Serialized Products in Pharmaceutical Industries: Update Strategies through Six Sigma to Decrease the Counterfeit

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Abstract *— This article discusses the serialization method established in the packaging lines on a manufacturing department of a pharmaceutical plant. It was developed an Installation, Operational and Performance Qualification to standardize and ensure the new requirements stablished by Food and Drug Administration (FDA). This process was design with the Six Sigma approach, using DMAIC. This process will allow the pharmaceutical to enhance the security of their products and comply with the Drug Supply Chain Security Act (DSCSA).*

Key Terms *— Drug Supply Chain Security Act, DMAIC, Installation, Operational and Performance Qualification (IOPQ), Serialization, Supply Chain.*

PROBLEM STATEMENT

Supply Chain builds upon a framework and seeks to achieve linkage and co-ordination between the processes of another entities pipeline i.e. suppliers and customers and the organization. In addition, supply chain refers to the process, or chains, and material information flows moving thorough the organization's operation [1]. The global pharmaceuticals industry faces problems of counterfeiting, which it implies a malfunction of the supply chain, specifically the tracking system. The pharmaceutical companies and governments of countries worldwide are convinced that counterfeiting by organized crime can be avoided significantly by implementing product serialization.

An estimate presented by The World Health Organization (WHO), mentions that counterfeit drugs are approximately 1% of the supply in developed countries and 30% to 40% in developing countries. Serialization requires a system track and trace the medical devices through the supply chain. The products should be identified by a unique serial number, batch number and expiration date day. This allow that the lifecycle of the product can be traced from production, through the distribution and in the end to dispensation to patients at the hospital [2].

As a fact, on April 10, 2017 the FBI published a news of a pharmaceutical Theft in which the criminals 40 shrink-wrapped pallets of pharmaceuticals, including thousands of boxes of popular medicines such as Cymbalta and Prozac [3]. This is the product serialization must be implemented.

Research Description

This research will create a complete plan to establish to develop the advantages of using the serialization of the medical devices. This will allow the pharmaceuticals industry to improve competitiveness, a reliable product, and a secure supply chain. At the end, it will decrease the counterfeiting, the organized crime, and the loss of medical devices.

Research Objectives

The objectives of this research are:

- Develop a strategy to standardize the supply chain distribution of medical devices.
- Guarantees broad knowledge about the importance of serialization in the pharmaceutical industry.
- Supports quality and customer service.
- Increases the leveraging of global best practices by the implementation of serialization.
- Reduce counterfeiting and organized crime.
- Provide a better tracking system of the medical devices.
- Increase the protection of the brand for the medical device.
- Deliver a secure medicine to the customer, in this case the patient.

Research Contributions

This research will ensure these contributions to the pharmaceutical industry:

- Standardizes the process in the labeling system of the packaging lines.
- Ensures that the pharmaceutical complete with the Drug Supply Chain Security Act (DSCSA).
- Enhance the procedures in labelling system of the FDA.
- Decreases the counterfeiting and the organized crime.
- Control of processes efficiencies.
- Provide wide tools of DMAIC to control the process.

LITERATURE REVIEW

Pharmaceutical industry is a complex world that only the people who are in it understand. Pharma is one of many industries where big data promises big changes. Pharmaceutical companies have been under increasing pressure to deliver innovation high-quality products and services at competitive process that is why they are mainly focused in innovation. [1] The 2017 edition of the *Health Distribution Alliance (HAD) Guidelines for Bar Coding in the Pharmaceutical Supply Chain* refers that Federal law requires that the 10-digit NDC, the basic identifier for all forms of pharmaceutical products in the U.S. This is critical component in the bar coding and serialization of pharmaceuticals. In contrast, the DSCSA requires that manufacturers affix a Product identifier that consists or standardize graphic that includes the human-readable format and on machine-readable data carrier that conforms the standardize numerical identifier (SNI), lot number and expiration date of the product [4].

The FDA- prescribed NDC is presents in one of three hyphenated, human-readable formats. The first field of four of five digits identifies the manufacturer/repackage of the product. Another field identifies the product, dosage and strength. The final field of one or two digits identifies the individual trade/package size [4].

