Standardization Times in a Blending (Flex 2 Unit Operation) Manufacturing Process

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Abstract *— The continuous evolution in standardization, digitalization, and changes in the ways of working in manufacturing in the pharmaceutical industry and the increase in production for product X by 2023, has made it necessary to study the work process and standardize the blending production unit of the Flex 2 production area. The Flex 2 area is dedicated to a single product only. For the preparation of the drug, the area of Flex 2 performs 2 different types of API mixing, since the drug in its final stage of compression is a Bi-layer tablet. The blending process requires standardizing the number of operators needed to execute the batches and the number of batches that can be manufactured in the Flex 2 Blending unit. In 2022, a total of 610 batches were processed and the average batch cycle time was 7.0hrs.*

Key Terms *— Blending, Cycle Time, Lean Manufacturing, Standardization Times.*

INTRODUCTION

The research will concentrate on studying and analyzing the complete production process (END to END) of the unit operation that is performed in Flex 2, analyzing the production times step by step, and analyzing the production capacity, due to the increase in production. The production expectation for the year 2023 is to manufacture a total of 892 batches of blending for the product X. In 2022, a total of 610 batches were processed and the average batch cycle time was 7.0hrs.

The objective is to develop, create, and analyze a standardized step-by-step agenda on the execution process with a new production cycle time to validate the hypothesis if the quantity of blending batches can increments reducing the cycle times of the blending process. Is necessary to analyze how many quantities of blending production batches can be made per year, establish the number of operators needed to manufacture the product, and analyze how many production shifts are required to manufacture the batch.

LITERATURE

The market of the pharmaceutical industry is constantly developing since different diseases are appearing in millions of people worldwide. The focus and mission of the pharmaceutical industries are based on the possibility to save lives, throughout making medicines that provide a better quality of life for their patients. Even those medicines cure diseases that are difficult to treat.

This type of industry is a very important business model in the health of the world, constituted by several governmental and private entities by which they are dedicated to the production, preparation, and marketing of medicinal chemicals and continuously develop new products to satisfy customer/patients needs. Its challenges as a business are in the research and development of drugs to treat or cure diseases.

The business of the pharmaceutical industry configures many dynamic factors, of which it represents the social, economic, and scientific areas, contributing to the export markets are multinational and global. The activities carried out in the pharmaceutical environment are based on regulations subject to laws and policies applicable to the approval, manufacture, quality, and sales of medicines. Research and Development expenses are mostly supported by large capital investments due to the associated expenses between marketing authorization, quality control, manufacturing, and sales. These terms establish good manufacturing practices (GMP's), guaranteeing the integrity of industrial operations, their safety, and efficacy in the product [1].

The mixing process in the pharmaceutical industry is one that is highly used, since it is an efficient unitary operation for the manufacture of a product. This process involves the active ingredient of the product and the excipients, achieving a uniform mixing with the exact quantities for the process. This mixing achieves that all the ingredients used maintain a homogeneity and manages to maintain the acceptance levels, as required by the process, complying with the GMP. The mixture of dry powder of an active ingredient (API) with excipients, as an example (mixtures of binders, diluents, flow modifiers and granulating agents), is necessary to produce physical, flow, and mechanical properties suitable for the formation of tablets. Its function is to separate the concentration differences within the dry powder mixture, so that each tablet contains a mixture with the same properties and with a strictly controlled amount of the API. These examples demonstrate that in a mixing process the objective is to reduce inhomogeneities in composition to an acceptance level to provide a more uniform processing environment and a more uniform product [2].

Product validation is the standardized process given to regulatory agencies on how the drug will be manufactured. It is an official prescription if there is no type of change, since it is established by means of calculations and procedures, the exact way to produce without changing or altering the composition of the drug. A validation process involves several months of planning, preparation, and coordination and stipulating step by step all the manufacturing processes of the product from its initial stage to the completion of the medication, whether in the form of tablet, capsule, injection, cream, etc. Once created and approved by the regulatory agencies, the agreement is given and a patent is created for a drug that will be invoiced by the industry for some years, without it being altered or carried out generically by another industry [3].

