How Serialization can Improve Drug Manufacturing Operations

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Abstract *— An estimated 10% of the global medicine supply chain is counterfeit with sales of counterfeit prescription drugs estimated to be around $75 billion a year. Although estimates about the magnitude of the global counterfeiting problem vary, it is widely recognized that the number of fake drugs being made is growing annually as criminals are increasingly attracted by the high returns and low risks that such activities represent. In 2013, the United States passed the Drug Supply Chain Security Act (DSCSA) requiring Serialization as part of an effort to protect patients from exposure to unsafe drugs that may be counterfeit, stolen, or contaminated. The new law required all prescribed pharmaceutical drug products sold in the U.S. be tracked and identified in every package with a unique identifier that includes essential product information. Although serialization is a compliance requirement, Pharmaceutical companies have embraced the challenge and have taken advantage of the opportunity to automate steps and improve manufacturing operations.*

Key Terms *— Counterfeiting, Improvement, Serialization, Track and Trace.*

INTRODUCTION

Serialization is the process of tracking and tracing prescription drugs as they go through the supply chain from manufacturing to patient dispensing. As part of an effort to protect patients from exposure to unsafe drugs that may be counterfeit, stolen, or contaminated, serialization was introduced in the United States after a new federal law, the Drug Supply Chain Security Act (DSCSA), was enacted by the U.S. Congress. The new law required all prescribed pharmaceutical drug products sold in the U.S. be tracked and identified in every package with a unique identifier that includes essential product information. Europe later introduced similar regulations requiring the ability to track and trace prescription drug products and many more worldwide jurisdictions followed as well. This posed a major challenge for pharmaceutical companies: invest in new equipment capable of meeting these new worldwide regulatory requirements or risk not being able to sell the products.

Initially, pharmaceutical companies received the new regulations in a reluctant manner as this would require millions of dollars of investment in new equipment and would potentially add additional steps to their current manufacturing process. However, companies decided budgets for new serialization equipment came with a caveat: process improvements. What began as dreaded regulatory compliance projects slowly transformed into massive manufacturing and operational improvement initiatives. Pharmaceutical companies saw the opportunity to challenge their engineers and external equipment providers with the requirement that serialization would not only not adversely affect current manufacturing operations but actually improve them.

The Drug Supply Chain Security Act (DSCSA) [1] requires that serialization be implemented in phases with several milestone deadlines over an 8-year period. The law was passed in 2013 and the first phase began implementation in 2015 with the requirement that drug manufacturing information be shared at a distribution level. Serialization should be fully implemented by 2023 when the smallest level of unit drug product, patient dispensing, should be able to be traced back

through it's supply chain cycle to its original manufacturer.

RESEARCH OBJECTIVE

The main objective of this project is to implement a serialization solution that meets all company and regulatory requirements while improving key manufacturing operations attributes such as Overall Equipment Effectiveness (OEE), cycle time, lead time, equipment layouts, process flow, changeover reduction, and designing workstations that are in sync with the workflow and have an ergonomic design for the operator.

RESEARCH BACKGROUND

The design project was conducted in a pharmaceutical manufacturing company in Juncos, P.R. The project was approved in order to meet new compliance requirements enacted in 2013 by the Drug Supply Chain Security Act (DSCSA). The new law required all prescribed pharmaceutical drug products sold in the U.S. be tracked and traced using a process called serialization.

Serialization is a compliance requirement, meaning pharmaceutical companies must comply with new laws or regulations in order to be able to sell a drug product in each global jurisdiction. Historically, new compliance requirements add steps to the pharmaceutical manufacturing process and therefore have usually had a negative impact on operations. Serialization, although a compliance requirement, is mostly an automated process and requires the integration of new automated packing machines that not only serialize but also are able to perform other process functions. Serialization, therefore, provides the unique opportunity to not only meet the compliance requirement but to also automate many manual operations of the packing process.

Serialization works [2] by assigning a unique identification code or serial number in the form of a 2-D Data Matrix Code (refer to Figure 1) to each unit of sale of a drug product. The Data Matrix Code should include the following product information: lot number, expiration date, GTIN-14, and 11-digit serial number.

Figure 1
Example of a Serialized Individual Unit of Drug Product. The Packaging includes GTIN-14 Number, 11-Digit Serial Number, Lot Number, Expiration Date and a GS1 2D Data Matrix Barcode.

A unit of sale is meant to include any form of sale units such as individual unit dispensing at the pharmacy level, a bundle or case at the distribution level, and pallets at the manufacturing level. Each must have their own unique identification code. The unique identification code can then be used to confirm the product's authenticity throughout the supply chain as shown in Figure 2.

