slurry mixture in a solvent. It is then passed into the second stage which involves the hydrogenation of the batch for 12 to 14 hours. After the batch is hydrogenated the batch is transferred to the third stage which is the carbon treatment and filtration. Carbon is mixed into the batch to remove the catalyst. The batch is then filtered through a Shenk filter which will recover all of the carbon in its filtering plates before it is transferred to the fourth stage. The fourth stage consists in concentrating the batch to a predetermined volume. In the fifth stage the batch goes through a solvent switch and crystallization process with the final stage involving isolating and drying the batch.

Figure 1 displays MK-0431 High Level Process Map. The 6 stages are:

- Stage 1: Enamine Amide slurry – EX-520
- Stage 2: Hidrogenation – ST-750
- Stage 3: Carbon Treatment/Filtration – VR-227/PF-580
- Stage 4: Concentration – TA-291
- Stage 5: Solvent Switch/Crystallization – ST-21/ST-511
- Stage 6: Isolation/Drying – ST-440/PF-45

If you are using Word, set the margin widths and paper size by selecting the “File” menu and select “Page Setup”. Select the above options and make sure you also apply to “Whole document”. To format the columns select “Column” from “Format” Menu. See Figure 1 below.

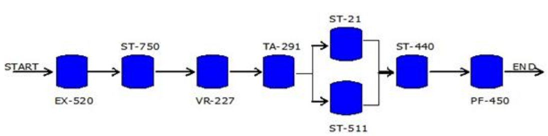

Figure 1
MK-0431 High Level Process Map

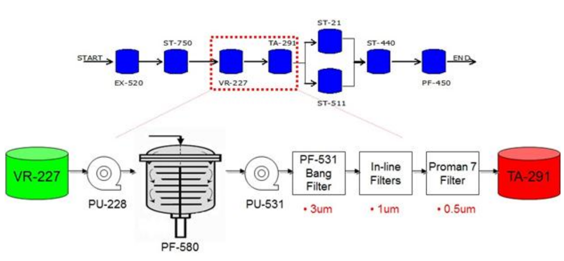

Figure 2
Format Columns Menu

Figure 2 displays the equipment located between VR-227 and TA-291 which is the equipment that is used in the process. The batch is treated with carbon in VR-227 after completing the hydrogenation stage in ST-750. The batch is then filtered through different compartments of the Shenk filter (PF-580) for a minimum of 3 hours. The upper section of the Shenk filter is known as the “Filtrate” compartment, the bottom section is known as the “Scavenger” compartment and when both compartments are used simultaneously it is known as the “Transfer” compartment. A sample is collected to measure the remaining carbon content in the batch after being recycled through PF-580 for 3 hours. Before the batch is transferred to the fourth stage in TA-291 the collected sample needs to be within a Disc range of 1 to 10 to be an acceptable result. Once the batch is being transferred it has to go through the PF-580, a 3 um bag filter, a 1 um line filter and a 0.5 line filter before reaching TA-291. The line located between VR-227 and PF-580 used to recycle the batch is blown with nitrogen for 20 minutes. Afterwards the different compartments in PF-580 are blown with nitrogen. The nitrogen blow through the “Filtrate” compartment is for 60 minutes. The nitrogen blow through the “Scavenger” and “Transfer” compartment is for 20 minutes each. A solvent flush is then charged into VR-227 and transferred to TA-291. The nitrogen blow sequence through PF-580 is repeated after transferring the flush.

Problem Statement

Inconsistent transfer times prevent TA-291 to reduce its process cycle time. On occasions after receiving an acceptable Disc result, the 3 um bag filter and the first 1um inline filter would clog with carbon while transferring the batch. On other occasions the batch would transfer from VR-227 to TA-291 without any incident. The Disc sample result was compared between batches where the filter clogged with carbon and batches without any incident. There was no correlation found due to the Disc sample result, on occasions a batch that received a Disc result of 1 would clog the filters while other occasions a batch with a Disc result of 1 would transfer without any incident.

For this project we simply focused on the batch transfer process between third and fourth stage of the MK-0431 process. No focus was placed to the process in VR-227 or TA-291.