The Federal Food and Drug Administration (FDA) has guidelines that help simplify and standardize these metrics, based on compliance and quality inspections. A relevant fact is that these metrics developed by the regulatory agency are used to improve the agency's ability to obtain better efforts and techniques to predict future inspections or shortages of medicines, as well as help industries adopt better technologies that make it possible to lower variability in processes. The agency supports innovation and continuous process improvements in the pharmaceutical industry, contributing to a strong control and quality strategy [4].

The concept of lean manufacturing, since it’s started in Japan, has successfully contributed to the processes of manufacturing industries, in this case pharmaceuticals, to develop and continuously improve processes to make them more agile, robust, and at lower cost.

To a better understand, the term "lean" as defined by Womack and Jones it is a system that uses less, in terms of manufacturing and capital, to create the same raw material that is offset by a traditional mass production system, while contributes and increases the customer's need. Lean means producing only what the customer needs, when they need it, in quantities ordered by the customer, and with only minimal resources. Specifically, to manufacture products in a way that minimizes the time required to deliver finished products, to a required amount of labor and required storage space, meeting quality standards, generally at the lowest cost by eliminating waste [5].

The Lean philosophy establishes the value of waste loss as a fundamental principle of improvement. Waste losses are summarized in over production, inventory, motion, transportation and over processing. These terms help to analyze how the processes have deficiencies and provide ideas to improve their times [6].

Another method widely used and developed in the pharmaceutical industry is the Kanban method, originated at the beginning of the 21st century, inspired by the Toyota Production System (TPS), with the mentality of improving processes. Kanban method help identify and remove obstacles during the testing period, increase the ability to collaborate among employees, and ultimately increase the

speed of process flow. Therefore, it helps you improve inventory, make production more flexible and maintain a continuous flow of specific needs in real time [7].

For the different industries whose important process role is manufacturing, they are forced to standardize using fewer tools and methods, of which they make use of the 5S technique through planning infrequently. This has caused the standardization methodology to have evolved during these years. Advances in technology came to create mathematical models with descriptive and quantitative data helping to make better decisions about the quality of processes and the continuous improvement of their times. These changes have been of improvement for the employees themselves since there is a need to establish a high-quality production behavior and with less time lost in the execution of manufacturing [8].

Another important methodology used to reduce times from hours to minutes in the operations is Single Minute Exchange of Die (SMED). The SMED technique dates to the 1950s when Japan's Shigeo Shingo wanted to eliminate bottlenecks created by three large body molding presses at Toyo Kogyo's Mazda Plant in Hiroshima (JMAC). This tool can be used by companies that need to improve their processes, and not just to reduce setup times.

In terms of problem reduction, a fundamental principle of lean manufacturing is standardization. Taiichi Ohno mentions: "Where there is no standard, there can be no kaizen." The standards lay the foundation for employee training and auditing. Standardization is particularly important for configuration reduction efforts because, most of the time, reducing translated configuration times is defining a new procedure for performing configuration operations [9].

To execute the SMED technique well, it is important to identify the area where an opportunity for improvement is required. Then the important elements to make the changes are identified. It is a good option to identify the specific points that are immersed in the process of change. It is necessary to establish a dynamic of observation of whether the process to be analyzed is a process that is mostly executed by a human or by a machine. The SMED technique helps to speed up and reduce changeover times, the lost times between one process and another decreases, and exact times of how a production should run is established [10]. In this way, the profitability of the company increases, contributing to the probability of lowering costs and increasing production, equivalent to more profits. It would allow to respond quickly to customer demands, minimize overproduction and therefore, the quantity and cost of inventory of the products that are stored in the plant, improve cash flow and decrease business risk and adjust the work group; that is, not having to ask for more for the hiring of an extra employee to meet the requirements, times and variety of delivery requested by the client.

Innovation and constant changes at a global level in industries generate effective governance in the projects that are carried out, to build and maintain an operation of excellence. For this reason, lean manufacturing techniques and project management are highly collaborative in industries, as they help streamline and adopt new work practices focused on success and safety [11].

METHODOLOGY

To meet the customer's need to analyze the times needed for the standardization of a blend batch in the production area of Flex 2, the following data was collected:

- The planning staff set a projection of manufacturing the amount of 892 lots by 2023.
- A detailed standardization table (SMED) was made, in which the complete time of preparation of a mixing batch will be measured. The table was based on an 8hrs shift of production, with a total of 3 operators per shift. Listed, step by step, the entire process from start to finish (see Table 1).

