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

Pedro A. Valles Afanador
Master of Engineering in Manufacturing Engineering
Advisor: José A. Morales Morales, Ph.D.
Industrial and Systems Engineering Department
Polytechnic University of Puerto Rico

Abstract *— This article 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.*

Key Terms *— Code of Federal Regulations (CFR), Critical to Quality (CQT), DMAIC, Food and Drug Administration (FDA), Lean Manufacturing, Process Characterization, Six Sigma, Test Method Validation, Theory of Constrains.*

PROBLEM STATEMENT

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. This is the problem that concerns us in this project.

RESEARCH DESCRIPTION

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.

RESEARCH OBJECTIVES

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.

RESEARCH CONTRIBUTIONS

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.

First, the contribution to Beta Company is to fulfill FDA expectation by executing a remediation project comprising of the following phases:

- A process characterization that demonstrates that equipment parameters are supported by studies, and that those parameters were understood to the range of possibilities of equipment capabilities and materials and process variations. This will provide data on how much is the correct amount of water that should be inside a bag.
- A Test Method Validation with Experimental and Statistical Considerations to determine if operators can distinguish between a good and a bad bag. The Attribute Agreement Analysis will verify consistency within appraisers, each appraiser vs. standard, and whether the appraiser's rating agree with each other.

Second, the contribution to the customers that use the products manufactured by Beta Company is that the product they receive has been thoroughly verified in its final manufacturing stage. Excess of water or moisture will be eliminated while the possibility of a broken or leaking bag (defective) will be substantially diminished.

LITERATURE REVIEW

The first literature that will be reviewed and analyzed, with a view to systematically solve the problem presented in this project, is about Six Sigma, Lean and Theory of Constrains. Six Sigma, Lean and Theory of Constrains are three of the most used methodologies to process improvement and problem solving in the modern era. Such programs have increasingly become tools of business management that, with the increase of competition in the market, the corporate need for renewal and constant improvement has arisen. There is where change and optimization programs as the ones mentioned above, have come into play.

Process improvers advocates the adoption of their improvement methodology in an organization. And almost all plead that by adopting their specific tools or following a specific way of thinking, all the business problems will be solved. However, choosing what is best under a specific situation, needs some type of further analysis and knowledge. Moreover, there are methodologies that make a better fit based on the culture of the organization. Following is a description and evaluation of the three improvement methodologies mentioned, and which are their most relevant differences and similarities.

Six Sigma, Lean and Theory of Constraints (TOC)

In terms of differences between the theory of six sigma, lean and theory of constraints (TOC), Dave Naves, on his article "How to Compare Six Sigma, Lean and the Theory of Constraints" highlights that the core emphasis (theory) can be described in short words or phrases. For Six Sigma is variation reduction, for lean is waste reduction and for TOC is constraints reduction [1]. In terms of differences between the application of six sigma, lean and theory of constraints (TOC), the managing tools inherent to each improvement model are described in Table 1.

For six sigma the DMAIC methodology is the basis of its application, for lean thinking it starts identifying value from the customer standpoint and after that essential first step is completed, additional model tools are applied. Tools such as value-flow through an optimized value stream, product or service pulled from the customer and finally strive for the perfection of the lean model. The application of TOC is by managing process constraints. To achieve such goal an investigation process is

initiated to identify the constraint and decide on how to exploit it (to obtain as much capability as possible from the constraining component). Everything else is subordinated to the constraint what in turn makes the constraint to operate at maximum effectiveness. The next step in the application of TOC is to take whatever action is needed to eliminate the constraint if it has not been eliminated on previous steps. The final step applies a theory like lean thinking which is to go back to initial steps to create a cycle of continuous improvement.

