Quality in the Pharmaceutical Industries

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Abstract−*There are various techniques to measure the productivity of a certain economic activity, which is one that generates a profit from three phases: production, distribution, and consumption. One restriction in choosing the ideal method is the availability of statistical information. In some localities, there is still insufficient data to measure total factor productivity systematically and periodically. However, there is information that allows calculating productivity for the labor factor in economic activities, notably the pharmaceutical industry. The simplest measurement of labor productivity occurs when there is a company or an industry with a single product. In this case, labor productivity is expressed in units of that single product, either per man hours or per worker. This is an exceptional situation, since it is usually necessary to measure the productivity of a company, or a sector of activity where different products are produced or where the labor platform in the production lines.*

KeyTerms **–** *DMAIC, Methodology, SMED, SIPOC.*

INTRODUCTION

We can define quality as compliance with established specifications to guarantee suitability for use. The quality of a drug is determined by its identity, purity, content, or potency and any other chemical, physical, biological, or manufacturing process properties that influence its ability to produce the effect for which it is intended.

Quality means all the features and characteristics that influence the ability of a device to satisfy the requirement of fitness for use, including safety and performance aspects. Quality is not achieved a program, rather, it is the result of a constant process where all the organization's personnel are involved. Quality is achieved through all business activity, which begins when inputs are received from suppliers and ends when the company delivers products to customers.

As a result of a good implementation of a quality program within the pharmaceutical industry, it is possible to obtain a set of guidelines and interrelated activities, aimed at ensuring that the pharmaceutical products produced have and maintain the identity, purity, concentration, potency, and safety, required for use. The benefits, then, are reflected in the positive results in the medium and long term in a company. Therein lies the importance of implementing it, beyond the fact that it is a challenge to perfect the processes to fulfill it.

At the beginning of the project implementation, it was observed that the levels of customer satisfaction, documentation, and inventory errors were increasing since they were at an unacceptable level for a company.

While the level of complaints by customers was decreasing, it may be noticed that after the project is implemented, all these goals were in a considerable increase and improvements for company.

Description

Quality control consists of making measurements of product parameters, determining if the values obtained are in accordance with established specifications. In most cases, this quality control is applied to the products produced and used by a company, whether they are final products, intermediaries, or raw materials.

Quality control in the pharmaceutical industry is a system for maintaining and improving quality

itself. It is carried out with the help of groups of people from an organization whose objective is to achieve a good quality control of the drugs developed with the intervention of a trained staff, without forgetting the cost and benefit for consumer satisfaction.

Objectives

The quality of products and services can be divided into nine basic areas, which can be considered as the 9 M`s (market, money, management, men, motivation, materials, machines, methods and increasing requirements of the product in each area).

- **Market**

Market is the number of new or modified products offered to the market grows in an explosive way. Many of these products are the result of new technologies that cover not only the product but also the materials and methods used in its manufacture. Today's businesses are carefully identifying the wants and needs of consumers as the basis for the development of new products, markets are expanding in capacity and functionally specializing in effects and services offered; as a result, businesses must be more flexible and able to change direction quickly.

- **Money (Globalization)**

Increased competition in many fields of industry, affected by global economic fluctuations, has reduced profit margins. At the same time, automation and mechanization have forced considerable outlays for new equipment and processes. The result of increased investments that must be amortized increased productivity has caused any significant loss of production due to waste and rework, to become an extremely serious issue in terms of quality costs.

- **Administration**

The responsibilities of quality have been distributed among several specialized groups. In other times, the head of the laboratory and the engineer were solely responsible for the quality of the product; now the marketing, due to its function of planting the product, must establish the requirements of this. Quality of service, even after the product has reached the consumer's hands, has become an important part of the "product package." This has increased the burden placed on top management particularly in view of the ever-increasing difficulty of locating accountability for deviating from quality standards.

