Cycle Time Reduction of a Crystallization Process in a Chemical Plant

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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 active pharmaceutical ingredient (API) for Diabetes Type II manufacturing process. Several stages in the manufacturing process have been identified for improvement. This project focuses in the Cycle Time Reduction of a Crystallization Process. 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 crystallization process, reducing the cycle time to ≤ 20 hrs of the vessel and helping the train ability to increase its manufacturing capacity with an output 6.0 lots per week in 5 days / 3 shift.*

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

INTRODUCTION

The 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 the chemical plant has incremented its production to not only meet this demand but to optimize its' process for any increase in future demand. The chemical Plant located in Barceloneta, Puerto Rico manufactures Crude and Pure, the active ingredient which treats Type 2 Diabetes. The crystallization process was mapped and verified to help improve the manufacturing process cycle time to meet consumer's demand.

The chemical plant process cycle times exceed the 24 hours. During the initial process analysis it was noticed that the crystallization process has the longest cycle time. During ideal crystallization process the measured cycle time was 20 hours without any visible incident. On other occasions the crystallization process seems to be more problematic requiring replacing filters several times within the same batch. Ultimately this contributed to longer cycle time.

LITERATURE REVIEW

Cycle Time Reduction is one business strategy that is worthy of being singled out as a major point to achieve a competitive advantage it is the strategy of speed. Refocusing attention from cost to time is enabling organizations to run circles around their slower competitors. Time-based competitors offer greater varieties of products and services at lower costs and in less time.

The Cycle Time Reduction process helps to examine each step in a core process and guides the responsible team in redesigning the process to make it more effective, more efficient, more flexible, and less expensive while maintaining or improving quality.

Cycle Time should be considered a viable option when an organization is trying to improve: efficiency, productivity, cost base, customer responsiveness, speed to market of new offerings, merging of processes post acquisition, and flexibility. By eliminating "fat" in the processes an organization is able to make itself "lean." [1]

Lean Six Sigma is a blend of the two most powerful improvement methods of the past 20 years: Lean and Six Sigma. It is a unique analytical business process that enables companies to drastically improve their profitability by designing and monitoring everyday business activities in ways that minimize waste and resources using DMAIC strategy.

Lean focuses on speed and inventory. Lean manufacturing is the generic version of the Toyota Production System that focuses on sources of waste: transportation, inventory, movement, work in progress (WIP), over production, over processing and defects. Improvements are made by working to reduce waste through a five-step process: Identifying customer value, Mapping the value stream, Creating flow, Seeking perfection and Pulling based on demand.

Lean needs the root cause analysis and culture changing structure of Six Sigma, and Six Sigma needs the speed, waste elimination and simplicity of solutions from Lean. [2]

Six Sigma focuses on defects from variation. In statistics, the "sigma" is used to identify variation. Companies that adopt Six Sigma as a philosophy seek to reduce variation in the business processes that cause waste and inefficiencies. A business operating at three sigma will produce 66,807 defects per million opportunities, while Six Sigma produces 3.4 defects per million.

Many successful companies, such as Motorola, use Six Sigma. In addition to Six Sigma's powerful technique for finding the root cause of defects, Motorola developed practical ways to use the theory of Six Sigma to achieve a 10-fold improvement in quality, cost and service in five years. Combined with a focus on prioritizing projects based on financial and customer impact, Six Sigma can transform a culture through continuous improvement. [3]

Six Sigma used as strategy of process improvement the DMAIC project methodology, which is divided into five main processes:

- Define: Identify the requirements and problem statement;
- Measure: Identify and document the process;
- Analyze: Collect data to determine cause;
- Improve: Select the best solution in order to improve;
- Control: Revised process to hold the gains.

Each of the previous stages involve and promote the use of tools for process improvement, reduction in variation and customer satisfaction.

METHODOLOGY

Six Sigma's most common and well known methodology is its problem solving DMAIC approach. The DMAIC (Define-Measure-Analyze-Improve-Control) is the classic Six Sigma problem solving process. Traditionally, the approach is to be applied to a problem with an existing, steady state process or product and/or service offering.

Variation is the enemy variation from customer specifications in either a product or process is the primary problem. Variation can take on many forms. DMAIC resolves issues of defects or failures, deviation from a target, excess cost or time, and deterioration. Six Sigma reduces variation within and across the value adding steps in a process. DMAIC identifies key requirements, deliverables, tasks, and standard tools for a project team to utilize when tackling a problem.

This classic or traditional Six Sigma methodology was designed to solve a problematic process or product and/or service offering to regain control. It addresses improvements in productivity (how many), financial (how much money), quality (how well) and time (how fast). The 5 step DMAIC method often is called the process improvement methodology.

The classic strategy reduces process variance (in total, across the activities and within step) to bring it back on target the customer specification or requirement. The DMAIC approach is designed to allow for flexibility and iterative work, if necessary. As more is learned through the 5 step process, assumptions or hypotheses as to the root cause of the problem may be disproved, requiring the project team to revisit them and modify or to explore alternative possibilities.

The DMAIC methodology uses a process step structure. Steps generally are sequential; however, some activities from various steps may occur concurrently or may be iterative. Deliverables for a given step must be completed prior to formal gate review approval. Step Reviews do occur sequentially.