Baseline

After defining the problem we created what is known in Six Sigma as a baseline. The baseline is a value that indicates how the process is currently performing. The baseline for this project was calculated using 29 previous batch transfers between VR-227 and TA-291. The baseline included the batch and flush transfers as well as both nitrogen blow sequences through the different compartments in PF-580. While creating this baseline we also documented the Disc sample result for each batch. This information would allow us to notice if the remaining carbon content in the batch has any effect on the transfer time. The resulting average transfer time for the 29 batches was 6.33 hours. Figure 3 displays the summary for the 29 batch transfer times.

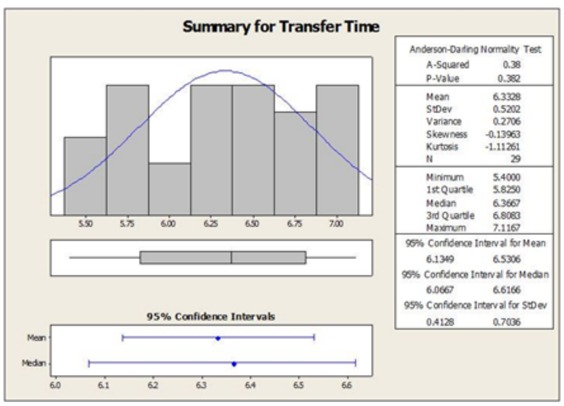

Figure 3

Summary of the Batch Transfers Used to Create the Baseline

This information can be further stratified into the different process steps in the batch transfer. On average, transferring only the batch from VR-227 to TA-291 would take 1.95 hours. The nitrogen blow through the recycle line between VR-227 and PF-580 takes 0.35 hours on average. The first nitrogen blow through all of PF-580's compartments took an average of 1.78 hours while VR-227's flush transfer took 0.56 hours. The second and final nitrogen blow sequence through PF-580's compartments averaged to 1.8 hours. Figure 4 displays the stratified process times in a value stream map. [4]

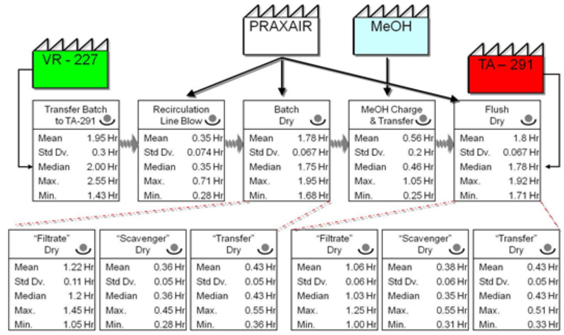

Figure 4

Value Stream Map of Stratified Batch Transfer Stages

A Gauge R&R study was completed to verify the accuracy and integrity of the data. The Gauge R&R tests the data for repeatability and reproducibility. It makes sure that any variability in the data is from the actual process and not from the person recording the data or from the measuring tool system. The Gauge R&R results proved a measurement system accuracy of 92%. With an error smaller than 10% allowed us to deduce that any variation in the measured data was from the actual process and not due to the measurement system or the personnel. [1]

At the same time the baseline was generated, the actual process was observed in the production floor for a total of 6 batches. A data collection plan was generated to help identify, measure and record different variables that could help identify problems in the process. One of the variables was the total time the batch in VR-227 was recycled through the Shenk filter (PF-580). Another recorded variable was the result of the Disc sample that measures the carbon content in the batch (431-CRD-7). Once the transferring process started, we measured are recorded the amount of time it took to transfer the batch as well as the amount of time it took to clog the filters with carbon. The two final variables in the data collection plan were the number of times the filters needed to be replaced as well as the final volume received in TA-291 after the transferring process was completed. Table 1 displays the Data Collection Plan.

There are two other factors dealing with personnel behavior that were observed during the 6 batch transfer. The first behavior was what the operator did if TA-291 wouldn't be available to receive the batch after VR-227 completed all of its processes. On most occasions this was due to the fact that TA-291 was not done concentrating the previous batch to its predetermined volume.