- **Personal**

This is the most delicate factor, because without its proper functioning the pharmaceutical industry does not work. The human factor must know how to carry out all the procedures; this is through continuous training by experts, but not only technically but also to function in the industry. The rapid growth of technical knowledge and the creation of entirely new fields have created a great demand for people with specialized knowledge. Specialization has become necessary because the fields of knowledge have increased not only in number but also in breadth.

- **Motivation**

The increasing complexity of bringing a quality product to market has increased the importance of the quality contribution from each employee. The incentive and motivation of the employee has shown that in addition to the reward in money, today's workers require efforts with a sense of achievement in their tasks and the positive recognition that they are personally contributing to the achievement of the company's goals.

- **Material**

Due to production costs and quality requirements, materials are currently used within narrower limits. The acquisition of raw materials, both active principles and excipients, is an important operation and a critical point in the drug manufacturing process.

- **Machines**

The responsibility and demand within the pharmaceutical industry to achieve cost reductions and greater production volume to satisfy the consumer in highly competitive markets has led to the use of increasingly complex equipment, which depends heavily on the quality of the materials. As

companies transform their work by making it more automatic and mechanizing to reduce costs, good quality becomes more critical that makes cost reduction real and raises the use of men and machines to satisfactory values.

Contribution

The manufacture of medicines implies a great responsibility and a strong commitment of all the employees of the pharmaceutical industry. The reason is obvious: the health and life of consumers depends on the quality of the product. To achieve quality, pharmaceutical companies have implemented a series of actions aimed at obtaining confidence that the processes (operational and administrative) are carried out correctly. They have incorporated a series of preventive measures, control mechanisms and, in general, a set of techniques aimed at permanently increasing their capacity to meet quality requirements. Together, all these resources, actions and tools make up the company's Quality System. In its basic essence, a Quality System includes all the necessary tools to achieve and maintain quality, so the quality system requires a constant effort in training and education by and for quality. Considering all that, Quality System is defined as the set of elements (mutually related) and coordinated activities to direct and control an organization with respect to quality. Any quality management system is established based on quality policies and objectives. Quality policies describe guidelines and management strategies related to quality. On the other hand, quality objectives are the ambitious purposes (in a set time) that seek to achieve all the results related to quality.

METHODOLOGY

An improvement methodology needs to be used for successfully project. In this case, the DMAIC methodology was selected as tools to achieve the goals of increasing the productivity and quality.

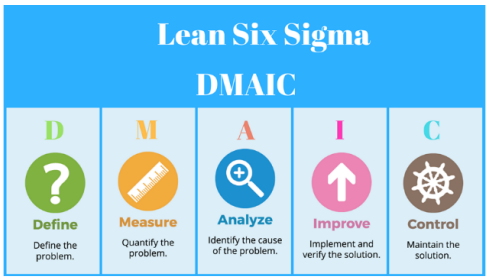

Figure 1
DMAIC

The tool at Define step was the Project Charter. Project Charter is a statement of the scope, objectives, and participants in a project. Provides a preliminary delineation of roles and responsibilities, outlines the project objectives, identifies the main stakeholders, and defines the authority of the project manager. Serves as a reference of authority for the future of the project.

At the Measure steps the following tools will be used:

- The SIPOC diagram - A tool that summarizes the inputs and outputs of one or more processes. The acronym SIPOC stands for Suppliers, Inputs, Process, Outputs, and Customers. The SIPOC diagram helps us to understand the relationship between the supplier and customer, in other words, the input and output variables of the process, and finally the process steps.
- Voice of the Customer - A technique that helps to understand in detail the customer needs organized and prioritized. This is showed in hierarchical structure arranged by customer comment, customer needs and customer.

Measure

There are different techniques to measure the productivity of a certain economic activity, which is one that generates a profit from three phases: production, distribution, and consumption. One restriction in choosing the ideal method considering the availability of statistical information.

The simplest measurement of labor productivity is when there is a company or an industry with a single product. In this case, labor productivity is

expressed in units of that single product, either per man hour or per worker.