The DMAIC method is primarily based on the application of statistical process control, quality tools, and process capability analysis; it is not a product development methodology. It can be used to help redesign a process any process, given that the redesign fixes the initial process problem. [4] Figure 1 display the High level process flow of the DMAIC method through its five steps.

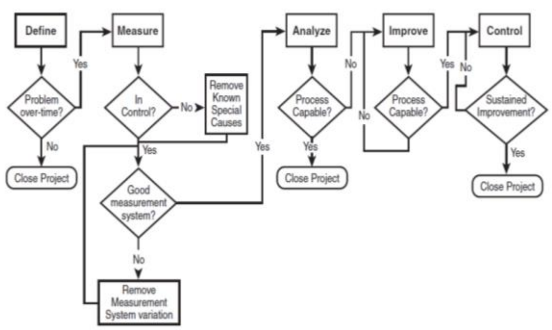


Figure 1
High Level Process Flow of the DMAIC

Results and Discussion

The results will be presented and discussed following de DMAIC methodology.

Define

To help improve production and supply consumer's demand for an active pharmaceutical ingredient (API) for Diabetes Type II, Barceloneta's Factory 2 management asked to improve the crystallization process Cycle Time. 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 pure process consists in five main tanks. MT-41 was identified as the limiting step of Pure Process (Figure 2). These tank present the longest cycle time > 20 hours. Figure 3 displays High Level Pure Process Flow Diagram. The 7 steps are:

- Step 1: TA-522 - Dissolution Batch
- Step 2: MT-41 - Crystallization Process
- Step 3: MT-51 – Holding Tank
- Step 4 : CE-960 – Centrifuge
- Step 5: DR-371 - Dryer
- Step 6: MI-96 – Co-milled
- Step 7: BN-95 – Blender

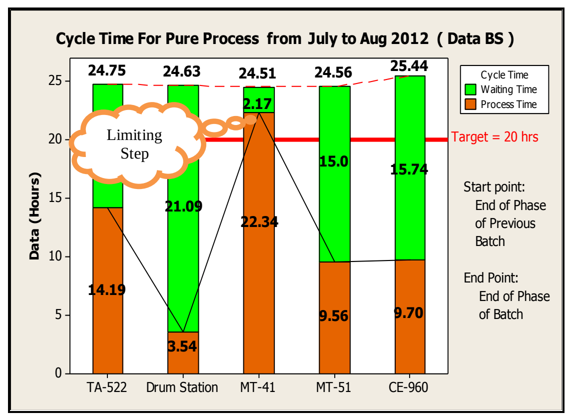


Figure 2
Limiting Step

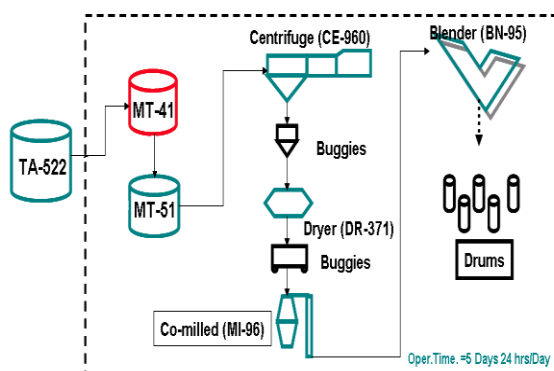


Figure 3
High Level Pure Process Flow Diagram

As identified the MT-41 are the limiting step the efforts will focus the crystallization process and its components.

The Crystallization process is divided into 11 stages. The first stage in the process is batch charge. It is then the phosphoric acid charge. After the batch and acid are charge the third stage is heat the batch. Then, continue with the aged and cool batch. Then proceeds to load the seed for the crystallization behave the same way in order to acquire the desired particle size. The seventh and eighth stages consist in aged and cool the batch. In the ninth stage is complete the IPA charge and tenth stage once again aged the batch. The Last stage involves the transfer batch to a holding tank (MT-51).

Problem Statement

Cycle time reduction is one of the most important elements of successful manufacturing today. Customers are demanding that manufacturers quickly respond to their wants and needs, deliver perfect quality products on time. This trend, which will continue, has led companies to focus more attention on their cycle time. Inconsistent crystallization process time and related activities increase the cycle time of the process. This project focused on the crystallization process.

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 13 previous batch crystallization process at MT-41. The baseline included all different steps that are necessary for the crystallization. The resulting average cycle time for the 13 batches was 24.51 hours. Figure 4 displays the summary for the 13 batch cycle times.

