Optimization of a Pharmaceutical Filling Process to Comply with Federal Regulations and Minimize Process Variability

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Abstract

This project analyzes the scientific methodology that was followed to solve a problem that arose in a pharmaceutical installation after a federal regulatory inspection. The route for a robust solution was framed by a Six Sigma approach and a DMAIC methodology, among other mechanisms. Staff with different backgrounds joined as a team to contribute their knowledge and experience using statistical tools, engineering methods and scientific fundamentals to the solution process. The realization of this project will allow the pharmaceutical facility to optimize, regulate and control its filling process for the welfare of its customers and compliance with federal regulations.

Introduction

The main objective of this research is the implementation of a plan that after its execution, satisfies the requirements of the FDA observation and enhances quality compliance on the manufacturing facility. Furthermore, it is also the objective of this research, to provide manufacturing engineers and management with the correct data so they can make sound decisions in terms of budget and level of compliance that we want to achieve. The contribution of this exercise is a mutual contribution which will benefit both the Beta Company and the customers that use the products manufactured by Beta Company.

Background

This research is performed to identify the essential elements required to successfully implement and manage the plan to comply with the observation given by the FDA inspector. A team of professionals with different backgrounds (engineering, sciences, and statistics) will gather to discuss the initial sources of information that will be used. Where the group presume that the first investigations will be related to: what the CFR establishes regarding visual inspection, Beta Company's customer complaints and corporate policies, and finally a benchmarking with other Beta Company subsidiaries to evaluate any approach or study they could have regarding the amount of water inside the bag. Gathering the appropriate documentation at the first stages of this process, will allow the company to deploy it to management for a strategy or final decision on how to tackle the problem.

Problem

The manufacturers of pharmaceutical solutions, administration of medicines and parenteral nutrition are committed to guarantee the identity, strength, quality, purity and power of the manufactured products. Beta Company, located in Puerto Rico, promotes continuous improvement to strengthen compliance and ensure the continuity of quality standards at every step of their supply chain. A manufacturer, such as the one mentioned above, must comply with the Code of Federal Regulations (CFR) in order to sell products within the United States. There is an agency that enforces compliance with the CFRs which is known as the United States Food and Drug Administration (FDA). In a recent visit of this regulatory agency to the manufacturing area of the Beta Company, the FDA inspector found that the amount of water inside a sealed bag (containing smaller bags of the product inside) was not constant from one bag to another. The inspector highlighted the great variability in the amount of water inside the bags and, furthermore, that there was no study or specification of how much is the correct amount of water that should be inside a bag.

Methodology

Figure 1: DMAIC

Phase I: Define

The Define Phase is the first phase of the Six Sigma improvement process. In this phase, the project team starts creating a Project Charter, a high-level map of the process, and strives to fully understand the problem under evaluation for future optimization. Once the problem statement is thoroughly defined and the process steps are clearly understood, maps of the product flow and a high level process map are basic elements of the starting phase of the project. The classic and most used tool here is called SIPOC, which stands for Suppliers, Inputs, Process, Outputs, and Customers. During this phase an essential task will be to contact internal/external customers to better understand their requirements and need of the process. Such task is better known as the Voice of the Customer. Finally, a Critical to Quality diagram, called CTQ Tree, will provide an insight on how to improve the process or solve the problem to achieve the project objectives and goals.

Phase II: Measure

During the Measure phase, detailed data will be gathered describing the current performance of the process. This baseline data helps to clearly understand the problem and allows for future comparison in performance before and after improvements implementation. The data collected in this phase will be important to delineate a baseline, identify bottlenecks, limitations and constraints. Tools such as flowcharts, data collection sheets, and graphs will be used to evaluate the collected data. Filling bags and the overpouches where the already filled bags are put for later customer delivery, is a mission-critical component of Beta Company manufacturing process. The effects of errors, water levels outside of the appropriate parameters and excessive variation, can be tremendous for the institution and patients as well. At a minimum, they may cause visual concerns on the distribution centers, pharmacies, and hospitals where the product is utilized, but it may also cause bacterial growth and therefore catastrophic harm to the patients. With the execution of this project, Beta Company is strengthening its quality control programs to ensure that the product delivered for commercial use is defect-free. In this aspect, Six Sigma is suitable because healthcare processes and federal regulations require a near-zero tolerance for mistakes.