- The mixing process ran simultaneously in two different process rooms, of which the table subdivides the tasks into each other.
- During the batch manufacturing process, the execution times of the two mixed active ingredients were measured separately.
- Once the complete data was collected during the 8 hours shift turn, each separate API blend process, the improvement actions was analyzed.
- The API Blend A for its mixing process used the active ingredient A and its excipients was composed of 2: excipient 1 and excipient 2. On the other hand, the API Blend B for its mixing process used an active ingredient B and a single excipient.
- During the process of collecting the data to perform the standardized process, step by step, two different tables were made, as different strategies emerged, from which the important steps continued to be simplified and added and thus facilitate the operator the best way to work [See Table 1 and 2].

Table 1

First SMED Standardized Table with Step-By-Step Times of the Complete Mixing Process

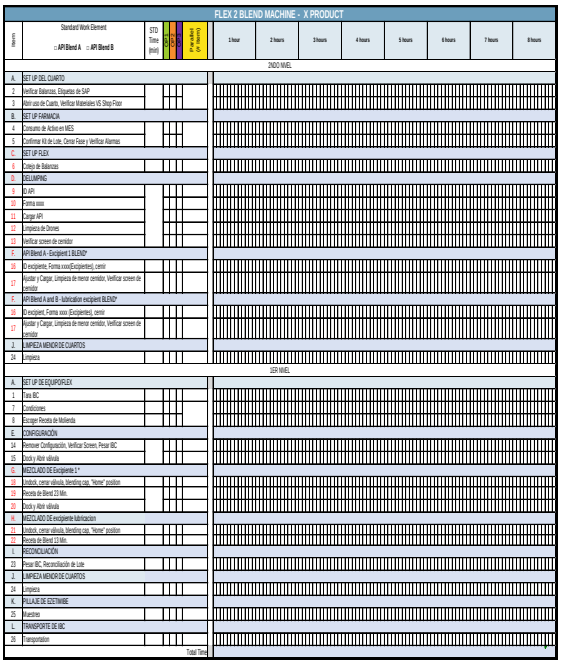

Table 2

Second SMED Table with More Specific and Standardized Details for Better Understanding and Visual Aid for Operators

FLEX 2 BLEND STANDARIZED WORK						
Item	Standard Work Element □ API Blend A □ API Blend B	STD Time (min)	OP1	OP2	OP3	Parallel (# Team)
A.	SET UP DEL CUARTO					
1	Abrir uso de cuarto y IBC					
2	Verificar Balanzas, Etiquetas de SAP					
3	Tarar IBC					
B.	SET UP FARMACIA (2nd floor)					
4	Abrir uso de cuarto y cernidor, verificar materiales vs Shop Floor					
5	Etiquetas de SAP, Consumo de API (MES)					
6	Confirmar Kit de Lote, Cerrar Fase y verificar Alarma					
C.	SET UP FLEX-MES (2nd floor)					
7	Abrir Drones y reconciliar					
8	ID API					
D.	DELUMPING (1st floor)					
9	Escoger receta de molienda					
10	Cargar API					
11	Limpieza de drones					
12	Verificar screen de cernidor					
13	Limpieza de Down Flow Booth					
14	ID (excipiente A), reconciliar componoentes					
E.	CONFIGURACIÓN (1st floor)					
15	Remover Configuración, Verificar Screen, Pesar IBC					
16	Dock y Abrir válvula					
F.	ATORVA- Excipiente A BLEND*					
17	ID Colloidal, Forma 3503 (Excipientes), cernir					
18	Reconciliar Componentes					
19	Ajustar y Cargar, Limpieza de menor cernidor, Verificar screen de cernidor					
20	ID (excipiente B) y reconciliacion de componentes					
G.	Mezclado de Excipente A *					
21	Undock, cerrar válvula, blending cap, "Home" position					
22	Receta de Blend 23 Min.					
23	Dock y Abrir válvula					
H.	Cernido de Excipiente B (2nd floor)					
24	Cernir excipiente B					
25	Reconciliacion de componentes					
I.	Mezclado de Excipente B					
26	Undock, cerrar válvula, blending cap, "Home" position					
27	Receta Blend 13 min.					
J.	Reconciliacion 1er piso					
28	Pesar IBC, Reconciliacion del lote					
K.	Limpieza Menor de cuartos					
29	Limpieza de cuarto, downflow booth					
30	Aprobacion					
L.	TRANSPORTE DE IBC					
31	Transportation					
32	Buscar materiales proximo lote en el airlock					
33	Pedir 2 lotes adicionales					
						Lot End Date/End Time
						Total Time