Serialization

This is the new regulatory initiative that is steadily gaining momentum cross the world. Serialization regulations in the pharmaceutical industry require a unique number to be assigned to each individual unit of saleable medicine [4].

Serialization is fast becoming a necessity for the pharmaceuticals industry because of the following factors:

- A highly complex distribution network from manufacturer to consumer in which products change hands as many 10 times.
- The authentication of the product at various levels in the supply chain becomes very difficult without data sharing across the supply chain.
- The high price of prescription drugs and the relative ease of duplication and diversion make them a prime target for counterfeiters.

Cognizant, a leader provider of information technology refers as the *drive for serialization it is not only to provide serial numbers for any saleable units*, but also maintaining those identifications to provide visibility and full traceability within supply chain. It is expected that the serialization system performs as higher level workflow as:

- Organizing serial numbers for the entire system.
- Ensuring number uniqueness and randomness.
- Ensuring that all serialization systems use common capabilities: product identification equipment (PIE), product identification middleware management systems (PIMMS) and electronic product code information systems (EPCIS). These must be designed to meet global standards and service all markets (“design once, use many”) [4].

Federal law requires that drug manufacturers register their establishments with FDA annually. The pharmaceutical industries must submit a list of the drugs they manufacture, including the National Drug Code (NDC) number. The FDA regulations in 21 C.F.R. Part 207 implement this requirement. [4]

The 10-digit NDC is the basic identifier for all forms of pharmaceutical products in the U.S.

healthcare industry. This is a critical component in the bar coding and serialization of pharmaceutical products. Also, the NDC is used for the monthly reposting of all incoming and outgoing controlled substance transactions and inventories. This is used to have a sequence through the manufacturer to the healthcare distributor, to the provider, the computer systems depend on the NDC in order to identify which pharmaceutical products are ordered, paid or returned. [4]

The DSCSA requires that the manufacturer imprint a product identifier to each package and homogeneous case of a product that a manufacturer intend to introduce into the commerce.

- A product identifier is a standardize graphic that includes, a human-readable format and a on a machine-readable data carrier that conforms the standards developed by international standards development organization, the standardize numerical identifier (SNI), lot number and expiration date of the product [4].

To comply with the DSCSA, the product should include the SNI, which identifies each product package. The SNI includes the NDC and a unique alphanumeric serial number of up to 20 characters. The DSCSA requires the inclusion of the product's expiration date in the product identifier. The format if this expiration date is "YYMMDD" but currently there it is not assigned a day in the format, so that is the new requirement from the FDA that all products serialized or non-serialized must include the last day of the month when the production is taking course [4].

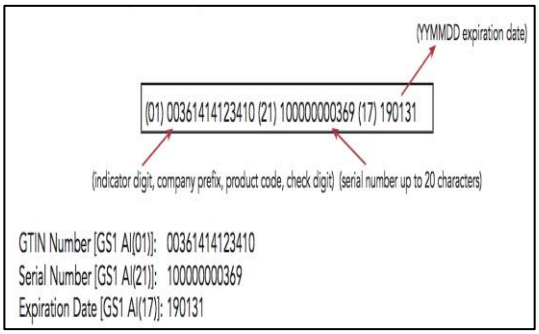

Figure 1
Example of GTIN, Serial Number and Expiration Date with Serialization [4]

Also, de DSCSA requires the inclusion of the product's lot number in the product identifier. The recommended in the GS1 Al (10) with one to 20 alphanumeric characters representing the batch or lot number.

Two-Dimensional (2D) Bar Code

The FDA's bar code rule, requires and encoded, standardized linear bar code containing the NDC number on human prescription drugs, biologics and non-prescription, over-the-counter- (OTC) drugs that are used commonly by patients.

To commit with the regulations of FDA it is important that all products of a pharmaceutical must be identified:

- Must have a NDC number.
- The product must be included in a 2D Data Matrix bar code when affixed to, or imprinted upon a package.
- The product must include a linear or 2D Data Matrix bar code when affixed to, or imprinted upon a package.