This is an exceptional situation, since it is usually necessary to measure the productivity of a company, or a sector of activity where heterogeneous products are produced or where the workforce participates in several production lines. When that is the situation, a unit of measurement is required that allows standardizing the quantities of various goods produced.

The SIPOC diagram is made up of the indices that express the variations in percentage over time, referred to a base year, which represents the index for the period of analysis. Production indices are compared with labor input indices to measure labor productivity.

The labor productivity indices report the variations in production in relation to the labor factor. However, by themselves they do not allow us to know to what extent the improvement in labor productivity is determined by the greater efficiency of the labor factor, or by physical capital and technology.

The importance of measuring labor productivity lies in the possibility of knowing the performance of workers, with all that this implies for the profitability of a company. It also allows knowing the room for maneuver to increase wages without exerting pressure on prices.

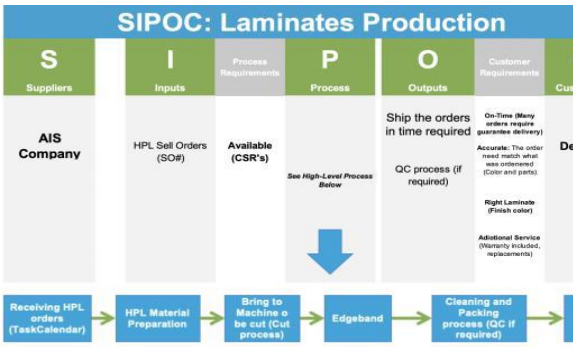

Figure 2
SIPOC Diagram

The SIPOC analysis helped to identify the relationship of the process from the suppliers to the customers. The process plays an important role between the suppliers and materials until the customer. The customer wants to improve the delivery time of the product, product quality, and lead time. The satisfaction of the customer and the lead time of every product has been challenging for the company to improve. The following analysis would be the key to reach the solution and reach the objective of the project.

The Data Collection Plan consists of identifying the Operational Definition of the process and how it will be measured. Through the Data Collection Plan, the operational definition of process can be understood. In this phase the process was separated in three elements: preparation time, changeover time, and transportation time. The preparation time consist of the set-up of the material to start the laminate process. This step starts where the product is prepared by the operator. The changeover time is defined as the change of the setup machine. This part plays a crucial role to improve the time and increase the capacity of the product. The operator needs to change the material and setup of the machine according to the order requirement and specifications. The transportation time consist of the traveling the operator must do every setup through the process. Through the final process the operator needs to bring the materials from one point to another.

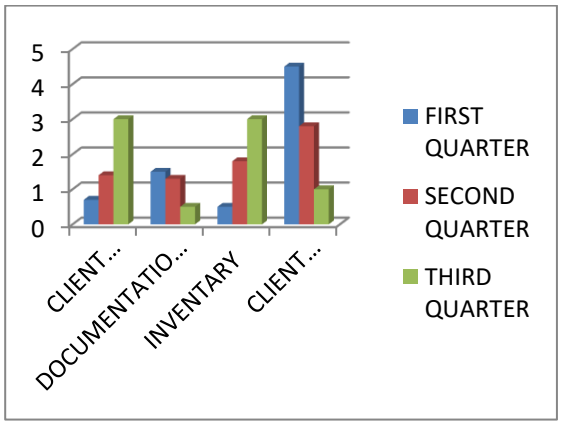

Figure 3
Chart per Quarter I

At the beginning of the project implementation, it was observed that the levels of productivity, hours / man, efficiency, and quality of the process were at

a level not acceptable for a company. After the project is implemented, all these goals were in a considerable increase and improvements for company.