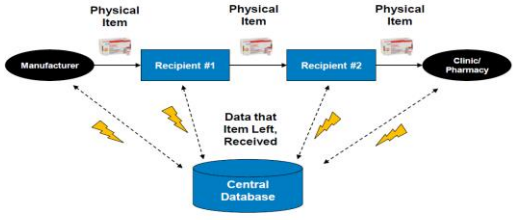

Figure 2
Track and Trace is the Ability to verify at Each Stage in the Supply Chain that a Product is Genuine and came from the Expected Source

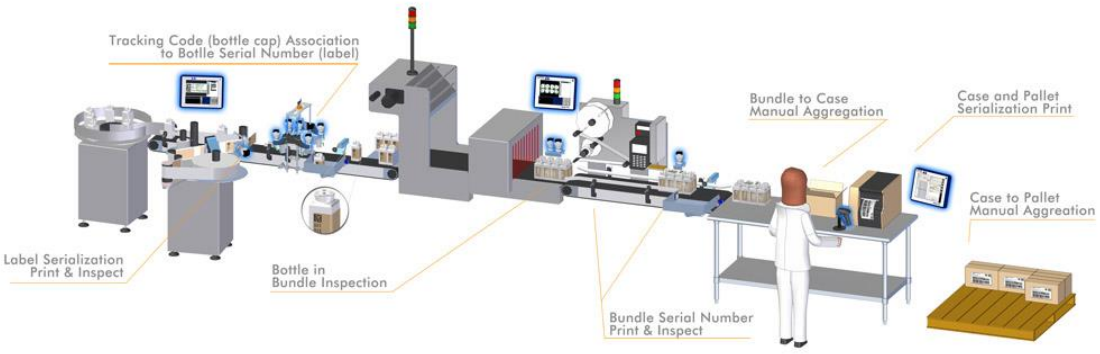

Figure 3
Overview of the Serialization Process

The serialization process [3] in a packaging line consists of a labeler where a label is printed and inspected by machine vision. If inspection passes the serial number printed is then associated with the individual unit. The individual unit then goes on to join other individual units in either a case or bundle. A new label is then printed for the case or bundle and then machine vision inspected. If inspection passes the individual units are then associated to the package. The same process is then applied to packages, which go on to be associated to pallets. As can be shown in Figure 3, serialization is merely a process of associating units throughout each packaging level so that they can be traced back to the lowest individual level ensuring product authenticity. Many of these steps were not previously required and were not being performed by packaging lines. By adding these additional steps, the assumption is that lead time, or the time between the initiation and completion of a production process, will increase. If the steps were to be done manually by the operator the assumption would be correct, the lead time and cycle time, or the time required to complete one unit from start to finish, would increase. By automating all of the new steps and also taking advantage of the new packaging machines that serialize but can also automate other previously manual processes the lead time and cycle time can be decreased while units per minute and OEE increased.

Serialization not only requires generating unique serial numbers, but also requires maintaining those identifications to provide visibility and full traceability within the supply chain. Serialization provides supply chain security by monitoring the complex distribution network from manufacturer to consumer in which products can change hands several times. By sharing data at various levels, product authentication can be maintained across the supply chain.

RESEARCH METHODOLOGY

The methodology used for this design project is the Six Sigma technique for process improvement called DMAIC (refer to Figure 4) which stands for: Define, Measure, Analyze, Improve, Control.

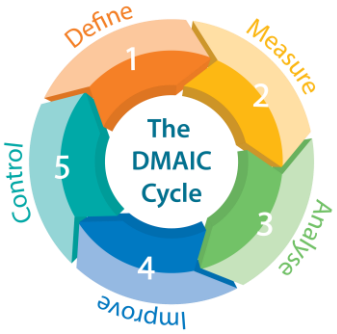

FIGURE 2
Six Sigma DMAIC Model

DMAIC is an integral part of any Six Sigma initiative and has proven itself one of the most effective problem solving methods that can be used. DMAIC can be implemented as a standalone

quality improvement procedure or as part of a greater process improvement initiative or project.

DEFINE – During this step, the Voice of the Customer (VOC) is used to describe and identify the problem and the products and services to offer as a solution. The activities performed in this step include:

- Setting project goals and expectations.
- Establishing the resources required and project scope.
- A high-level map of the process is drafted.
- Client data is requested and reviewed to identify areas of opportunity in the process.
- A project charter is prepared using all of the information gathered from the client.

The project charter is the purpose of the "Define" step as it defines roles and responsibilities, outlines project objectives, identifies the main stakeholders, and defines the authority of the project manager.

In this project, there are two "Customers" in the VOC. The first customer is the FDA and meeting the requirements of the DSCSA. The second is the pharmaceutical company and meeting their specific process requirements. The Pharmaceutical Company requires that after serialization has been fully implemented, key manufacturing operations attributes such as Overall Equipment Effectiveness (OEE), cycle time and lead time must all be at pre-serialization levels or better. The new equipment required for serialization must meet the requirements of process flow and low changeover time. New operator workstations required for serialization must be in sync with the workflow and have an ergonomic design. All of the requirements, from the FDA and the pharmaceutical company, must be met in order for the project to be completed successfully.