In terms of differences between the **focus** of six sigma, lean and theory of constraints (TOC), six sigma focuses on the primary problem that needs to be tackled; variation that produces product defects. Dave Naves shares the same thinking as Margaret Rouse (from TechTarget) in her Six Sigma article of April 2017, where she states that Six Sigma is an approach to data-driven management that seeks to improve quality by measuring how many defects there are in a process and systematically eliminating them until there are as close to zero defects as possible. Lean, on the other hand, focuses its philosophy with emphasis on flow [2]. Lean thinking achieves the objective of cost reduction by employing a system-view of an organization that is centered on the notion of customer-defined value. The result is a process with less non-value steps which in turn reduces flow time, requires less inventory and increases quality, between others. In terms of TOC, it focuses on improvements achieved by identifying bottlenecks (constraints) within a system, and eliminating them. (Is important to realize that a system is a series of interdependent processes). The weakest link on a chain of events is what TOC pursue, because this link is the one that slows the speed of product through the system. Sergio Rattner, expressed that: "*TOC advocates the familiar adage that a chain is only as strong as its weakest link*" [3]. Sharing Dave Naves' postulate which states that system constrains are the focus of TOC tools and philosophy.

Process Characterization

Another vital element of Continuous Improvement is Process Characterization. Where process characterization is the fourth literature (first three are Lean, Lean six sigma and Theory of Constraints) that will be necessary to review in order to successfully address the problems highlighted in this project. Characterization [4] is used mostly when:

- Bringing a new process or tool into use.
- Bringing a tool or process back up after maintenance.
- Comparing tools or processes.
- Checking the health of our process during the monitoring phase.
- Troubleshooting a bad process.

Table 1
Six Sigma, Lean Thinking, and Theory of Constrains

Program	Six Sigma	Lean Thinking	Theory of Constraints
Theory:	Reduce Variation	Remove Waste	Manage Constraints
Application guidelines:	**D**efine **M**easure **A**nalyze **I**mprove **C**ontrol	Identify Value Value Stream Flow Pull Perfection	Identify constraint Exploit constraint Subordinate Elevate constrain Repeat cycle
Focus:	Problem focused	Flow focused	System constraints

U.S. Department of Health and Human Services, in its Guidance for the Industry "Process Validation [5]: General Principles and Practices", highlights that "designing an efficient process with an effective process control approach is dependent on the process knowledge and understanding obtained". Studies that can develop process knowledge and help on the detection of presence and degree of variation, are characterizations and design of experiments.

Test Method Validation

The last literature that will be reviewed, with a view to preparing strategies to solve the problem presented in this project, will be Test Method Validation (TMV). Generally, TMV is defined as a process or methodology used to gather objective evidence to demonstrate conformance of a test article to its requirement or acceptance criteria [6]. The test method includes the required equipment, environmental controls/parameters, qualification people, and the test procedure. The validation process of a Test Method is the demonstration by objective evidence that the method is appropriate for its intended use and that it can provide consistent repeatable and reproducible results.

METHODOLOGY

Based on the review and analysis of the literature depicted in the last chapter, "Six Sigma, Lean and Theory of Constraints (TOC)", "Process Characterization" and "Test Method Validation", it is considered that the appropriate approach to solve the problem outlined in this project is by using the DMAIC methodology for Process Improvement. It is important to highlight that the final scope and action plan described in this section was influenced by the fact that Beta Company has several customer complaints related to the lack of studies/specifications of their filling lines in regards to "what is the correct amount of water that should be inside a bag".

The decision that was taken in consensus, by the group of professionals with different backgrounds included in this team, was to characterize the process to statistically and scientifically determine the amount of water and variation that the current process yields. In fact, the characterization process, the output of such investigation activity and the analysis of data is within the scope of this project. It is important to realize that after such characterization is concluded, then Beta Company needs to conclude which will be the boundaries for the acceptable amount of water and furthermore, modify the process to assure that it remains in the acceptable parameters and then control it. But this phase is a future activity that is not part of the scope of this project. The methodology towards the optimization of the process is as follows:

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. This is a critical phase in which the team outlines the project focus for themselves and the leadership of the organization.

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. Another key objective of the Measure phase is to get a full understanding of how the process is currently performing. 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.

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. Solutions to the problems that were defined are now implemented and measured to confirm success. After the identification of problem root causes and sound statistical data delivered (this is the output of firsts three DMAIC phases), the approach to improve the process is the generation, evaluation and selection of the solutions to the already identified causes. 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. Process improvement professionals generally tend to close activities after improvements are applied and they overlook the importance of maintaining the upgraded process in control, monitor it and establish continuous improvement efforts between others. 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.