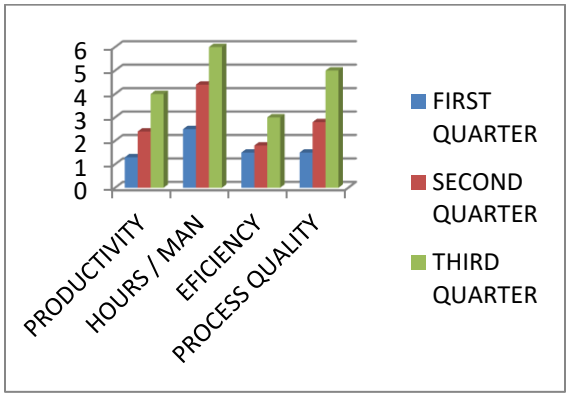

Figure 4
Chart per Quarter II

The operator needs to change the material and setup of the machine according to the order requirement and specifications. The transportation time consist of the traveling the operator must do every setup through the process. Through the final process, the operator needs to bring the materials from one point to another.

Improve Phase

The training must have a prior analysis to analyze and evaluate where in the organization it is necessary to improve or solve a problem, or simply update the information every day. This should be discussed by the person in charge of designing or selecting a training program.

On the other hand, it is necessary to express that training programs must be tailored, according to the needs of the company, since it is not the companies who have to adapt to these, but quite the opposite.

It is worth mentioning that it is necessary to ensure that what is taught is really a need of the organization, then what is taught is learned, that what is learned is transferred to the task and finally that what is transferred to the task is sustained over time. The only way to ensure that all this happens through a good evaluation, study, and analysis, during and after the implementation of any training program in a company.

The human factor is fundamental and is the engine of any company and its influence is decisive in its development, evolution, and future. The man is and will continue to be the most valuable asset of a company; that is why more emphasis has been given to the training of personnel within companies. When asking how people in organizations learn, we could say that it is simply through training. His answer would be absolutely correct, except that it actually explains a process that is unknown about learning, through another process that is training.

Taking this into account, it could be concluded that training is a fundamental tool for the administration of human resources, which offers the possibility of improving the efficiency of the work of the company, allowing it to adapt to new ones. There are situations that arise both inside and outside the organization. It provides employees with the opportunity to acquire greater skills and knowledge, and eventually impact their competencies to perform successfully in their position. In this way, it also turns out to be an important motivational tool.

Concept and Importance

Pharmaceutical products have special characteristics that dictate the need to adhere to very specific conditions, requirements, controls, and standards. For the elaboration of medicines, rules, standards, and measures have been defined that seek the manufacture of quality products. Pharmaceutical companies have a vital, functional and at the same time, legal tool to produce quality drugs: Good Manufacturing Practices (GMP).

Good Manufacturing Practices are a series of principles, preventive measures, activities, and basic rules that define the correct way to manufacture and handle a product, controlling its manufacture (and all the activities involved), so that the required quality is achieved and maintained.

In any case, GMP shows the correct path that should guide the production of quality products and the measures to preserve it. Therefore, every union employee must, by obligation and conviction, have a thorough knowledge of GMP; they must personally comply with them and enforce them; must be

convinced of its importance and usefulness; and engineers must pass on their knowledge and experience to other people. It must be up-to-date and permanently applied in your daily work. By knowing and correctly applying GMP, the employee will be complying with the objectives of the company's Quality System, thus ensuring that the products comply with their design characteristics and, therefore, that they are suitable for use. All sector regulations, the need to ensure that operations are carried out under controlled conditions and include, at least, the following topics:

- Have written procedures and, in general, an adequate documentation system.
- Have a product traceability system (records).
- Have qualified personnel who meet a series of basic characteristics.
- Have adequate facilities and equipment.
- Control purchases and receipt of supplies, as well as their assortment.
- Have an inspection and testing system in the transformation processes.
- Control defective materials and products and have an adequate destruction system.
- Attend and properly handle complaints and returns.

It is important that the employee knows the content of the rules that apply in the company and are aware of the responsibility that they imply; in fact, it is common to find companies that, in addition to the "official" standards that are imposed in their country, require a series of "internal" rules that must be complied with by employees of that organization.

It should be noted that when two or more standards have been accepted in a company, it is common to find differences, especially in the degree of severity of the standard. When this happens, the company will have to assume stricter criteria so that, logically, those established in the other regulations that apply in the organization are met.