This information can be further stratified into the different steps in the crystallization process. On average, charging the batch from TA-522 to MT-41 would take 2.69 hour. The phosphoric acid charging takes 0.92 hour on average. The heat batch took an average of 3.32 hours. The first aging averaged to 1.07 hours. The cool batch would take 0.66 hour. The seed charging takes 0.13 hour. The second aging averaged to 3.09 hours. The cooling ramp took an average of 5.79. The IPA charge takes 2.30 hours on average. The third aging averaged to 1.13 hours. The transfer batch from MT-41 to MT-51 took an average of 0.44 hour. And finally, the receiving time average of IPA and Process Water (PW-100) at MT-41 and transferring to the flush to MT-51 was 0.37 hour. Figure 5 displays the stratified process times in a value stream map. [2]

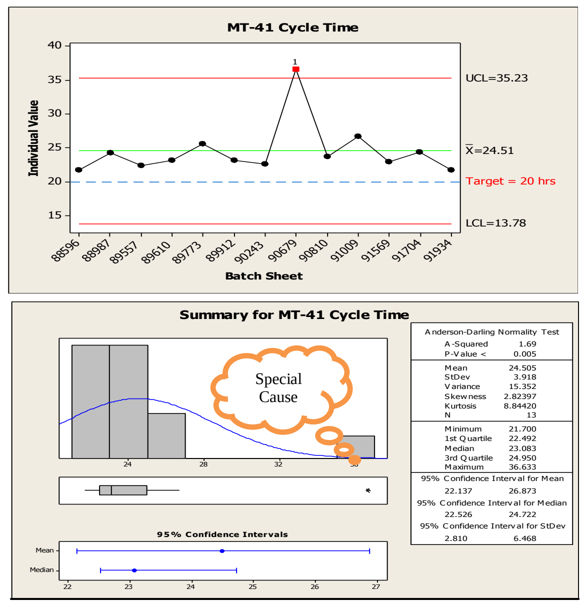


Figure 4
Control Chart and Summary of the MT-41 Cycle Time Baseline

A Measure System Analysis (MSA) study was completed to verify the accuracy and integrity of the data. The Measure System Analysis is a specially designed experiment that seeks to identify the components of variation in the measurement. 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 Measure System Analysis results proved a measurement system accuracy of 99.3%. With an error smaller than 1% 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. [5]

At the same time the baseline was generated, the actual process was observed in the production floor for a total of 13 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 MT-41 cycle time. Another recorded variable was the MT-41 waiting time. The two final variables in the data collection plan were the MT-41 process time and output per week. Table 1 displays the Data Collection Plan.

There are two other factors dealing with personnel behavior that were observed during the 13 batch transfer. The first behavior was what the operator did if MT-41 wouldn't be available to receive the batch after TA-522 completed all of its processes. On most occasions this was due to the fact that MT-41 was not done crystallization process the previous batch on time. Another factor that was observed in the production floor during the batch transfer the line filters become clogged as the lot is transferred very viscous.

Analyze

An important finding was made during the 13 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 during the crystallization process. The batch sheet does not provide an instruction on what the operator should do for example; if 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 heating the batch in TA-522 until MT-41 became available. On case, operators would simply stop heating the batch in TA-522. The same lack in process standardization occurred whenever

MT-41 became available to receive the batch. Some operators would start transferring the batch from TA-522 to MT-41. Other operators do other tasks before they began the transfer process. This operation is important because whenever the batch transfer process the batch have become for viscous and is more difficult the transferring. According to the viscosity level, it would clog the filters located between the vessels once or several times during the batch transfer.

The other observation made during the 13 batch that operators manipulated some operation like temperature ramp and other sequential or automatic steps. 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 Kaizen exercise to come up with possible ideas to improve the process [4]. During the Kaizen Exercise participated different resources of various department or discipline including operators to evaluated possible improvement opportunities to work on floor. Figures 6, 7 and 8 displays the Kaizen Exercise with the A3 Template to performs the event.

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; Move the aging step to the next vessel MT-51. Another suggestion was during the temperature adjustment begin to aging and dissolve the batch at TA-522.[1] After prioritizing all of the possible solutions and analyzing their benefit versus effort and risk, we came up with nine possible solutions. Figures 9, 10 and 11 displays the Prioritization Matrix with the selected ideas for implementation displayed with a green indicator. The blue indicator was work in other project.

The ideas that were selected for implementation were; standardizing the batch transfer instructions if MT-41 isn't available to receive the batch. We will also standardize the process steps to start transferring the batch once MT-41 becomes available. 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 TA-522 is ready to transfer the batch but MT-41 isn't available, the operator would communicate with their supervisor to estimate how long it would take for MT-41 to finish its process. If MT-41's process would take less than 1 hour to complete, then the operator would continue to heating the batch in TA-522 until MT-41 became available. If the supervisor indicated that MT-41's process would take more than 1 hour, then the operator would follow the instruction to aging the batch in TA-522. To implement this idea we needed to make sure that the batch's yield and quality wouldn't be impacted.

Samples of MT-41 cycle time to measure the different steps that interact with the crystallization process were collected. The data was compared with the original MT-41 cycle time captured at the baseline project. In this way one can identify if it was an improvement in the process. On Figures 9, 10 and 11 displays the Prioritization Matrix of the Brainstormed Ideas of the different departments or disciplines.

