Implementation of Six-Sigma Methodology to Reduce Costs in Pharmaceutical Industry: A Case Study

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Abstract:

The concept of Six Sigma is considered as one of the most important management concepts in total quality management, as it is based on the principle of focus efforts to provide manufacturing and services characterized by the highest levels of quality and compliance, at the lowest cost, and in standard time. With full commitment to avoid defects. This paper describes the theoretical and practical aspects of Six Sigma methodology and the advantages of its application in improvement and development. The paper also aimed at defining the DMAIC model for developing operations in order to encourage its adoption by local institutions to contribute to upgrading it towards globalization and moving it towards institutional excellence.

The goal of this research paper is to introduce a problem-solving technique to reduce costs within a manufacturing site without affecting the production required to increase product quality. The used case study was manufacturing process of tablets at IBN Hayan Pharmaceuticals Factory; data were collected through the production process of solid dosage form. A sampling plan was

used to collect samples of finished products during the entire lot compression at equally spaced time intervals during the tableting process of the production time.

The presented results demonstrated that Six Sigma methodology and tools are effective for reducing costs for continuous improvement of work quality and reducing costs and defects in production and industrial processes.

Keywords:

Six Sigma (6σ), DMAIC model, Good manufacturing practice (GMP), Statistical Process Control (SPC), Process capability, In Process Control (IPC).

Introduction

Recently, there has been a rapid development of many modern administrative concepts, which in turn push industrial and service institutions to search for the best methods, techniques and appropriate strategies that achieve the goals of companies and enhance the quality of their services and products. The "Six Sigma" method is considered one of the latest management methods adopted by institutions around the world. A method that aims to bring the level of defects to zero in the product in order to obtain a high-quality product where, achieving quality in any industrial or service process is an urgent necessity for the continuation of these process and continuous development. [2]

The researchers, based on their job position, seek to conduct this study to demonstrate the impact of using Six Sigma methodology in improving the quality of the industrial process for producing medicines.

Research Problem

As a result of using advanced technology and the assistance of experts specialized in production and operations management who work through the application of total quality management in all

production and industrial processes, there is still a need for continuous improvement of work quality and reducing errors in processes, which is reflected in the quality of the product and gives it a competitive advantage over other products. The research problem is to answer several questions, which are:

1- How can the Six Sigma methodology be applied in the pharmaceutical industry?

2- How can the industrial process be measured and reduce costs?

Research Objectives

1- Develop a specific mechanism for how to apply the Six Sigma methodology in the pharmaceutical industry.

2- Provide recommendations that help pharmaceutical factories reduce expected defects in industrial processes.

3- Improve the product quality and gain customer confidence in Pharmaceuticals industries.

Research Hypotheses

There is no statistically significant relationship between the application of the Six Sigma methodology and the quality of products.

There is no statistically significant relationship between the application of the Six Sigma methodology and the continuous improvement.

There is no statistically significant relationship between the application of the Six Sigma methodology and the quality of production processes.

Theoretical framework of the study

1. Six Sigma Concepts

Six Sigma (6σ) is a team-focused managerial approach that seeks to improve performance by eliminating waste and defects while boosting the standardization of work. It combines Six Sigma

methods and tools and the manufacturing enterprise philosophy, striving to reduce the waste of physical resources, time, effort, and talent while assuring quality in production and organizational processes. Any use of resources that does not create value for the end customer is considered a waste and should be eliminated [1].

The term 6 Sigma originated in manufacturing as a means of quality control. Six Sigma quality is achieved when long-term defect levels are below 3.4 defects per million opportunities (DPMO) [2].

Table-1 Six Sigma Performance Level Per Million Defects [5].

Six Sigma Level	defects per million operations
1	690000
2	308537
3	66807
4	6210
5	233
6	3.4

The term six Sigma originates from statistical quality control, a reference to the fraction of a normal curve that lies within six standard deviations of the mean, used to represent a defect rate.

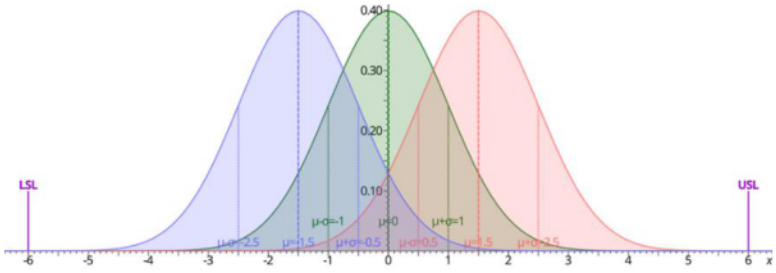

Figure-1: Normal distribution underlies the statistical assumptions of Six-Sigma (6σ)

Normal distribution underlies the statistical assumptions of 6 Sigma. At mean (μ) marks the mean, with the horizontal axis showing distance from the mean, denoted in units of standard deviation (represented as or sigma). The greater the standard deviation, the larger the spread of values; for the

green curve, and, the upper and lower specification limits (USL and LSL) are at a distance of 6σ from the mean [3].

