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Process Capability and Six Sigma: A Necessity of Pharmaceutical Industry

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ABSTRACT

The need of the day is to produce the product that meets customer requirements. As pharmaceuticals are related to health care this should be vital part of industry to produce a product such as tablets, capsules, ointments, creams, gels and emulsions etc. with minimum variation satisfying the needs of customer. Customer requirements are translated into 'Critical to Quality' (CTQ) characteristics of the products that they are about to produce by the formulation scientists. As example, hardness, thickness, uniformity of weight, assay, dissolution etc are CTQ characteristics of tablets, Content uniformity, viscosity, density are CTQ characteristics of a gel etc. There are various sources of variation which can be monitored by the Quality by Design i.e., QbD approach. Process should be monitored and controlled by using statistical process control which includes six sigma approach, process capability and control charts. Some of the more frequently used indices are Cp and Cpk. Cp represents process capability while Cpk is the process capability index which are determined between USL and LSL which signifies upper specification limit and lower specification limit. Cpk of at least 1.33 is desired, and 1.5 is excellent and if there are not more than 3.4 defects per million units, then six sigma is achieved.

Keywords: Quality by design, Cpk, Cp, Customer requirements, variation

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INTRODUCTION

Many industries typically use process capability indices to assess, monitor and communicate the capability of their processes and products to meet tolerances and specifications. Capability assessment and improvement are integral components of the ever-expanding six sigma philosophy. These indices also provide valuable internal information for setting priorities and identifying processes that need improving. There are many numerical ways to quantify capability of variables-type data. Some of the more frequently used indices are Cp and Cpk[1]. A pharmaceutical company produces products such as tablets, capsules as per customer requirements. Customer requirements are the significant features that the customers expect to find in a product. Development scientists translate those requirements into 'Critical to Quality' (CTQ) characteristics of the products that they are about to produce. As example, hardness, thickness, uniformity of weight, assay, dissolution etc are CTQ characteristics of tablets. When these CTQ characteristics are assessed and quality targets are determined, development scientists specify upper and lower limit within which variables of CTQ characteristics must fall. To evaluate production process performance, the CTQ characteristics are monitored when production in progress[2]. Control chart is one of the tools which used to monitor the characteristics. We can see whether the data of CTQ characteristics are within limit or not from control chart. Even if all the monitored data are within set limit, there is a possibility to produce defective product. The tool by which we can say the process is capable to produce product complying customers requirements is process capability index Cpk. The tool frequently used to monitor a process performance while the production is in progress is the control chart. It helps detect assignable causes of variations and facilitate corrective actions[2].

Principle Sources of Quality Variation[3-6]

Identification and a clear understanding of possible source of variation(s) is of utmost important before applying any statistical tool in an experimental study designed with Quality by Design approach for pharmaceutical product development. These controlled or uncontrolled variations have an impact on the entire process and its outcome. The principal sources of quality variation to a process include the following.

- Material attributes
- Process parameters
- Equipment design
- Measurement system
- Environment

❖ Person

Figure 1 shows the benefits of statistical control. It is important to note that the total process variation as measured by the variance or standard deviation (σ) of the average batch data is a function of all sources and is expressed as follows.

σ Total = f (σ Material + σ Process + σ Equipment + σ Measurement + σ Environment + σ Person).

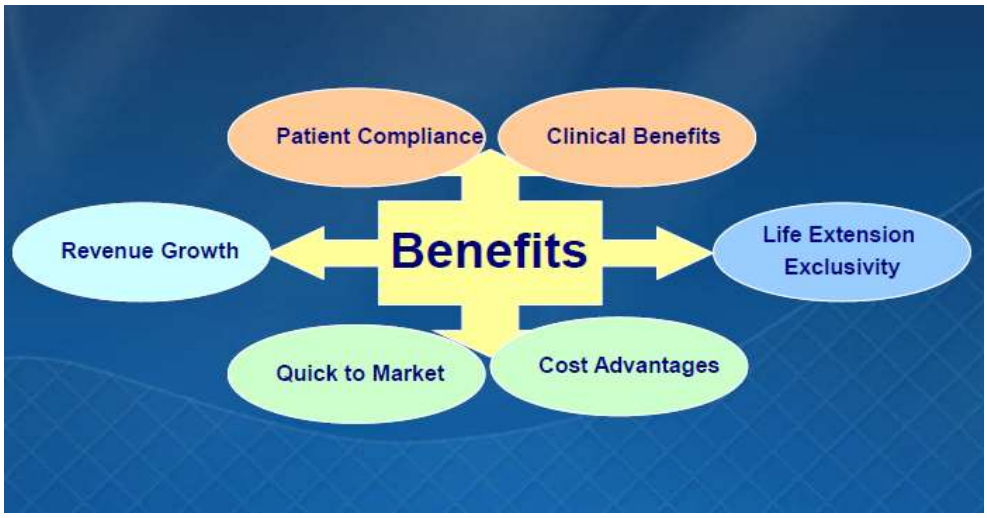


Figure 1: Benefits of Statistical Approach[7]