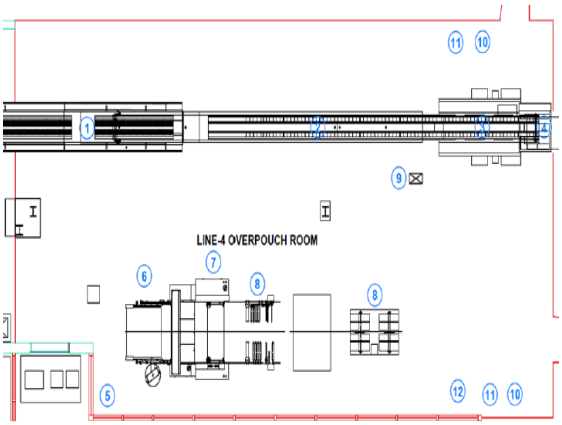

Figure 1
Production Line

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.

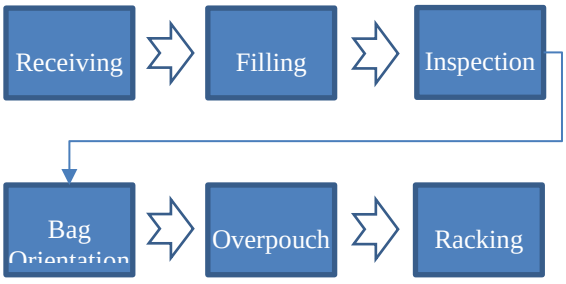

Figure 2
Process Flow

The construction of a Critical to Quality (CTQ) Diagram, as the one in Figure 3, focuses on key metrics of customer satisfaction. In other words, key metrics in this case are used to satisfy customer requirements regarding the amount of water inside a bag.

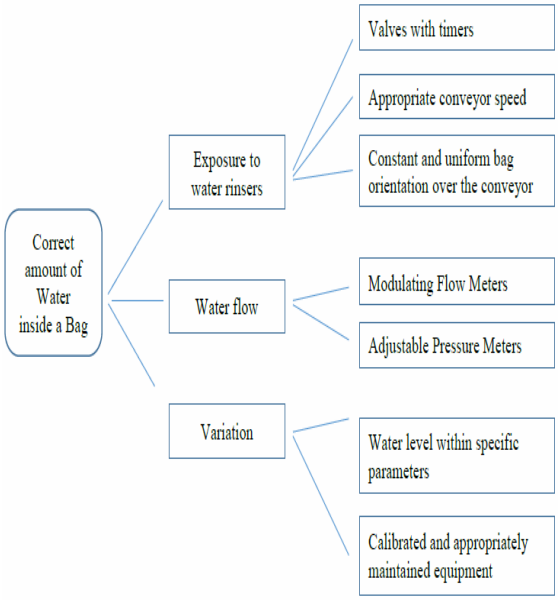

Figure 3
CTQ Diagram

Sampling

The plan contained a detailed summary of the measurements that were wanted to be taken, at what time and in what manner. This resulting data contains a representative sample of the parameters of interest of the Process Characterization.

Exploring Relationships

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 4, indicates that there are very different distributions that probably will have no correlation between them. To visually analyze correlation, scatterplots as the ones shown in Figure 5, were developed where no relationship or association was found between the amount of water variable (Y) and the point in time (X) the sample was taken (see scatter plot below). 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.