Table 1
Data Collection Plan

Measure (Output)	Operation Definition	Where will the data be obtained?	How will the data be collected?	Who collects the data?	When will the data be collected?
VR-227 Batch Recirculation Time	The total time the batch was recirculating through the PF-580.	VR-227's Recirculation Time was measured using the PI system database.	Data Collection Form	Agustín Felipe	Historical Data from January 2011 to February 2011
431-CRD-7 Laboratory Results	Laboratory disk results for the remaining carbon in the solution after the 3Hr recirculation is complete.	Results are provided by the laboratory in an Excel form	Excel Computer Format	Laboratory Technicians	Historical Data from January 2011 to February 2011
VR-227 Lot Transfer Time	Total time it took to transfer the batch, the flush and both blow dry sequences.	The time stamps were obtained from the Batch Sheet records.	Time calculations from the Transfer Time database file.	Agustín Felipe	Historical Data from November 2010 to December 2010.
Transferring Stops	# of times the batch transfer was stopped to change any filter.	Will be obtained from PI historical data	Observable interruptions while transferring the batch	Agustín Felipe	Historical Data from January 2011 to February 2011
Filter Clog Time	The amount of time it took for the filter to clog above 75 psi of differential pressure.	The data will be observed while transferring the batch to TA-291	Data Collection Form	Agustín Felipe	Data from Pilot Trial on April 2011
TA-291 Final Batch Volume	TA-291's Batch volume after VR-227's transfer and blow dry sequences.	TA-291's volume was obtained from the PI system database.	TA-291's tank level value after VR-227's transfer procedure.	Agustín Felipe	Historical Data from January 2011 to February 2011.

Another factor that was observed in the production floor during the batch transfers was the amount of fluids out of PF-580 during the nitrogen blow through its different compartments.

Analyze

An important finding was made during the 6 batch transfers observed in the production floor. It was discovered that the manufacturing process wasn't standardized and that it needed more detailed instructions. The current batch sheet instructions informed operators on what they need to do to transfer the batch from VR-227 to TA-291. The batch sheet does not provide instructions on what the operator should do if TA-291 isn't available to receive the batch. Since there was a lack of instructions, every operator ends up doing what they think is correct. On several occasions some operators kept recirculating the batch in VR-227 through PF-580 until TA-291 became available. Other operators stopped recirculating the batch through PF-580 and cleared the recirculation line between VR-227 and PF-580 with nitrogen. On the last case, operators would simply stop recirculating the batch in VR-227 but kept the recirculation line between VR-227 and PF-580 full of fluids. The same lack in process standardization occurred whenever TA-291 became available to receive the batch. Some operators would start transferring the batch from VR-227 to TA-291. Other operators would recycle the batch in VR-227 through PF-580 for 30 minutes before they began the transfer process. This operation is important because whenever the batch transfer process is started it creates a small disturbance in the carbon collected in PF-580. According to the level of the carbon disturbance in PF-580, it would clog the filters located between the vessels once or several times during the batch transfer.

The other observation made during the 6 batch transfer was when fluids flowing out of each of the Shenk filter's compartments during the nitrogen blows. It was noticed that fluids stopped flowing out of PF-580 long before the nitrogen blow was completed. This process was design and implemented in the production floor but it was never challenged to see if it could be optimized.

The next step of the project was to do a brainstorming exercise to come up with possible ideas to improve the process [5]. These ideas were placed in a prioritization matrix were their benefit would be evaluated against their effort and risk of implementation. Some of the brainstorming ideas were such as; bypassing the Shenk filter once the carbon sample result in VR-227 was in range. Another suggestion was the addition of line filters in the transfer line between VR-227 and TA-291 to increase the surface area between the vessels.[3] After prioritizing all of the possible solutions and analyzing their benefit versus effort and risk, we came up with four possible solutions. Table 2 displays the Prioritization Matrix with the selected ideas for implementation displayed in green.