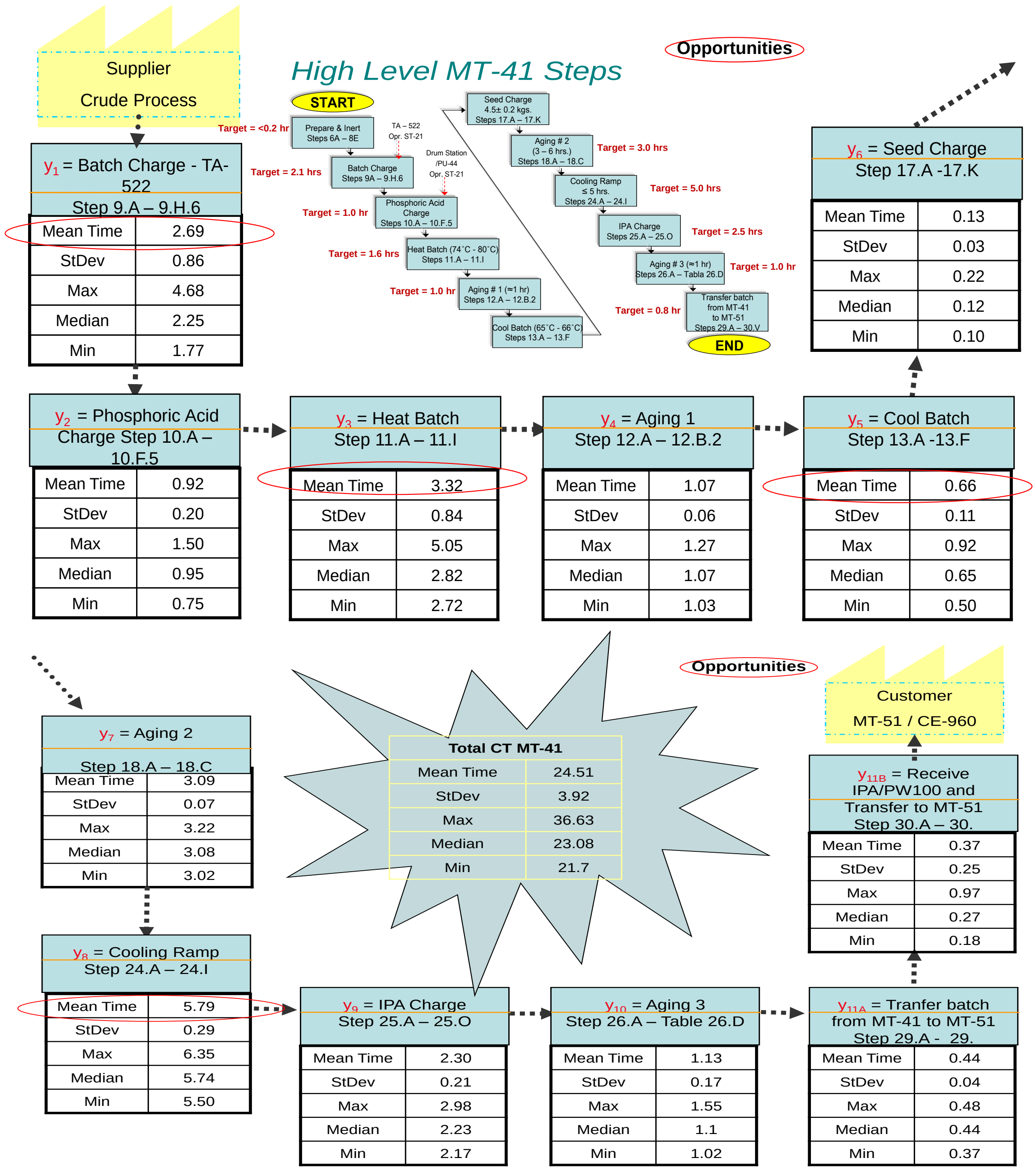


Figure 5

Value Stream Map of Stratified Crystallization Process Stages

Table 1

Data Collection Plan

Measure (Output)	Operational Definition	Where will the data be obtained?	How will the data be collected?		When will the data be collected?	How much will be collected?
MT-41 Cycle Time Type: Continuous	Time from when the vessel starts its preparation until the flushes are transferred to MT-51.	The database time were obtained from the batch record, SAP and PI System.	Cycle Time Calculation from the cycle time database obtained from the Visual Board and PI System Daily. From Batch sheet and SAP Monthly.		Historical Data from July 2012 to August 2012 for Baseline.	All the batch produced during July 2012 to December2012
MT-41 Waiting Time Type: Continuous	Time from when the vessel stop until the vessel start with the new batch.	The database time were obtained from the batch record, SAP and PI System.	Waiting Time Calculation from the database obtained from the Visual Board and PI System Daily. From Batch sheet and SAP Monthly.		Historical Data from July 2012 to August 2012 for Baseline.	All the batch produced during July 2012 to December2012
MT-41 Process Time Type: Continuous	Time that results from the difference between the Cycle time and the Waiting time.	The database time were obtained from the batch record, SAP and PI System.	Time Calculation from the cycle time database obtained from the Visual Board and PI System Daily. From Batch sheet and SAP Monthly.		Historical Data from July 2012 to August 2012 for Baseline.	All the batch produced during July 2012 to December 2012
Output per week Type: Count	Number of lots produced in a week from Monday to Sunday.	The database time were obtained from the batch record. batch record, SAP and PI System.	Count of batches produced in a week from Monday to Sunday.		Historical Data from July 2012 to August 2012 for Baseline.	All the batch produced during July 2012 to December 2012
How will the data be used?			**How will the data be displayed?**			
Determine baseline data Identification of largest contributors Process Stability			Bar Chart Time Series Plot Control Chart Process Capability			