Sigma (σ) is measure of dispersion of data around the mean of the distribution of the normal curve, the mean (μ) and Sigma (σ) describes the normal distribution of data where:

68.27% of data lies between the mean and ± 1σ

95.45% of data lies between the mean and ± 2σ

99.73% of data lies between the mean and ± 3σ

99.9937% of data lies between the mean and ± 4σ

99.999943% of data lies between the mean and ± 5σ

99.9999998% of data lies between the mean and ± 6σ

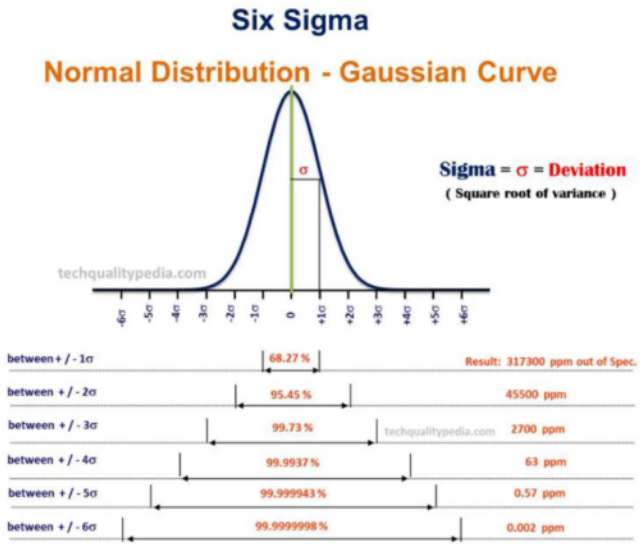

Figure-2: Normal distribution "GAUSSIAN CURVE"

2. The five steps of Six Sigma

The Six Sigma method uses an approach called DMAIC that stands for Define, Measure, Analyze, Improve, and Control. According to Six Sigma adherents, a business may solve any seemingly unsolvable problem by following these five steps.

Define: A team of people, led by a Six Sigma expert, chooses a process to focus on and defines the problem it wishes to solve.

Measure: The team measures the initial performance of the process, creating a benchmark, and pinpoints a list of inputs that may be hindering performance.

Analyze: Next, the team analyzes the process by isolating each input, or potential reason for any failures, and testing it as the possible root of the problem.

Improve: The team works from there to implement changes that will improve system performance.

Control: The group adds controls to the process to ensure it does not regress and become ineffective once again [1].

3. Pharmaceutical industry

Pharmaceutical industry is defined as the industry subject to the laws regulating all regarding this industry practices and methods of manufacture, and due to the content their manufacturing process of complexity and as the control and quality assurance of pharmaceuticals is the first duties of the pharmaceutical industry, and test ready-made material is no longer alone sufficient to ensure quality.

The efforts are being made for the application of "good practice for the manufacture of pharmaceutical" from the purchase of raw materials, production and control during manufacturing and control on the final product quality and release, storage, handling and distribution of the product, and most important of all documentation of those methods and practices, and is considered the rules and established Good Manufacturing Practice the spirit of regulations governing the pharmaceutical industry [4].

Control of quality during the manufacturing process (In-process control, IPC) might be done using Statistical Process Control (SPC), which is considered as an industry-standard methodology for measuring and controlling quality during the manufacturing process, It is also defined as a major statistical tool for monitoring of production process to make sure that it works stably. The stability of the production process is reflected by the conformance of the quality characteristics of its products to their designed requirements [5].

4. Manufacturing Process

Pharmaceutical manufacturing process is a multi-steps process. Each manufacturing step is called a "Unit Operation" Each unit operation produces an intermediate with pre-determined quality specifications that will ensure the quality of the finished product. Pharmaceutical dosage forms, such as tablets, are widely used in today's drug product manufacturing. One of the unit operations in the process of producing tablets is the tablet compression machine. This equipment will apply compression force on the powder mixture containing the active pharmaceutical ingredient and other ingredients. The result of the compression process is a solid entity known as a tablet. This tablet must have number of critical quality attributes that give the product its identity.

Tablet hardness, friability, disintegration, dissolution, content of active ingredient and dimensions are the important quality attributes to ensure the suitability of the tablet for the intended use. To evaluate the tablet compression process, samples of tablets were taken at random from each subgroup and the hardness of each tablet was measured using tablet hardness tester. The test results are used to monitor the manufacturing process output that is more likely to cause finished product variability. Routine quality monitoring of a production process can be accomplished by process control charts.