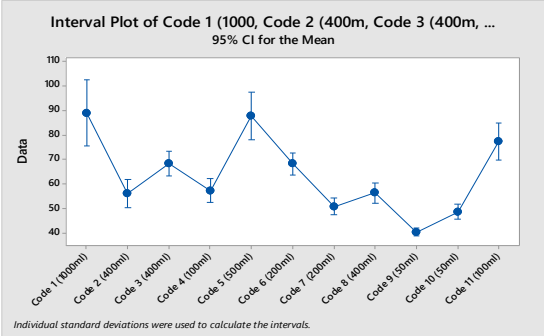

Figure 4
Interval Plot

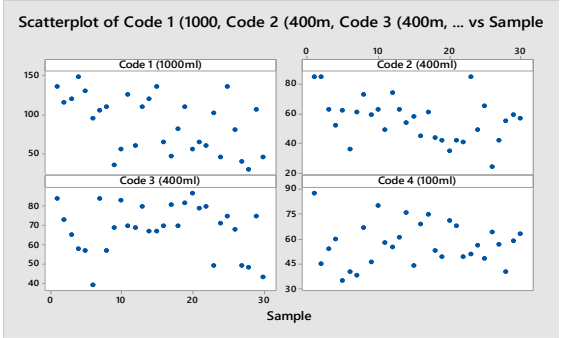

Figure 5
Scatter Plot for Codes 1 to 4

Analysis of Variance

The Analysis of Variance (ANOVA) table demonstrates that the confidence intervals, at a 95% Confidence Level, are too wide to consider the process to be stable or a controlled one. The pharmaceutical process that is under study pursues to minimize the variation that has been proved and assure that under a confidence level, any sample taken in the control phase, will fall within a narrower and stricter bracket.

Another important factor that the ANOVA report yields is that the model that has been chosen to analyze the sampled data represents approximately 43% of the variability. This means that there are other factors to consider in future analysis and that there is still variability within the process that needs to be determined. If we state that the current variability of the process is considered uncontrolled and too high, then an improve phase to the actual process needs to be recommended.

Improving the Process

The IMPROVE phase is not within the scope of this project. The strategy established when the process was deployed was to present upper management the data collected and the statistical analysis, to then they be able to submit for approval appropriate optimization alternatives or improvements to minimize the variability presented with the analysis of the data.

However, during the time assigned for the project, the interdisciplinary team developing this characterization study started to assess local firms knowledgeable in providing solutions to control the dispensed water in the packaging line; which was one of the factors found as contributors to the water level variability. Other contributors found were conveyor speed and the bag placement at the conveyor transporting the bags from the filling area to packaging.

Companies specialized in carrying and installing water regulators, pumps, and pressure monitors, between others, scrutinized the process under characterization and established that appropriate solutions could be implemented. A logical step to start is the implementation of water regulators and pumps to assure a stable stream of water over the product conveyor. Another step recommended is to establish constant velocities to assure the time that the product is exposed to water is maintained within a controlled range. Another improvement step that was recommended for the process was to install pumps that maintain the pressure within the piping as constant as possible. This will help to maintain a constant flow of water and in the eventuality that the inlet of water from the main system decreases, the pumps switches ON and the packaging segment is not affected.

Due that a pharmaceutical process is very strict in incorporating changes and new pieces of equipment, such enhancements remain out of the scope of this project and will be carried out in a future phase.

Controlling the Process

The CONTROL phase is not within the scope of this project. However, while the characterization process was taking place and the sources of variation were under disclosure, management agreed on the recommendations that have been stated on the previous section. At the moment of the presentation of this project, Beta Company was solidifying logistic steps and possible contract to install water regulators, conveyor's frequency drivers and water pumps, between others. After such improvements are completed and, in pharmaceutical terms "validated", then the facility will pursue the control of the water level limits. To achieve such control condition, monitoring and investigations tools are key elements of this phase.

The initial logistic to follow after the improvement has taken place is to take a snapshot of how the new process performs and calculate control limits for the expected measurements of the output of the process. Obviously, such limits should fall within or near the ones already accepted by upper management and found to be safe for the pharmaceutical product. Then it will become a regular activity to collect data from the process and compare the data to the control limits. Typical statistical tools used in this control phase are Histograms, Pareto Charts, Scatter Diagrams and Control Charts.

CONCLUSION

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.

Such initial evaluation resulted in a go-ahead to the process improvement and DMAIC methodology resulted the appropriate tool to further refine the project and deliver quantifiable and sustainable results. The methodology guided the team significantly throughout the statistical thinking, with an increased emphasis on quality control, analysis, and troubleshooting.

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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