MEASURE – Now that the customer has provided in the previous step the requirements, expectations and key process attributes to measure it is time to collect data in order to establish a baseline to compare performance after project implementation. Historical data can be requested from the customer, but it is important to collect new data as well in order to establish a solid, unbiased and objective performance metric from which to compare to at the conclusion of the project and determine whether significant improvement has been made.

The measure step is not only to gather data but to also get to know the different types products and suppliers that either will impact the project or be impacted by the changes that will be implemented. Defects and opportunities for improvement must also be identified and preparing a detailed process map of the areas included in the project should be done in this step.

Before gathering data for improvement projects a Data Collection Plan is usually prepared in order to ensure the data collection process and measurement systems are stable and reliable and that the data collected can be used to support the next step in the DMAIC methodology: Analyze. The data collection plan usually contains:

- A description of the project.
- The specific data that needs to be collected.
- The number of observations needed.
- The methodologies that will be used to collect the data.

For this project time studies were performed to all of the steps in the packaging process, including changeover time, to gather data about current process output in order to evaluate the impact that additional tasks added due serialization may have on the defined capacity, UPM, OEE, standard times and headcount of the affected packaging lines. The current process layout was studied in order to analyze how to incorporate new tables and equipment that will be added due to serialization and assure serialization achieves ideal process and material flow.

ANALYZE – The purpose of this phase is to make sense of the data collected and process map to determine root causes of defects, poor quality and identify opportunities for improvement. It is important for teams to only use the collected data to reach conclusions and not mix past experiences to

reach conclusions about the root causes of problems.

When following the DMAIC methodology for an improvement project the tools that are usually used to analyze the data collected in the previous step are Histograms, Pareto charts, Fishbone diagrams, 5 Whys and statistical analysis. The data that was gathered in the Measure step is now used to:

- Identify the steps that add value or do not add value to the process.
- Determine root cause of the problems or defects identified.
- Identify sources of variation.

For serialization, the data collected from the time studies was used to establish a baseline UPM output for several packaging lines. Most importantly, because the time studies were recorded it allowed for a detailed breakdown of all the steps performed from start to finish and how long each step takes on average. The data was then used to identify unnecessary steps to the packaging process. The biggest areas of opportunity identified were during changeover and setup. There are many paperwork steps, idle time due to waiting for material and signatures from quality personnel, challenges that need to be performed to machines prior to beginning a packaging lot, and many changeover parts needed when changing from one packaging set up to another.

IMPROVE – In the Improve step the goal is to design creative solutions to the defects, waste, unnecessary steps and opportunities identified in the Measure step. The original design and budget discussed in the Define step must be taken into consideration when designing solutions and fixes to the problems identified. .

Because serialization can be implemented as fully automated, semi-automated or manual processing, it is important to invest the effort into assessing the suitability of any proposed solution with the data collected in the Measure step in order to provide the ideal solution based on customer needs and budget.

The machines used for serialization [4] provide a solution to many of the problems identified in the previous step. By automating, many of the processes and designing one machine that consolidates several tasks that were performed by several different machines and operators into one decreases line stops and increases line output. The challenges that need to be performed before being able to start a packaging lot are significantly lower due to consolidating tasks and increasing automation. The serialization machines are also designed requiring little to no changeover parts by using machine adjustments to change from one packaging set up to another instead of actual change parts. The proposed solution addresses or eliminates most of the problems identified.

CONTROL – Once the proposed solution is implemented, the purpose of this phase is to prevent old problems and defects from returning and to keep improvements to the process on course. In this step, statistical process control should be implemented and process capability determined. A Process Control Plan should be created to ensure the improvements established will not deteriorate once the improved process is returned to the process owners.

Because serialization is not a small process change and is one that "takes over" the process does not mean problems won't arise. There is a learning curve when new machines are implemented, operators should be properly trained, and Standard Operating Procedures (SOPs) prepared to ensure optimal process performance.

Measurements should be performed again in order to assess the level of improvement, verify benefits and costs, and to confirm the customer requirements are met.

CONCLUSION

The many challenges that serialization poses have created a negative stigma to the process requirement. Despite the challenges that serialization poses, when properly implemented, it provides a solution that not only meets but also

exceeds both manufacturing and compliance goals. Serialization leads to increased transparency and visibility by reducing counterfeiting, diversion and theft. It also provides the ability to trace product locations, supply chain has increased shipping accuracy and recalled and defective products can be removed from the market more quickly.

Serialization, although expensive and federally mandated, should no longer be seen as a compliance burden to pharmaceutical companies but as an opportunity to improve processes and reduce costs. Most importantly, serialization improves patient safety and improves sales by reducing the probability that a patient will consume a counterfeit drug. This is a win-win solution for consumers and pharmaceutical companies.

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