Statistical Process Control (SPC)[8]

SPC was pioneered by Walter A. Shewhart at Bell Laboratories in the early 1920s. Shewhart developed the control chart in 1924 and the concept of a state of statistical control. SPC is applied in order to monitor and control a process which ensures that it operates at its full potential. Key tools used in SPC include control charts; a focus on continuous improvement; and the design of experiments. An example of a process where SPC is applied is manufacturing lines. Figure 2 represents ICH Q6 Decision characteristics. Statistical process control (SPC) in QbD i.e., Quality By Design is the application of statistical methods to identify and control the special cause (nonrandom variation caused by a specific factor) of variation in a process. Process capability is a statistical measure of the inherent process variability for a given characteristic. Process capability is denoted by Cp and Process capability index is denoted by CpK. Widely accepted formula for process capability is 6 σ. Process capability (Cp) = + 3 standard deviation (total of 6 σ).Cp refers the variation in a process about the average value, but average of process not often the midpoint so it is useful to have the process capability index that reflects the both variation of process and the location of process variation. Statistical Process Control (SPC) is one of techniques used to monitor processes and provide immediate feedback control. The feedback control is used to

maintain and improve the capability of the process that result in product / service conformance to meet customer satisfaction. Some techniques associated with SPC include histograms, and control charts. A histogram is a visual display of frequency distribution to show shape, location, and spread of data. While, a control chart is a statistical tool used to monitor the variation and trends occurring in a process and ensure that the process is in a state of control. A control chart has its limits: Upper Specification Limit (USL), Central Limit (CL), and Lower Specification Limit (LSL) measured from the dispersion happened in the process[8].

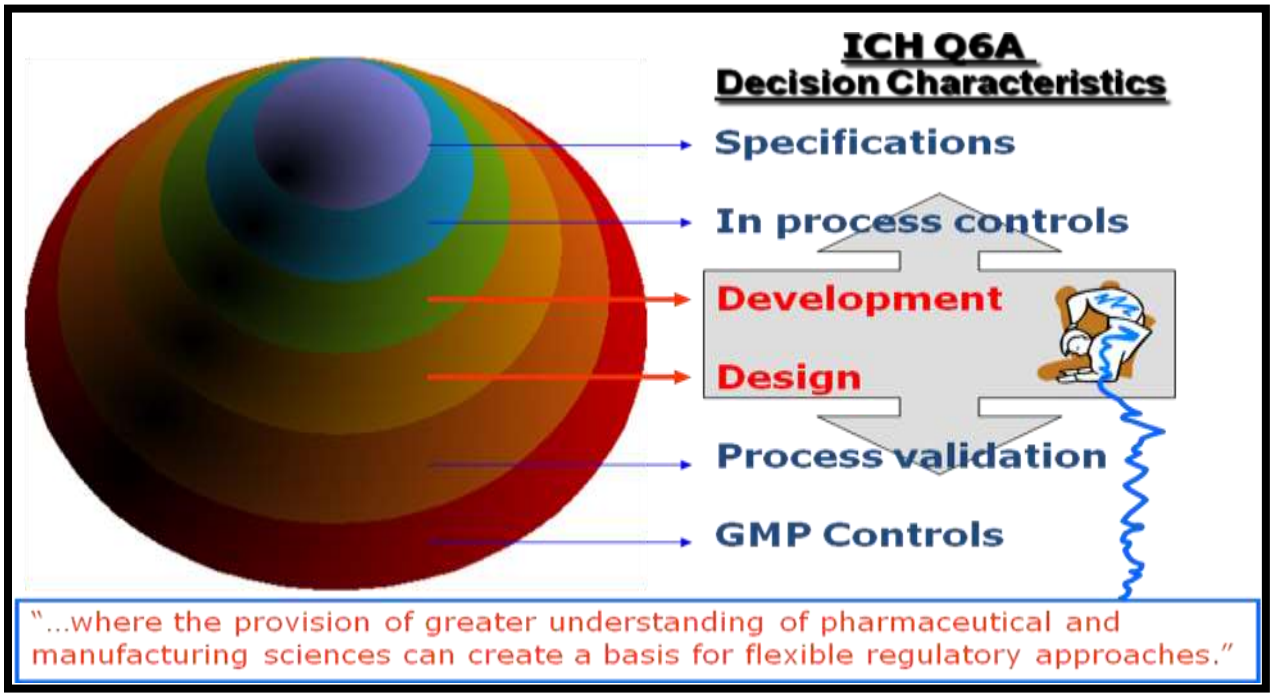
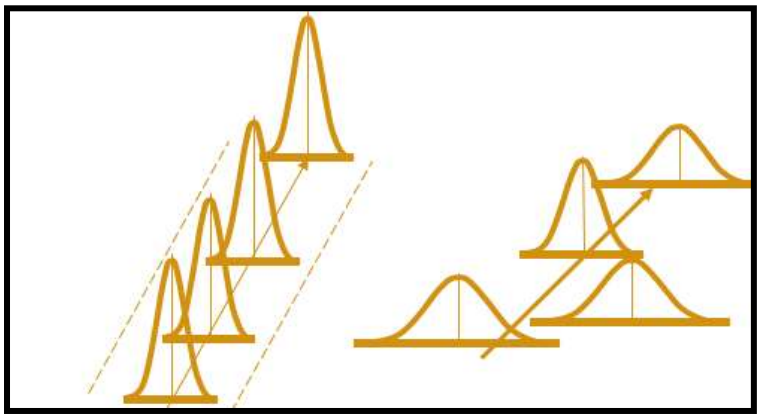