GOOD DOCUMENTATION PRACTICES (BPD)

Documentation is one of the most important mechanisms to establish the quality system of each of the stages of work in the company. To achieve this, it is necessary to establish who will be responsible for the development and implementation of this quality system.

With the implementation of management systems or models (quality, environmental or other), having an efficient documentation system has become a fundamental need for their proper management and control. In this context, the application of Good Documentation Practices (GDP) can become an efficient and helpful tool.

The objective of the GDP is basically to define controls that prevent communication errors, thus ensuring that the staff follow the corresponding procedures, in parallel the application of the GDP facilitates the traceability of the products, in fact an appropriate documentation system allows to reconstruct the history of a product, including the use and disposal of raw materials, inputs, intermediate products, bulk products and finished products.

The documentation used in our process must be able to show that the products and the raw material associated with their manufacture were controlled throughout the process. To achieve the above, it is required that all specifications, formulas, and production instructions, as well as procedures and records, are formalized, that is, written and that they also do not contain errors, it is essential to ensure therefore the integrity and legibility of the documents.

The documentation must record the activities that manifest the life of a company, the result being the global control of the operations of an industry according to what is established as a quality policy, in accordance with national and international standards.

Documentation Classification

According to different recommendations of international standards, the documentation system is generally classified into 5 levels (Classification according to the Documentation Systems Guide).

- **Generate greater efficiency**. Companies with an auditing and monitoring system have the objective of maximizing the efficiency and quality of their processes. They establish guidelines to be followed by all employees to carry out simpler and less time-consuming business processes and trainings in terms of time or financial expense.
- **Boosts employee morale**. Clear and defined roles help established training systems, as well as a clear understanding of how their roles view quality and business success, are inherent to an effective program approach. This seeks that the employees are motivated and satisfied, since this way they will perform adequately in the organization.
- **Offers international recognition**. ISO 9001, the standard that establishes the requirements for the implementation of an effective audit program, is a global brand for quality management. By implementing this system, any business will appear trustworthy. The goal of many companies is to export internationally, and ISO accreditation greatly contributes to establishing credibility in the international business arena.
- **Improves process management**. Management must decide what improvements are necessary in their company through a documentation and analysis system. This is a carefully planned and implemented procedure, which will ensure the correct decision making for the business and the elimination of the risks of any costly mistakes.
- **Offers higher levels of customer satisfaction**. ISO 9001 is based on the principle of continuous improvement. The standard allows companies to define what a quality product should be and how it should meet customer needs. Thus, it provides companies with the framework to periodically review whether these needs are met, with the aim of continuous improvement.

The benefits are reflected in the positive results in the medium and long term in a company. Therein lies the importance of implementing it, beyond the fact that it is a challenge to perfect the processes to fulfill it.

Corrective actions are monitored based on how long they are on the list and the number of actions taken. One way to graph the "status" of problem solving through corrective actions is by graphing the months of the year against the actions carried out during those months.

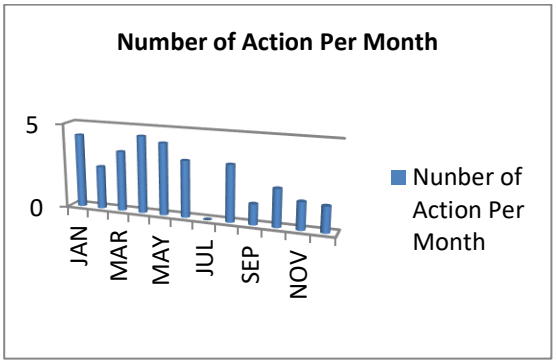

Figure 5
Chart of Action per Month
Errors Description Chart

With the following graph, it can be clearly seen that the three main problems for which there are too many errors and the factors to attack are firstly the incomplete signatures or dates, followed by the errors in reconciliation, and then the blank spaces.