RESULTS AND DISCUSSION

Once concluded, the time analysis and step-by-step standardization of the process of Blending the active ingredients API Blend A and API Blend B in the Production Unit of Flex 2 was made. The results were:

- Batch lot preparation in the Flex 2 production unit for the API Blend A was **5.5** hrs. average, and **4.5** hrs. for the API Blend 2.
- According to the standardized schedule to support the manufacturing times of each batch, a total of 3 operators per shift were required to support production**.**
- Define the specific tasks that operator 1, operator 2, and operator 3 perform individually.
- The tasks that are performed jointly between the 3 operators were defined**.**
- The additional step that corresponds to the API Blend A was established in the standardized table, since this process includes the operation of sifting an additional excipient (Steps G and H).

- Times were established using an Electronic Bath Record (EBR) process.

Once the standardized duration terms of the mixed batches for API Blend A and API Blend B have been established, the researcher analyzed the number of hours that can be manufactured with the Flex 2 equipment. A margin of error of 0.5hrs was given to the mixing batches, and the cleaning time between batches of 0.5hrs was given to obtain a more realistic view of the production process. The cycle time average for the study for both standardized blends (A and B) was 6.1hrs (See Table 3).

Table 3

Cycle Time Average

API Blend A STD Hours	6.0
API Blend B STD Hours	5.0
Sampling	0.0
Minor Clean/Movements	0.5
CYCLE TIME AVERAGE	6.1

Table 4

The SMED Standardize Workflow with the Standard Times, Quantity of Operators, Role Executions and Work in Parallel

FLEX 2 BLEND STANDARIZED WORK						
Item	Standard Work Element □ API Blend A □ API Blend B	STD Time (min)	OP1	OP2	OP3	Parallel (# Item)
A.	SET UP DEL CUARTO	35				
1	Abrir uso de cuarto y IBC	35				4 y 6
2	Verificar Balanzas, Etiquetas de SAP					
3	Tarar IBC					
B.	SET UP FARMACIA (2nd floor)	35				
4	Abrir uso de cuarto y cernidor, verificar materiales vs Shop Floor	35				1 y 3
5	Etiquetas de SAP, Consumo de API (MES)					
6	Confirmar Kit de Lote, Cerrar Fase y verificar Alarma					
C.	SET UP FLEX-MES (2nd floor)	30				
7	Abrir Drones y reconciliar	30				
8	ID API					
D.	DELUMPING (1st floor)	90				
9	Escoger receta de molienda	90				
10	Cargar API					11
11	Limpieza de drones					10
12	Verificar screen de cernidor					
13	Limpieza de Down Flow Booth					
14	ID (excipiente A), reconciliar componoentes					
E.	CONFIGURACIÓN (1st floor)	20				
15	Remover Configuración, Verificar Screen, Pesar IBC	20				13
16	Dock y Abrir válvula	10				
F.	API Blend A- Excipiente A BLEND*	30				
17	ID excipiente 1, Forma 3503 (Excipientes), cernir	30				15
18	Reconciliar Componentes	30				
19	Ajustar y Cargar, Limpieza de menor cernidor, Verificar screen de cernidor					
20	ID (excipiente B) y reconciliacion de componentes					
G.	Mezclado de Excipente A *	10				
21	Undock, cerrar válvula, blending cap, "Home" position	10				
22	Receta de Blend 23 Min.	40				24
23	Dock y Abrir válvula					
H.	Cernido de Excipiente B (2nd floor)	10				
24	Cernir excipiente B					22
25	Reconciliacion de componentes	10				22
I.	Mezclado de Excipente B	20				
26	Undock, cerrar válvula, blending cap, "Home" position					
27	Receta Blend 13 min.	20				
J.	Reconciliacion 1er piso	20				
28	Pesar IBC, Reconciliacion del lote	10				
K.	Limpieza Menor de cuartos	30				
29	Limpieza de cuarto, downflow booth	30				23
30	Aprobacion					
L.	TRANSPORTE DE IBC	25				
31	Transportation	20				
32	Buscar materiales proximo lote en el airlock					31
33	Pedir 2 lotes adicionales	5				
						Lot End Date/End Time
						Total Time