The ideas that were selected for implementation were; standardizing the batch transfer instructions if TA-291 isn't available to receive the batch. We will also standardize the process steps to start transferring the batch once TA-291 becomes available. The other ideas that were selected for implementation were reducing the nitrogen blow times through each of the PF-580's compartments. Finally, it was decided to place a chart in the production floor to act as a remainder to the operators. With the process standardization, whenever VR-227 is ready to transfer the batch but TA-291 isn't available, the operator would communicate with their supervisor to estimate how long it would take for TA-291 to finish its process. If TA-291's process would take less than 1 hour to complete, then the operator would continue to recirculate the batch in VR-227 through PF-580 until TA-291 became available. If the supervisor indicated that TA-291's process would take more than 1 hour, then the operator would follow the instruction to send the entire batch back to VR-227 and blow the recirculating line with nitrogen. Once TA-291 becomes available, they would recirculate the batch through PF-580 for a minimum of 15 minutes before starting to transfer it to TA-291. Another brainstorm idea that would be implemented was to reduce the nitrogen blow times through the different compartments of PF-580. The original nitrogen blow times were blowing for 60 minutes through the "Filtrate" compartment, blowing for 20 minutes through the "Scavenger" compartment and blowing for 20 minutes through the "Transfer" compartment would be reduced to 45 minutes, 15 minutes and 5 minutes respectively. The risk of reducing the nitrogen blow times was that there was a possibility of not completely emptying each compartment of the Shenk filter. To implement this idea we needed to make sure that the batch's yield and quality wouldn't be impacted. For this reason we ran a 3 batch pilot trial with the new nitrogen blow times.

Table 2
Prioritization Matrix of the Brainstormed Ideas

Improvements Ideas to Optimize Transfer Time from VR-227 to TA-291.							
Cause	**Idea**	**Requirements**	**Benefit**	**Risk**	**Impact**	**Effort**	**Priority**
X_1	Transferir lote del VR-227 al TA-291 sin pasar por PF-580 mientras se sopla el PF-580 hacia el VR-227 en paralelo.	1. Tomar muestra de disco a la entrada del PF-580. (Existe Sampling Port) Comparar contra la de la salida para demostrar efectividad del Schenk luego del recirculado. 2. Cambiar parámetros de la lógica. 3. Se necesitan válvulas automáticas en PROMAN.	1.75 hr	Los polishing filter se pueden tapar más frecuentemente porque el contenido de carbón en el VR-227 puede ser mayor al del PF-580.	High	High	Low
X_1	Tomar muestra a la entrada y salida del schenck y cuando los resultados sean iguales transferir hacia el TA-291. Soplar en paralelo del PF-580 hacia el VR-227 mientras se transfiere el lote al TA-291.	1. Tomar muestra de disco a la entrada del PF-580. (Existe Sampling Port) Comparar contra la de la salida para demostrar efectividad del Schenk luego del recirculado. 2. Cambiar parámetros de la lógica. 3. Se necesitan válvulas automáticas en PROMAN.	1.75 hr	Los polishing filter se pueden tapar más frecuentemente porque el contenido de carbón en el VR-227 puede ser mayor al del PF-580.	High	High	Low
X_1	Duplicar filtros aumentando área de transferencia en la línea de transferencia hacia el TA-291 (1 & 0.5 μ).	1. Posible Proyecto Capital. 2. Diseñar experimento para confirmar caída en presión a través de los diferentes filtros.	0.5 hr	N/A	Medium	High	Low
X_1	Dar el lavado de metanol al PF-580 y dejarlo en el VR-227 para el próximo lote.	1. Version Control.	2.16 hr	Pérdida de Yield.	High	High	Low
X_1	Utilizar Metal Scavenger en lugar de Carbon.	Proyecto Capital			High	High	Low
X_1	Colocar tanque, de 3,000 gals, para recibir el lote del VR-227.	Proyecto Capital		No bajaria el tiempo de ciclo del TA-291. El TA-291 prodria ser el proximo paso limitante.	Low	High	Low
X_1	Estandardizar las instrucciones de transferencia para que todo los operadores sigan los mismos pasos.	1. Definir cGMP para la transferencia.	0.25 hr	Operadores no sigan las instruciones. Los filtros en linea se sigan tapando devido a disturbios en el carbón.	Medium	Low	High
X_2	Eliminar soplado luego del lote.	1. Version Control.	1.6 hr	Pérdida de Yield.	High	High	Low
X_2	Reducir tiempo de soplado luego del lote.	1. Definir tiempo de reducción de los soplados monitoreando filtraciones actuales. 2. Reducir tiempo de soplado por el Filtrate, Scavenger y Transfer compartments.	0.66 hr	Pérdida de Yield.	Medium	Medium	High
X_2	Reducir tiempo de soplado del lavado de MeOH.	1. Definir tiempo de reducción de los soplados monitoreando filtraciones actuales. 2. Reducir tiempo de soplado por el Filtrate, Scavenger y Transfer compartments.	0.66 hr	Pérdida de Yield.	Medium	Medium	High
X_3	Colocar tabla de produción visible como recordatorio del proceso	1. Creear Run Chart para apuntal los tiempos de transferencia	0.05 Hr	Operadores no apunten los tiempos de transferencia.	Medium	Low	High