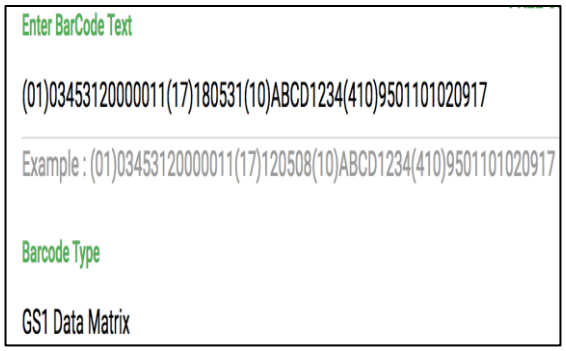

Figure 2
Example of GTIN, Serial Number and Expiration Date with Serialization with Barcode Generator Application [5]

Figure 3
Example of 2D Barcode, Serial Number and Expiration Date and Serialization with Barcode Generator Application

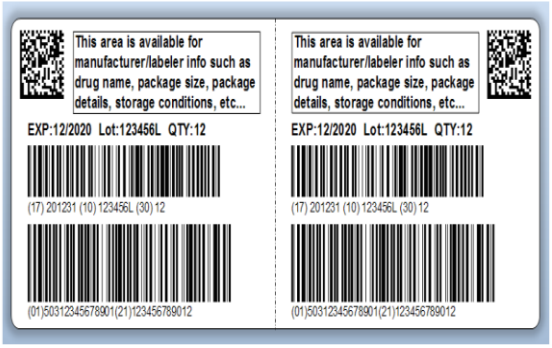

Figure 4
Final Product Identification Label Homogeneous Case, Serialized Corner Wrap [4]

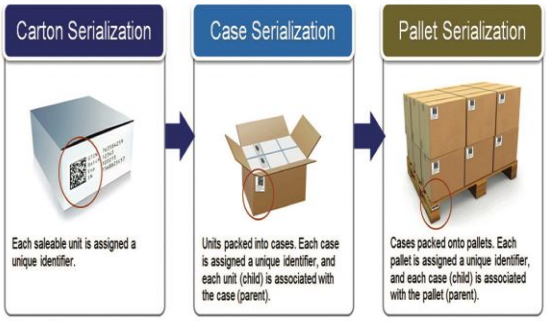

Figure 5
Types of Serialized Labels and their Application in the Boxes for Distribution

Six Sigma Methodology

Ronald Snee [5] describes six sigma as a improvement approach for businesses. This description seeks to focus on reduction of variation or to eliminate the causes of mistakes in business processes. Dave Nave describes that by using a set of statistical tools to understand the fluctuation of a process, management can be predict the expected outcome of the process [6].

Six Sigma highly effective implementation of proven quality principles and techniques. This concept was originated by Motorola Inc. in the USA in 1985. This methodology was created by incorporating tools and processes from the work of leaders in the manufacturing industry [7].

DMAIC

The activities that a company propose for the performance of the process can be accomplished by DMAIC, this is a methodology that consist of a close-loop process that eliminates unproductive steps, it focus is in the new measurements and applies technology for continuous improvement [7]. The Six Sigma team must recognize the metrics to create a reliable experience of the process.

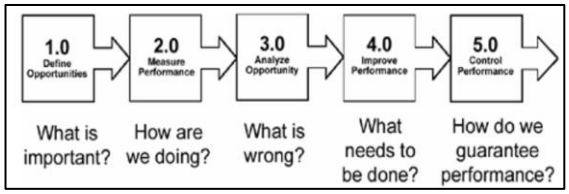

Figure 6
Questions for Critical Thinking during the DMAIC Process [8]

DMAIC is a data-driven quality strategy used to improve processes. It is an integral part of a Six Sigma initiative, but in general can be implemented as a standalone quality improvement procedure or as part of other process improvement initiatives such as lean [9].

DMAIC Acronym

DMAIC is an acronym for the five phases that make up the process:

- Define the problem, improvement activity, opportunity for improvement, the project goals, and customer (internal and external) requirements.
- Measure process performance.
- Analyze the process to determine root causes of variation, poor performance (defects).
- Improve process performance by addressing and eliminating the root causes.
- Control the improved process and future process performance.