Table 5 listed the total of 25.0 lots per week considering the 7 days that can be produced. The takt time of 3.6 lots manufactured per day was the result of the Total Available Hours EQ lots, less the time of planned times "downtimes" EQ lots, unplanned times "downtimes" EQ lots, time of the Major Parts EQ lots, and the cleaning time in the electronic system (MES) EQ lots.

Table 5

Total of Lots per Week

													TOTAL
Lots per week	21.5	21.0	27.2	26.3	25.2	27.2	23.6	25.7	26.6	27.2	24.5	23.8	25.0
Takt Time (Lots/day)	3.1	3.0	3.9	3.8	3.6	3.9	3.4	3.7	3.8	3.9	3.5	3.4	3.6

Table 6 is subdivided into the number of days per month, the number of shifts per day, the number of hours per shift, to obtain the available number of total hours and the total number of batches per hour. A total of 1012 lots per year can be produced in the flex 2 Unit Operation. The value of 4317.1 hours per year is the result of the total available hours subtracting the 4 other different scenarios.

The total of 707.8 lots per year refers to the number of lots with the standardized cycle time value of 6.1 hours. To get a more concrete idea of the goal, with the actual standardization target of 5.5hrs. and 4.5hrs, it takes to produce a blend in Flex 2, the researcher calculates with a more realistic 1.0 Unit Scenario process and the number of batches can be produced increase to 1012 batches per year (See Table 6).

Table 6

Total Available Hours EQ Lots, Planned Times "Downtimes" EQ Lots, Unplanned Times "Downtimes" EQ Lots, Major Cleaning Time EQ Lots and Electronic System (MES) Time EQ Lots

														1.0 Unit Process	
Flex 2	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	Total- One Unit	1	
Days/Month	26.0	24.0	27.0	26.0	26.0	26.0	26.0	27.0	26.0	26.0	26.0	27.0	313.0		
Shifts/Days	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0			
Hours/Shift	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5			
Total Available Hours	585.0	540.0	607.5	585.0	585.0	585.0	585.0	607.5	585.0	585.0	585.0	607.5	7042.0		
EQ Lots	95.9	88.5	99.6	95.9	95.9	95.9	95.9	99.6	95.9	95.9	95.9	99.6	1154.5	1154.5	1691
Production Windows (Days)	9.0	6.0	0.0	0.0	0.0	0.0	6.0	0.0	0.0	0.0	0.0	6.0	27.0		
Holidays (Days)	2.0	0.0	0.0	2.0	1.0	0.0	1.0	0.0	1.0	0.0	2.0	1.0	10.0		
Planned Downtime (Hrs)	247.5	135.0	0.0	45.0	22.5	0.0	157.5	0.0	22.5	0.0	45.0	157.5	832.5		
EQ Lots	40.6	22.1	0.0	7.4	3.7	0.0	25.8	0.0	3.7	0.0	7.4	25.8	136.5	136.5	195
Uptime (%)	0.85	0.85	0.85	0.85	0.85	0.85	0.85	0.85	0.85	0.85	0.85	0.85			
Downtime (Hrs)	87.8	81.0	91.1	87.8	87.8	87.8	87.8	91.1	87.8	87.8	87.8	91.1	1056.4		
EQ Lots	14.4	13.3	14.9	14.4	14.4	14.4	14.4	14.9	14.4	14.4	14.4	14.9	173.2	173.2	248
Major Cleaning Hrs	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0			
Time per Month	1.0	2.0	1.0	1.0	2.0	1.0	1.0	2.0	1.0	1.0	2.0	1.0			
Total Hours	26.0	52.0	26.0	26.0	52.0	26.0	26.0	52.0	26.0	26.0	52.0	26.0	416.0		
EQ Lots	4.3	8.5	4.3	4.3	8.5	4.3	4.3	8.5	4.3	4.3	8.5	4.3	68.2	68.2	98
MES Clean Hours	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0			
Time per Month	2.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0			
Total Hours	24.0	36.0	36.0	36.0	36.0	36.0	36.0	36.0	36.0	36.0	36.0	36.0	420.0		
EQ Lots	3.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	68.9	68.9	98
												total	4317.1	707.8	1012

Figure 1 below represents the scenarios of batches per month that can be manufactured in the

Flex area vs the number of batches required per manufacture. Additionally, shows the four-time scenarios (planned downtime, Uptime 85%, Major Cleaning, Special Cleaning) subtracted from the total number of hours available. The quantity of 892 is the total batches required for the forecast 2023 year (See Table 7 and Figure 1).