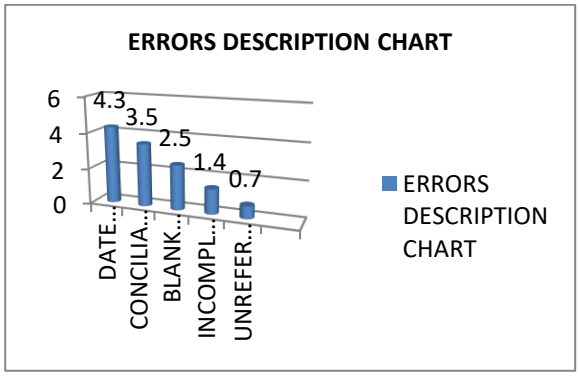

Figure 6
Chart of Errors Description

Defects

At each stage of the process, characteristics will be given to the product that is developed. A defect is how it is known to any characteristic that does not comply with the established specifications and that results in customer dissatisfaction. Each stage of the process will be influenced by different types of defects, in an analytical way they can be observed as follows:

Expressed in a mathematical form they can be expressed as follows:

DE= (DC + DI) – DO (1)

Where,

DE= Escaped Defects

DC= Created Defects

DI= Included Defects

DO=Observed Defects

The template was created as a standard document for quality control. The quality agent must fill it up every month to audit the process and make sure that the operators are following the process by standards that work correctly.

Line		Required Setup tools		Standard setup time	
Machine					
Operators					

N°	Task / Operation	Actual time		Improvement	Target time		Necessary activities
		Internal	External		Internal	External	
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							

Figure 7
Standard Worktable to Audit Process

CONCLUSION

The manufacture of medicines implies a great responsibility and a strong commitment of all the employees of the pharmaceutical industry. The reason is obvious: the health and life of consumers depends on the quality of the product. They have incorporated a series of preventive measures, control mechanisms and, in general, a set of techniques aimed at permanently increasing their capacity to meet quality requirements. Together, all these resources, actions and tools make up the company's Quality System. In its basic essence, a Quality System includes all the necessary tools to achieve and maintain quality, so the quality system requires a constant effort in training and education by and for quality.

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REFERENCES

[1] US Food and Drug Administration, 21.CFR Part 210. Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General. *US Food and Drug Administration*, Vol 4. Revised as of April 1, 2013. https://www.fda.gov/drugs/development-approval-process-drugs/pharmaceutical-quality-resources [Accessed: April 4, 2021].

[2] Six-Sigma-Material, "Throughput Yield (TPY)," *Six-Sigma-Material.com*, March 20, 2016. [Online]. Available: http://www.six-sigma-material.com/Throughput-Yield.html.[Accessed: April 8, 2021].

[3] Pan Learn, "DMAIC Approach in Lean Six Sigma", *msystraining.com*, June 29, 2018. [Online]. Available: https://www.msystraining.com/articles/quality-management/dmaic-approach-in-lean-six-sigma/. [Accessed: April 10, 2021].

[4] GoLeanSixSigma, "DMAIC – The 5 Phases of Lean Six Sigma," *GoLeanSixSigma.com*, March 7, 2016. [Online]. Available: http://www.goleansixsigma.com/dmaic-five-basic-phases-of-lean-six-sigma/. [Accessed: April 11, 2021].

[5] J. M. Juran and J. A. De Feo, Eds., "Lean Techniques: Improving Process Efficiency," in *Juran's Quality Handbook*, 6th ed., New York: McGraw Hill, 2010, pp. 327-353.

[6] Admin, "Single Minute Exchange of Die (SMED) Definition and Example", *sixsigmadaily.com*, April 4, 2018. [Online]. Available: https://www.sixsigmadaily.com/single-minute-exchange-of-die-smed-definition-example/. [Accessed: April 13, 2021].

[7] US Food and Drug Administration, 21.CFR Part 211. Current Good Manufacturing Practice for Finished Pharmaceuticals, *US Food and Drug Administration*, Vol 4. Revised as of April 1, 2013 https://www.fda.gov/medical-devices/postmarket-requirements-devices/quality-system-qs-regulationmedical-device-good-manufacturing-practices [Accessed: April 17, 2021].