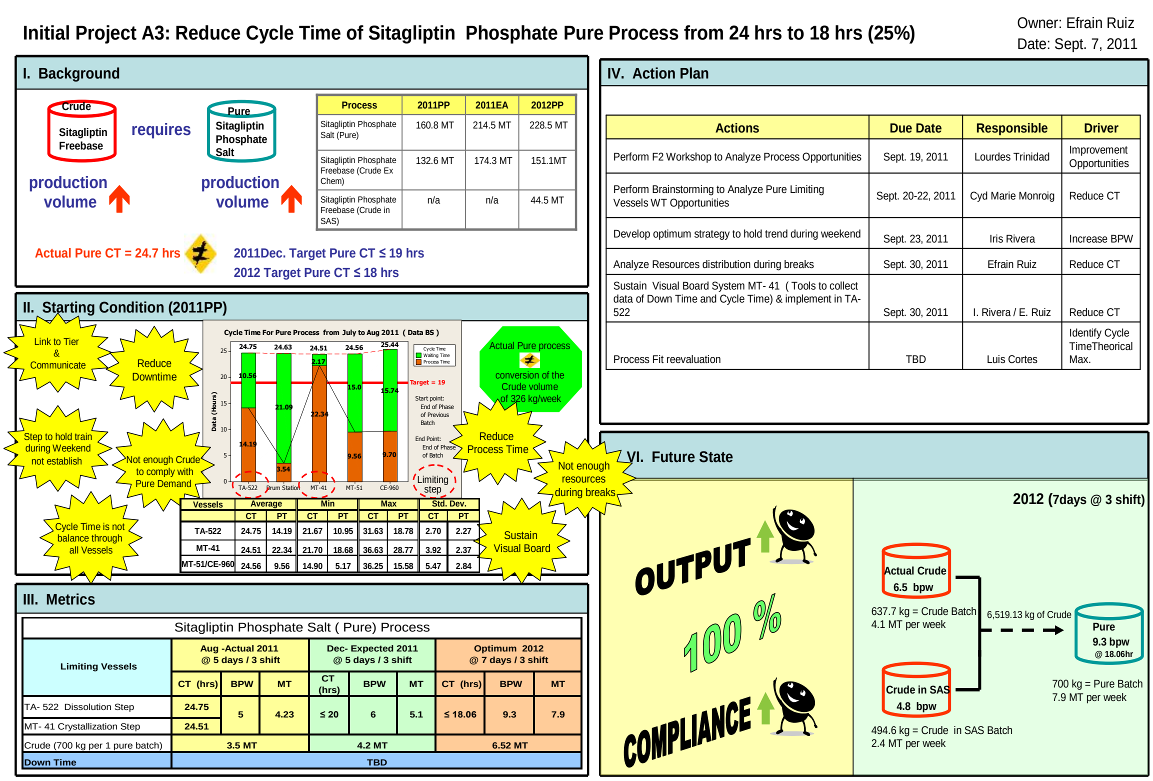


Figure 6

Initial Project A3

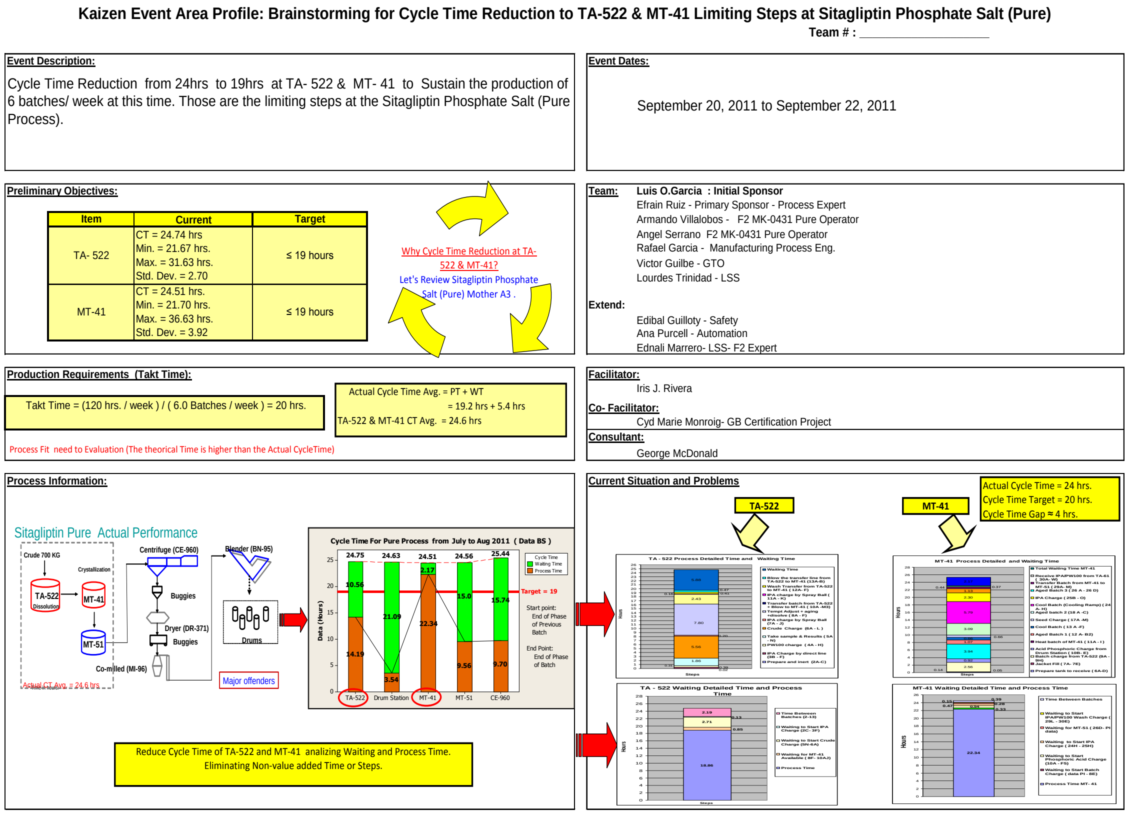
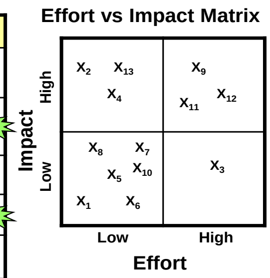