Table 7

The Total Available Hours Lots Subtracting Four Different Scenarios Vs 2023 Forecast Quantity Lots

1.0 Units Scenario	Lots		2023 FC
Available Hours	1651		892
Planned downtime	1456	195	892
Uptime 85%	1208	248	892
Major Cleaning	1111	98	892
Special Cleanning	1012	98	892
Flex MFG Lots (1.0 Units)	1012		892

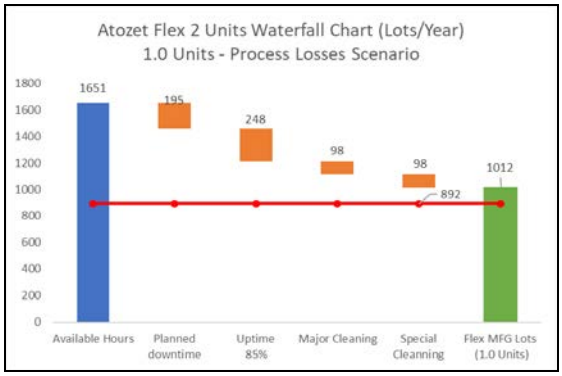

Figure 1

Batches Manufactured in the Flex Area

As a result, the obtained data establish the quantity of 1012 lots of batches can be manufactured with the standardize agenda, validating that with the anterior cycle time (Miu A) of 7.0 hrs. of duration of the blend process without standardization vs. the new standardized process with a cycle time (Miu B) of 5.0 hrs. the production capacity increase in relation of the last quantity of 610 batches.

The researcher can conclude, in relation to the hypothesis, that with 95% reliability it is validated that the Cycle time (Miu A vs Miu B) is greater than the new after the implementation of the project (See Table 8).

Table 8

Student T Distribution Hypothesis with Unknown Variance

Hypothesis			
Ho: μ CT Before	EQUALS TO	μ CT After	
Select one	MORE THAN	LESS THAN	NOT EQUAL
1 = YES	1		
H1: μ CT Before	MORE THAN	μ CT After	
Test with Unknown Variance (Student T Distribution)			
Hypotheis Test Results			
Miu	7.00	5.00	
Std. Dev.	0.5	0.5	
X Bar	7.0	5.00	
N	610	1012	
T exp	78.04		
V	1284.0		
Pvalue	0.0000		
Alpha	0.05		
Miu A is more than Miu B			

CONCLUSION

Any operation that requires a standardization of its processes requires time for planning and development to obtain results. The manufacturing process in the pharmaceutical industry is a challenging one, due to the large number of regulations and constant organizational changes to increase its production. By obtaining the results of the Flex 2 production unit and being able to analyze the number of batches that can be made vs. the quantity that they grant management, it has been a success, since a process could be standardized through lean manufacturing techniques and there was a great commitment to help among operators to maximize the areas of operations within manufacturing.

This provides a better understanding of the projected quantities over a year of production and how economically speaking resources can be defined to support production. These results confirm:

- The amount of 3 operators per shift for production.
- A standardized agenda, where there are defined times in the production of 2 batches mixed with different active ingredients.
- The quantity 1012 lots that can be manufactured per year.

- Know that an average of 3.6 lots can be made per day.
- Availability for 7 days x 3 shift turn production.

These results contribute to the standardization of the process and to a better understanding of production performance. As an opportunity for improvements in the process, it is possible to better define the times to reduce downtimes by 5% more in the process, the holidays and shutdowns days, the break relief of 30 minutes, the lack of personnel due to absenteeism can be add a 1hr/lot to the process, standardization in the times of major and minor special cleanings, the challenges of a significant increase in production and support standardized times so that the production time between batches does not increase.

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