We collected samples of VR-227's flush to measure the remaining batch in PF-580. This data was compared to flush samples collected with the process original nitrogen blow times. The results were compared with a Two Sample T-test which proved that the batch's quality wouldn't be impacted. We also compared the volume received in TA-291 before and after the project implementation. Another Two Sample T-test proved that there was no difference in volume received in TA-291, so we concluded that the batch's yield wouldn't be impacted. [2] Figure 5 displays the Two Sample T-test of the flush's samples.

- Two-Sample T-Test and CI: Original (g/L), Pilot (g/L)

	N	Mean	StDev	SE Mean
• Original (g/L)	3	8.900	0.567	0.33
• Pilot (g/L)	3	8.32	1.02	0.59

- Difference = mu (Original (g/L)) - mu (Pilot (g/L))
- Estimate for difference: 0.580
- 95% CI for difference: (-1.293, 2.453)
- T-Test of difference = 0: T-Value = 0.86 P-Value = 0.438 DF = 4
- Both use Pooled StDev = 0.8264

Figure 5
Two Sample T-Test of the Flush Samples

CONCLUSION

After completing the pilot trial we successfully were able to prove that the nitrogen blow time reduction and the process standardization wouldn't affect the overall quality or yield of the product.

These changes were made permanent and monitored during the next 30 batches to make sure the changes would improve the batch transfer process [6]. The next 30 batches were organized, summarized and compared to previous batch transfer times. A Two Sample T-test allowed us to verify that the process did actually improve. The batch transfer time was reduced from 6.33 hours to 4.9 hours. The process standardization also reduced the amount of times the filters located between the vessels would clog with carbon. Figure 6 displays an I-MR Chart with the transfer times before and after the project implementation. Here we can clearly observe the transfer time reduction as well as a reduction in process variability.

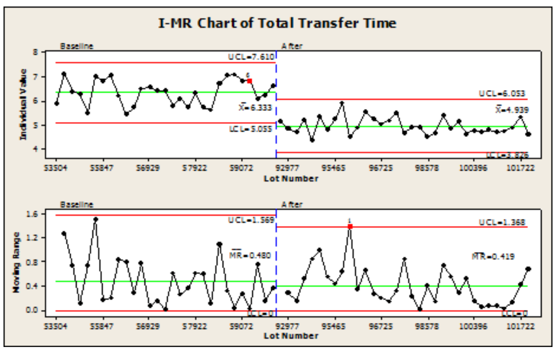

Figure 6
I-MR Chart of the Before and After the Project Implementation

Control

To comply with Factory 2 management's request that any process changes should be permanent, we introduced a Run Chart into the production floor. This would enable operators to calculate the amount of time each batch transfer takes and record it on the table in the production floor. This would act as a remainder of the process improvement and provide them with a visibility tool on how the process is actually running. Figure 7 displays an example of the Run Chart introduced to the production floor.

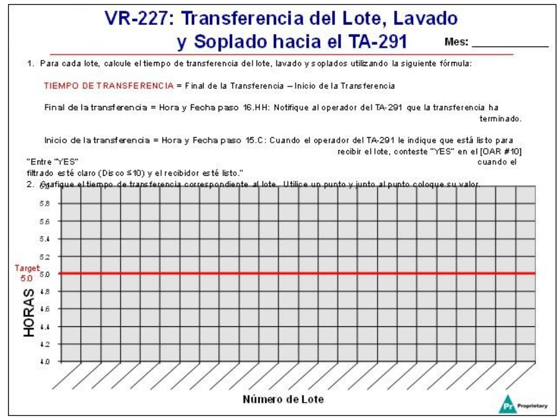

Figure 7
Run Chart Placed in the Production Floor

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