Figure 7
Kaizen Event Area Profile

Figure 8
Kaizen Exercise

Prioritization Matrix of the Brainstormed Ideas

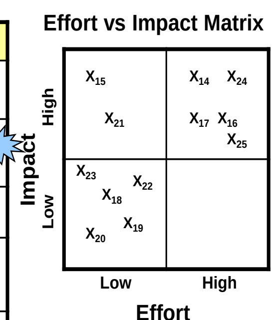
	X	Root Cause	Solution
Factory 2	X_1	Falta de Coordinación	Asegurar que los materiales estén disponible al momento que los necesiten
	X_2	Falta de Coordinación	Asegurar que el proceso esté balanceado para disminuir el tiempo de espera
	X_3	Capacidad del filtro de línea	Aumentar capacidad de los filtros de línea
	X_4	Falta de Comunicación entre Opr	Estandarizar tareas
	X_5	No todos los Opr tienen acceso a SAP	Asegurarse que todos los Opr tengan acceso a SAP.
	X_6	Paso es redundante	Eliminar Paso.
	X_7	Mal Relocalización de la caja para colocar la muestra	Relocalizar caja para colocar muestras.
	X_8	Instrucciones del BS establecido	Bajar solado de 5 min a 1min
	X_9	Capacidad de la bomba de Tank Farm	Aumentar flujo y capacidad en la bomba desde el tank farm
	X_{10}	Pasos incesesarios	Eliminar pasos
	X_{11}	Temperatura muy alta	Reducir la temperatura a alcanzar el MT-51 de 25C a 23C.
	X_{12}	No tiene un enjuague adecuado	Dividir la carga de IPA por sprayball y Dip Pipe
	X_{13}	Tareas no estandarizadas.	Estandarizar tareas para asi bajar el tiempo de ciclo



GO Solution

Figure 9
Factory 2 Prioritization Matrix of the Brainstormed Ideas

	X	Root Cause	Solution
GTO	X_{14}	Desbalanceo de Tareas	Balancear tareas del TA-522 (ácido/ calentamiento)
	X_{15}	Tareas no balanceadas	Mover el paso de añejamiento al MT-51.
	X_{16}	Tareas desbalanceadas entre el MT-41 y TA-522	Balancear tareas entre MT-41 y TA-522 Calentar el lote en el TA-522 hasta donde lo permita el proceso
	X_{17}	Para evitar mal manejo de la muestra.	Evaluar para comprar instrumento para medir concentración de agua para hacer la muestra in- line la muestra al lab luego del paso 5C. (Batchsheet).
	X_{18}	Temperatura muy baja alcanzada por el lote	Activar jacket del MT-41 tan pronto se comienza a recibir el lote (Paso 9 del MT-41).
	X_{19}	Lote viscoso	Transferir el lote a una temperatura igual o mayor a 35°C
	X_{20}	Opr tienen que salir del área de Puro para tomar muestra	Evaluar si con solo Observar por la mirilla que se formó la camada se puede eliminar la muestra.
	X_{21}	Tareas no estandarizadas	Durante el ajuste de temperatura comenzar a Añejar y disolver el TA-522
	X_{22}	Tareas no estandarizadas	Asegurar lote este disuelto en el paso de ajuste de temperatura 25-35°C (TA-522) y no identificarlo luego del añejamiento.
	X_{23}	Lavado esta mas frio o viscoso	Apagar el agitador y dejar el jacket en "ON" para que el lavado se transfiera más caliente por lo tanto se reciba más rápido al MT-41.
	X_{24}	Tareas no balanaceadas	Convertir el MT-51 en un tanque paralelo al MT-41
	X_{25}	Tamaño de Particula no es el adecuado	Enfriar más el lote. ("Cold Crystallization")