In the production unit, there are many different types of defects that can occur, for example that the product is cracked, that there are errors in the design, or that information on the product is not correct [6].

5. Process Capability

There are two formulae to calculate process capability:

(a) Process capability ratio (Cp), and

(b) Process performance index (Cpk)

Process capability, for a stable manufacturing process, is the capacity of the process to reach a certain level of quality. For a stabilized process in which factors affecting the standard deviation are properly controlled, process capability, as measured by the quality characteristics of the products of the process, is usually expressed as the mean value plus or minus three times the standard deviation [6].

The Process Capability Index (Cp) is expressed as a ratio to the specified value. It is used to quantitatively evaluate the adequacy of the process capability - whether the variation in the process is within the limits of the specifications.

$Cp = ((USL-LSL))/6\sigma$, where, σ= Standard deviation

Cp is defined as process capable, and should be $Cp \geq 1$

$Cpk = \min.\{ ((USL-\mu))/3\sigma , ((\mu -LSL))/3\sigma \}$,

where, σ= Standard deviation

Cpk is defined as process performance, and should be $Cpk \geq 1.33$ [7]&[8].

TABLE 1: Interpretation of Process Performance (Cpk) [7]&[8]

Cpk	Evaluation	Assessment
Cpk > 1.33	Good	Process Capability completely meets specifications
1.33 ≥ Cpk <1.00	Acceptable	Process Capability does not completely meet specifications; process control should be continued
1.00 ≥ Cpk	Inadequate	Process capability inadequate; improvements should be made

TABLE 2: Cpk index value means) [7]&[8]

Cpk	Good products
0.33	68.27%
0.67	95.45%
1.00	99.73%
1.33	99.9937%

Methods

The methodology used in this study is by collection of data during production process (In-process control) in Pharmaceutical Factory, where producing of Tablets process was chosen to ensure conformity of the GMP requirements. The chosen product was Brufen 600mg coated tablets, the measured specifications for three following success batches were written in the batch manufacturing record, and the samples were taken during the entire lot compression at equally spaced time intervals during the compression process of the production time. The numbers of sub-groups of samples were (10 samples), the critical measurement parameters are weight (mg), Hardness (N), Friability (%), Disintegration Time (min), Dissolution time (min) and Content of active ingredient.

In this paper analysis of the process capability and performance using the critical parameters: weight variations had been done to show the capability of production process to produce product complying with the specifications. The specifications are as following:

Samples Mean (μ) = 682.0 mg

Upper specification limit (USL) = 716mg

Lower specification limit (LSL) = 648mg

Results and Discussions

The study is take place in a pharmaceutical factory IBN Hayan pharmaceutical factory "IH pharma" located at Tripoli-Libya. The factory is producing solid dosage form (Tablets). Products are manufactured and released as per Good Manufacturing Practices GMP.

To evaluate the production process, IPC data from "IH pharma" Batch Records were taken as a case study, the chosen product was Brufen 600mg Tablets, samples for three followed batches were taken during the production process (In-Process control). The obtained data were in real-time during compression of tablets process for each 5 minutes of production time, the number of sub-groups of samples were (10 samples). In this paper the weight of tablets (mg) studies a as critical measurement parameter, the IPC data obtained from the batch records are shown in Table (3).

Table 3: IPC data (weight) of Brufen 600mg tablets

	Weight, mg		
	Batch # 1	Batch # 2	Batch # 3
Sample # 1	701.4	680.1	666.4
Sample # 2	690.0	680.5	666.9
Sample # 3	692.5	679.4	667.2
Sample # 4	698.5	679.9	666.8
Sample # 5	695.5	680.3	665.6
Sample # 6	700.2	680.5	665.9
Sample # 7	698.6	679.8	664.1
Sample # 8	701.5	678.9	664.2
Sample # 9	703.9	679.5	670.1
Sample # 10	702.3	680.8	665.8
Sample # 11	706.1	681.9	665.7
Sample # 12	709.0	682.1	666.5
Sample # 13	701.5	685.5	664.8
Sample # 14	699.9	689.3	662.9
Sample # 15	699.5	695.1	662.1
Sample # 16	700.1	701.5	661.7
Sample # 17	698.6	705.3	661.4
Sample # 18	697.1	685.0	662.5
Sample # 19	700.8	685.5	662.9
Sample # 20	696.2	685.9	663.8

The procedure for calculation of weight of Tablets (mg) was made through collection and registration of Average mean (μ), Sigma (σ), Process capability ($C_{p)}$ and process performance (C_{pk}) results obtained by using a designed MS Excel spreadsheet and are shown in Table (4).