Figure 2: ICH Q6A Decision Characteristics[11]

Quality Control Charts[10]

Sometimes the specification limits are not set; instead, statistical control limits are computed based on the actual data collected (e.g., the number of defects in a manufacturing line). The upper specification limit (USL) and lower specification limit (LSL) are computed, as are the central line (CL) and other sigma levels. The resulting chart is called a control chart, and if the process if out of control, the actual defect line will be outside of the USL and LSL lines. Figure 3 represents capable and incapable process. Capability measures in Six sigma are the central analytics in quality control. Defective Proportion Units (DPUs) are the number of defects observed with respect to the total opportunities or outcomes, and can be measured with respect to a million opportunities (defective parts per million, DPPM, or also known as the defects per million opportunities, DPMO). Process Capability Index or Cpk takes into account the off-centered distribution and analyzing it as a centered process producing a similar level of defects (defined as the ratio between

permissible deviation, measured from the mean value to the nearest specific limit of acceptability, and the actual one-sided 3 sigma spread of the process). Simplistically, it measures how many times you can fit three standard deviations of the process between the mean of the process and the nearest specification limit. Assuming that the process is stable and predictable, if you can do this once, Cpk is 1, and your process probably needs attention. If you can do it 1.5 times, your process is excellent, and you are on the path to being able to discontinue final inspection. If you can do it 2 times, you have an outstanding process. If Cpk is negative, the process mean is outside the specification limits. Cpk of at least 1.33 is desired. Finally, the sigma of the process is determined. Typically, this process sigma value can be used to compare before and after effects of some quality improvement program, or to see if the process is up to par in terms of a target sigma level. This statistical capability model uses as inputs, the statistical properties of the process, including the observed mean and standard deviation (sigma), as well as predefined lower and upper specification limits (LSLs and USLs). In contrast, the Unit capability model computes some of the same capability measures but uses actual number of defects and population size. In addition, the Cp index is computed, which relates to the potential of the process to meet specification, regardless of where the process distribution falls. The process may not be performing within specifications, but the index tells you how the process will perform if you can shift the distribution mean to the desired target (without changing the distribution). If we have a Cp of 2.0, it has the potential to be a six sigma process. In contrast, Cpk actually compares the distribution of the data to the specification limits to determine its actual performance. If we have a Cpk of 2.0, you have a six sigma process. As discussed, a Cpk of at least 1.33 is desired, and 1.5 is excellent[10-12].