Solutions were implemented under Parallel Crystallization Project

Figure 10
GTO Prioritization Matrix of the Brainstormed Ideas

	X	Root Cause	Solution
	X_{26}	Falta de mantenimiento al DFA	Evaluar frecuencia del PM de limpieza del DFA(Detonation Flame Arrestor)
Utilities	X_{27}	Falta de PM en los jackets	Aumentar flujo de los jackets y realizar PM al Jacket del MT-41
Utilities	X_{28}	Presión baja durante la transferencia	Evaluar si se puede aumentar presión de transferencia de 10 psig hasta (15 a 20 psig)
Utilities	X_{29}	Baja Razon de flujo	Analizar el sistema de agua para subir la razón flujo de carga de PW100.
Utilities	X_{30}	Bajo flujo de IPA	Aumentar el flujo de IPA a lo máximo que viene del tanque del Tank Farm.
Utilities	X_{31}	Proceso de monitoreo de cuarto no eficiente	Revisar proceso de monitoreo de condiciones de los cuartos y ajuste con relación a cuartos y analizar oportunidad de seguir trabajando cuando este en fuera de condiciones y ver si hay impacto.
Utilities	X_{32}	Bajo Gradiente de Temperatura	Aumentar el interlock de temperatura.
LSS	X_{33}	Falta de estandarización.	Estandarizar para asegurar entregar la muestra al lab del TA-522 luego del paso 5C.
LSS	X_{34}	Falta de Visual	Asegurar de usar los visuales necesarios para capturar areas de opportunidad y hacer visibles los problemas
LSS	X_{35}	Falta de Estandarización	Estandarizar carga de ácido fosfórico y Lote
LSS	X_{36}	Set Point de temperatura no adecuado	Hacer Propuesta con respecto a los set point de la rampa de enfriamiento en el MT-41 y MT-51
LSS	X_{37}	Filtros se tapan	Estandarizar el paso de transferencia por medio de filtros de linea

GO Solution

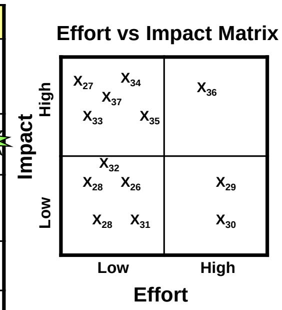


Figure 11
Utilities and LSS Prioritization Matrix of the Brainstormed Ideas

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 (Figure 12). 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 12 displays an example of the Run Chart introduced to the production floor.

During the project development the crystallization process cycle time was reduced from 24.51 hours to 19.7 hours, representing a 69% of cycle time reduction with the effort of all the personnel involved in the continuous improvement project. Also, a cooling ramp improvement was implemented. The set point were evaluated and challenging in a dummy run at the crystallization process. Figures 13, 14 and 15 displays the result of that improvement. Therefore, it could be increased the current output of 5.0 to 6.0 lots per week in 5 days / 3 shifts in order to meet the customer demand.

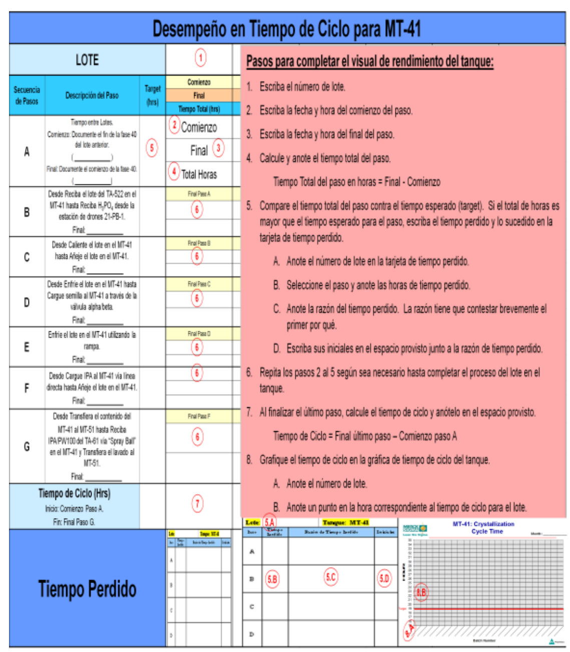


Figure 12
Run Chart Placed in the Production Floor

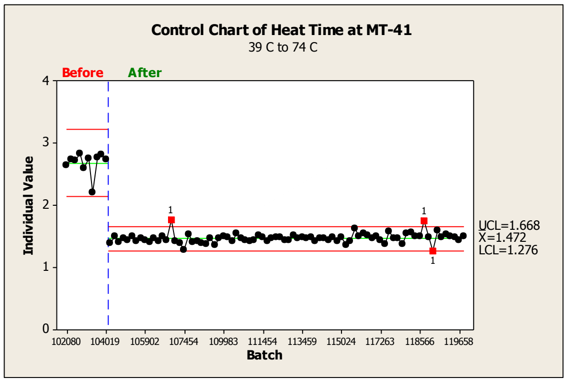


Figure 13
Control Chart of Heat Time Before and After the Project Implementation

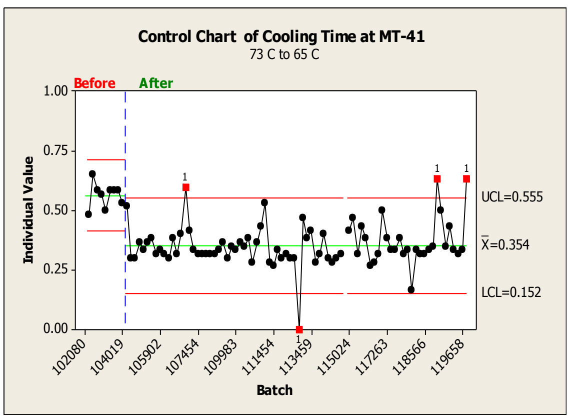


Figure 14
Control Chart of Cooling Time Before and After the Project Implementation