Table (4) Calculations of process capability indices for Brufen 600mg Tablets

	Average mean (μ)	Sigma (σ)	C_p	C_{pk}
Batch # 1	699.66	4.30	2.64	1.27
Batch # 2	684.84	7.50	1.50	1.38
Batch # 3	664.87	2.20	5.09	2.56

Table (4) represents that for all batches the Process capabilities ($C_{p)}$ are greater than 1.0, which means that the manufacturing process is capable to produce Tablets within the specification.

The process performance (C_{pk}) for:

Batch # 1: C_{pk} = 1.27, less than 1.33, which means 99.97% of products are good, it is acceptable but the Process Capability does not completely meet specifications and process control should be continued.

Batch # 2: C_{pk} = 1.38, slightly more than 1.33, which means more than 99.9937% of products are good, it is mean that process capability is completely meets specifications.

Batch # 3: C_{pk} = 2.56, more than 1.33, which means 99.999943% of products are good, it is mean that process capability is completely meets specifications.

In general, produced products of related batches are good quality and to identify, organize, factors that caused defects in Batch #1 using fishbone diagram is elaborated as shown in Figure (3), the analysis conducted only in the manufacturing process of tablets.

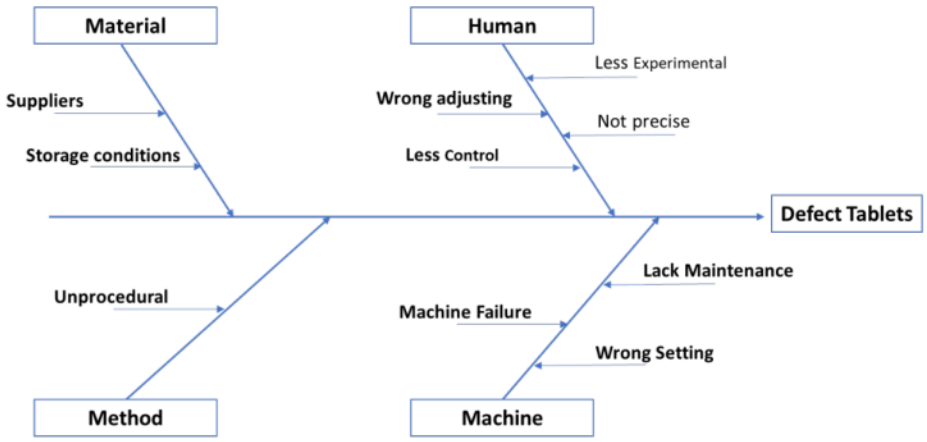

Figure-3: Fishbone Diagram

In this case use 5W-1H method which mean that every improvement action for the problems are listed in the action plan which consists of every improvement details according to the principle of When, What, Where, Who, Why and How.

1- What, the improvement action needed to minimize production defect of tablet.

2- Where, the area of improvement action took place to minimize production defect of tablet.

3- Why, the reason to do improvement action to minimize production defect of tablet.

4. Who, the person who will do and be responsible for the improvement action to minimize production defect of tablet.

5. When, the period time to do improvement action to minimize production defect of tablet.

6. How, the way used to do improvement action to minimize production defect of tablet.

The improvement action proposed to minimize production defect of tablets are shown in Table 5.

Table (5) Improvement Action using 5W+1H Method

What	Where	Why	Who	When	How
Weigh of Tablets	On the tableting machine	To minimize weight variation	Technician	Before each production batch	Optimizing weight setting
Tableting Process control	On the machine	To minimize weight variation	Tableting supervisor	During the tableting process	Controlling the tableting process
Tableting Machine inspection	In the Production department	To meet the product requirement	Tableting supervisor	Before each production batch	Applying preventive maintenance
Operator Capability	Production department	To minimize unqualified tablet result	Production manager	Every 3 months	Training the operators

For control, in this step, train all employees for new processes, and create monitoring and action plan for new processes. It is important to ensure that control can be done to any variances avoiding possibly costly defects and loss of quality. This step intended to control the improvement action, which is the beginning of a continuous improvement.

Conclusions and Recommendations

1- Six Sigma is used to examine, manage, and enhance operational performance by eliminating and preventing defects in products and related to the operational activity.

2-Six Sigma is to improve the quality of process outputs by identifying and reducing the defects and minimizing variability in manufacturing and business processes.

3- Measuring of processes is one of the monitoring requirements by GMP, measurement of process using process capability (Cp) and product performance (Cpk). If Cp greater than 1.0 and Cpk greater than 1.33, which indicate that process is capable to meet specifications.

4- In this paper the manufacturing process for producing of Brufen 600mg tablets at IBN Hayan pharmaceutical factory had been measured and analyzed using sigma measurement and process indices, and found that the production process is statistically capable repeatedly and reliably to produce finished product of predetermined quality.

5- To improve the production process based on the DMAIC analysis above to minimize the number of defects are by-

- Optimizing weight setting.
- Controlling the tableting process.
- Applying preventive maintenance and,
- Training the operators.

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