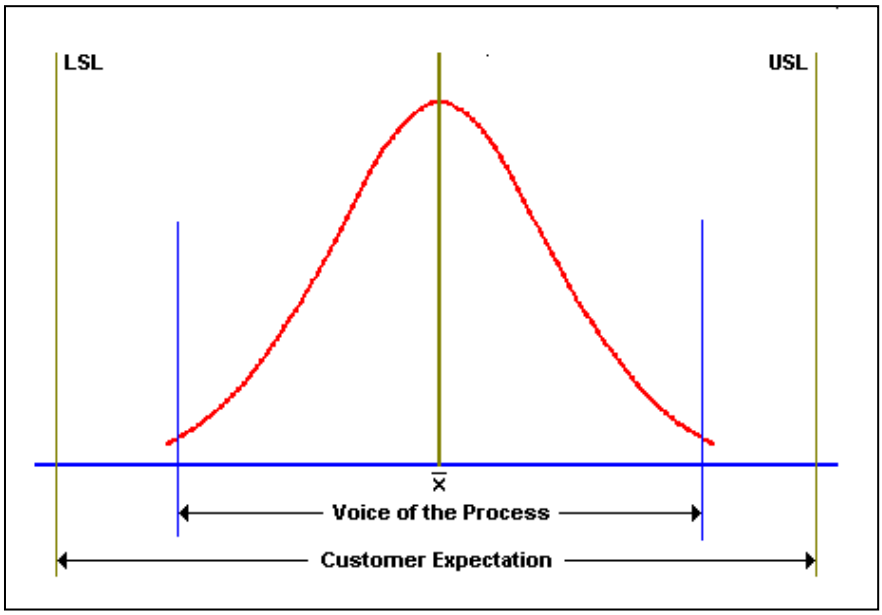
(a) (b)

Figure 3: (a) Process capable (b) Process incapable[11]

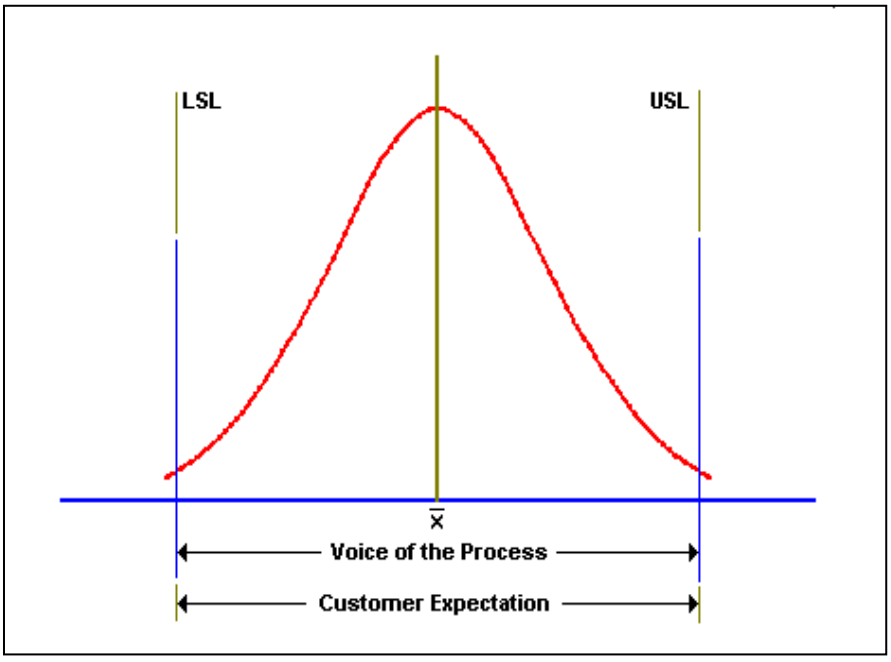
Process capability study is a scientific and a systematic procedure that uses control charts to detect and eliminate the unnatural causes of variation until a state of statistical control is reached. Cp,

Cpu, Cpl and Cpk are the indices as shown Figure 4. Indices determine how capable a process is if certain conditions are met essentially, if the mean of the process' natural variability is centered to the target of the standard specifications. The actual capability indices do not require the process to be centered to be accurate[11].