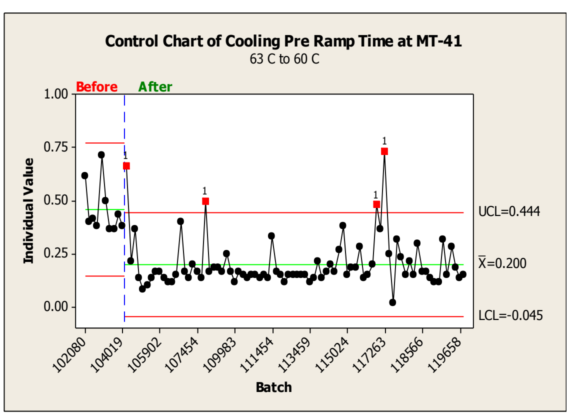


Figure 15
Control Chart of Cooling Time Before and After the Project Implementation

CONCLUSION

After completing the pilot trial we successfully were able to prove that the cycle 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 crystallization process cycle times. The process standardization also reduced the amount of times the filters located between the vessels would clog. Figures 16, 17 and 18 displays an I-MR Chart, Process Capability and Box plot with the crystallization process cycle time before and after the project implementation. Here we can clearly observe the transfer time reduction as well as a reduction in process variability.

The Cycle Time Reduction of Crystallization Process in a Chemical Plant was successfully achieved with cycle time reduction techniques, such as: performing activities in parallel, changing the sequence of activities, reducing interruptions, improving timing, process standardization and standardized visual board. In addition, within a few weeks of implementing the changes, the chemical plant guarantees the manufacturing of the customer demand of 300 MT of their active ingredient. It could be increased the current output of 5.0 to 6.0 lots per week in 5 days / 3 shifts in order to meet the customer demand.

Finally, the team was able to reach the target of \$1.3MM, resulting in substantial profit to the chemical plant.

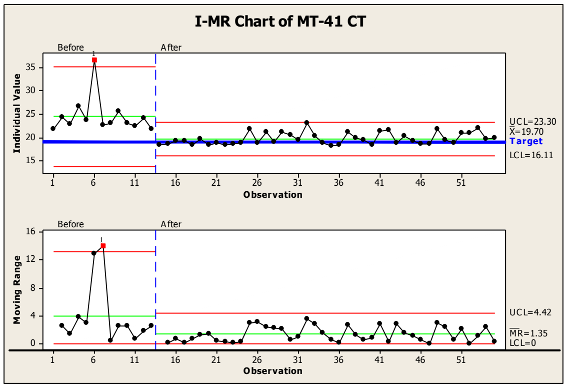


Figure 16
I-MR Chart of Cycle Time Before and After the Project Implementation

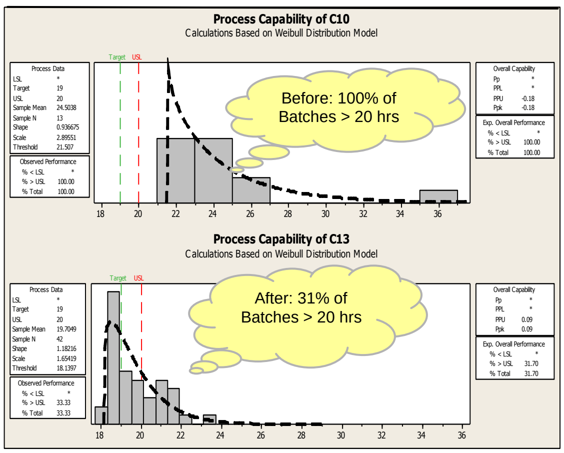


Figure 17
Process Capability of Cycle Time Before and After the Project Implementation

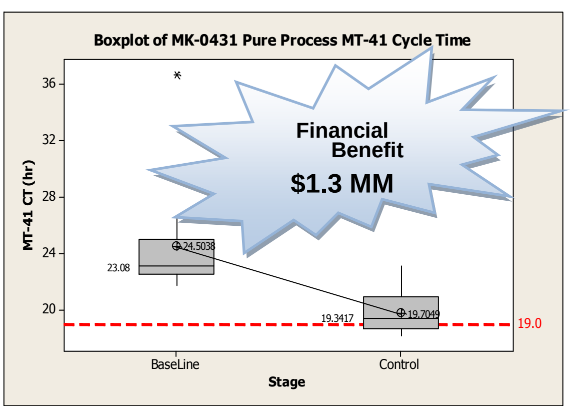


Figure 18
Box Plot of Cycle Time Before and After the Project Implementation

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