Phase III: Analyze

The goal of the Analyze phase will be to identify potential root causes for the process problem being addressed and then confirm actual root causes with data. Having completed the Measure phase, the project team will have a clear problem statement which specifies what the problem is and under what circumstances it occurs. At such point in the DMAIC process there is substantial data to establish the baseline performance of the process, relative to the Critical to Quality measures established based on customer input. Tools to be used during this phase are quantitative (regression, ANOVA, correlation, etc.) and graphical (histograms, scatter plots, box plots, etc.) to provide reliable data for appropriate decisions during the next DMAIC step.

Methodology

Phase IV: Improve

At this point is time to improve the process by establishing ways to successfully fulfill the requirements of the problem established in the first DMAIC phase. This phase will be executed by Beta Company engineers in a future time taking into consideration manufacturing windows and timing strategies. To successfully complete this portion of the "improve" step, a series of essential tasks need to be executed such as evaluation of "proposed water level boundaries" versus "process capability" to adopt the way of redesigning or optimizing. Brainstorming solution ideas using creativity techniques and the use of "solutions priority matrixes" to rank solutions and decide primarily based on business requirements such as cost, compliance and customer safety.

Phase V: Control

The last phase of the DMAIC methodology is unfortunately known as the step where less effort is put. The team of professionals executing this DMAIC optimization process will be very strict on taking advantage of this "Control" phase to maintain the gains by standardizing processes, providing the necessary trainings and closely observing the optimized process performance. As improvement is not a separate activity and must be built into the work process, a plan–do–check–act (PDCA) cycle, known also as the Shewhart cycle will be developed with the intention to repeat it again and again for a continuous improvement effort.

Results and Discussion

The in-depth analysis of the process, carried out by the team of professionals designated to present a solution to the problem, resulted in a concise definition of the process steps and the critical to quality (CTQ) elements. Such definitions were summarized and depicted in the following figures. Figure 1 is a pictorial of the production line along with the conveyors where the bags receive the water that is under characterization.

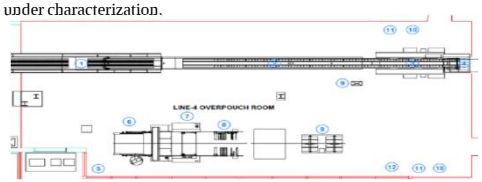

Figure 1: Production Line

Figure 2 demonstrates an element of importance in the analysis of any process. A general flow of the process where the study areas within the project are clearly established.

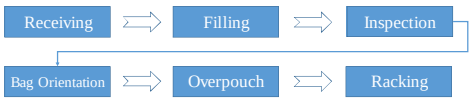

Figure 2: Process Flow

Results and Discussion

Descriptive statistics show that the response variables of all the codes of this characterization, have a large standard deviation and means that are substantially far from the others. The Interval plot resulting from the samples, and shown in Figure 3, indicates that there are very different distributions that probably will have no correlation between them.

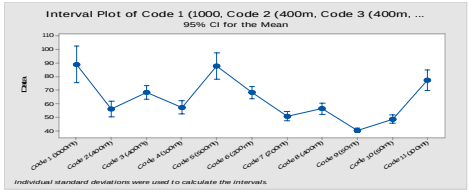

Figure 3: Interval Plot

Figure 4 shows the Scatter Plots, meaning that the amount of water within each bag, which is the objective of this characterization, is uncontrolled and no specific pattern was observed over time.

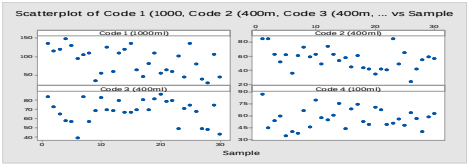

Figure 4: Scatter Plot

Conclusions

Before starting this process improvement voyage, it was vital to make an evaluation to decide if this project was a good candidate for improvement. Before any other consideration, some of the elements evaluated by the interdisciplinary group were the following:

- There is a specific problem within an existing process.
- The optimization has the potential to reduce lead time or defects while resulting in cost savings or improved productivity.
- Process is measurable (has collectable data) and results in a quantifiable improvement.

The structured execution of this project and the measurable results acquired will not only help Beta Company to successfully respond to the observations made by the Food and Drug Administration, but it will also give confidence to millions of patients in the world who use this product that now is manufactured with higher controls and stricter quality standards.

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