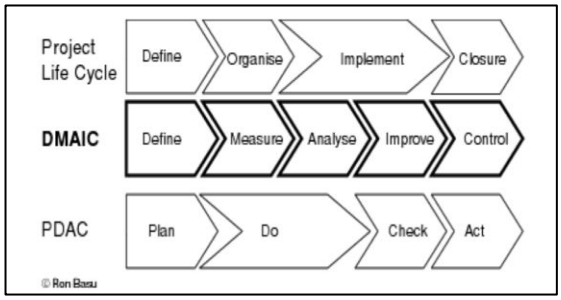

Figure 7
The DMAIC Base Model [10]

The DMAIC process easily lends itself to the project approach to quality improvement encouraged and promoted by Juran [9].

METHODOLOGY

DMAIC is the tool used to develop this project.

Define Phase

In the process identification, will be realized, in this case, perform the label with the serial number, the lot number, the expiration date and the 2D-Barcode. A Project Charter is going to be executed, it which is defined the scope of the project, the objectives and it will be determined the people that will be part of this project. In this case the scope of the project is to identify all the products that go through a packaging line and perform the serialization of the product. The members of the team will be the Senior Technician and the operators that have the training to perform the changes in the Label System. The team will be in charge for validate the protocol performing a SIPOC Diagram.

Measure Phase

In the measure phase, the sample will include ten (10) case labels of each product in which can be verified that the label commit with the proposed parameters. The challenge of the phase measure is that the label includes the serialization number, the expiration date, the lot number and the 2D-Barcode. Also, a software backup will be performed. A 200% case label verification will be performed. The people in charge of this activity will going to be the Senior Technician and one of the operators. It is important to document all these parameters following the Good Manufacturing Practices. In this phase a flowchart will going to be performed to better comprehend of the process.

Analyze Phase

In the phase of analyze the labels collected are going to be analyzed with the objective of identify the labels that have the acceptance criteria and to recognize is there is a fail on the Labelling System. This phase is crucial to commit with the objective of the project, because this is the result that the team are going to present to the pharmaceutical and to the FDA. In this phase the past label is going to be compared with the actual label. If the analyze phase has the approval of the pharmaceutical managers the process will going to be standardize.

Improvement Phase

In the Improvement Phase a process of implementation will going to be performed. The process will be validated and the changes in the label will be permanent to commit with the laws of FDA and to avoid the counterfeiting. Also, the benefits of this implementation will be going to be evaluated.

Control Phase

In the control phase, there will be performed the Standard Operation Procedures (SOP's), and the procedure of the new changes must be provided to the people of the Manufacturing Plant to notify the changes and to commit with the federal laws. After the implementation of the procedure and trimestral report must be completed to confirm that the process does not have changes and if an improvement can be made.

RESULTS AND DISCUSSION

Due to the accomplishment with the approval of the pharmaceutical managers the procedure was executed and the results expected were the actual results. The project charter was effective and the SIPOC diagram. The procedure was evaluated to determine actual status of the criteria acceptance for the Serialized products and that the label complete with the serial number, the format of the expiration date, the lot number and the 2D-Barcode. The process was performed for Packaging Line one (1), two (2) and three (3). All the parameters were accepted and the respective training were performed to the employees. The data collected from the labels were validated from the supervisors from Packaging Line one (1), two (2) and three (3). Now, the products commit with the Drug Supply Chain Security Act (DSCSA). The SOP'S were developed and training for the procedure was given to the

personnel to belong to the manufacturing area. The Manufacturing personnel are waiting to perform the trimestral report to confirm that the process did not suffer any change and if an improvement can be made.

CONCLUSION

Serialization promotes a secure way to protect the products in the Pharmaceutical Industry. This project ensures the new requirements stablished by Food and Drug Administration (FDA). Examples of serialization were proposed in this project. New methodologies like Six Sigma and DMAIC were used as performance tools in order to create a strategic plan to develop the procedures and techniques of quality. Realizing this project the pharmaceutical to enhance the security of their products and comply with the Drug Supply Chain Security Act (DSCSA). A decrease in the counterfeiting and the organized crime is expected because now the product can be traced trough the supply chain. The pharmaceutical plant staff will going to validate the process and now the products are going to be serialized. By the developing of the SOP the personnel of the Manufacturing Department will going to be trained.

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