Capability Measures (Cp and Cpk) and Specification Levels (USL and LSL)



(a)



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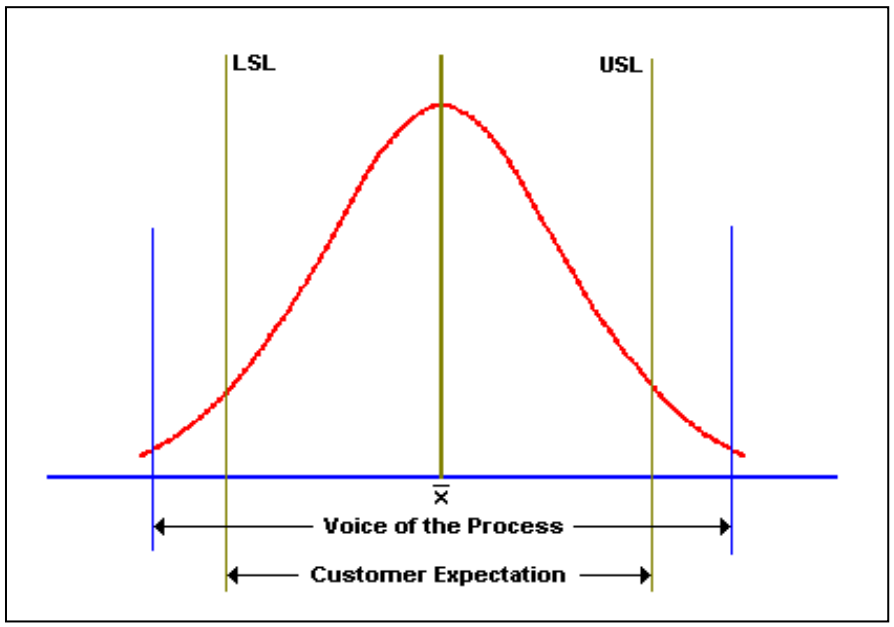

(c)

Figure 4: Histograms of Process Capability Indices (a) Case 1: Cpk > 1.33 (A Highly Capable Process) (b) Case 2: Cpk = 1 to 1.33 (A Barely Capable Process) (c) Case 3: Cpk < 1 (The Process is not Capable)[13]

Potential Capability, Cp[11-12]

A process is said to be capable if the spread of the natural variations fits in the spread of the specified limits when the ratio of the specified range to the control limits is greater than one. In other words, the following ratio should be greater than 1. The value of Cp = 1 if the standard specified limit equals the limit of the natural variations of the process (control limit) , in which case the process is said to be barely capable ; it has the potential to only produce non defective products if the process mean is centered to the specified target. Approximately 0.27 percent, or 2700 parts per million, are defective. The value of Cp > 1 if the standard specified limit is greater than control limit, in which case the process is potentially capable if the process mean is centered to the specified target and is (probably) producing products that meet or exceed the customers' requirements. The value of Cp < 1 if the standard specified limit is smaller than control limit then the process is said to be incapable.

Actual Process Capability, Cpk

The reason why Cp > 1 does not necessarily mean that the process is not producing defects is that range of the control limits might be smaller than the one of the standard specified limits, but if the process mean is not centered to the specified target, one side of the control limit might exceed the specified limits. If the process mean is not centered to the specified target, Cp would not be very

informative because it would only tell which of the two ranges (process control limits and standard specified limits) is wider, but it would not be able to inform on whether the process is generating defects or not. In that case, another capability index is used to determine a process' ability to respond to customers' requirements and it is Cpk. The Cpk measures how much of the production process really conforms to the standard specifications. The k in Cpk is called the k factor; it measures the level of deviation of the process mean from the specified target.

Six Sigma[14-17]

Six sigma terminology originated with statistical modeling of manufacturing processes. This term basically defines the quality which is almost near to the perfection limit. It is a data driven approach which helps in eliminating defects (driving toward six standard deviations between the mean and the nearest specification limit). It is said that if there are not more than 3.4 defects per million units, then six sigma is achieved. The main idea behind the six sigma concept is process improvement and reduction of variation. The six sigma DMAIC process (define, measure, analyze, improve, control) is an improvement system for existing processes falling below specification and searching for incremental improvement. The six sigma DMADV process (define, measure, analyze, design, verify) is an improvement system which is used to develop new processes or products at Six Sigma quality levels. The six sigma management system drives clarity around the business strategy and the metrics that most reflect success with that strategy. The Greek letter σ (sigma) marks the distance on the horizontal axis between the mean, μ, and the curve's inflection point. The greater this distance, the greater is the spread of values encountered. For the green curve shown above, $\mu = 0$ and $\sigma = 1$. The upper and lower specification limits (USL and LSL, respectively) are at a distance of 6σ from the mean.

Assertion of Six Sigma

- It is important for a successful business to maintain continuous efforts to achieve stable and predictable process results (reduce process variation).
- Manufacturing and business processes have characteristics that can be measured, analyzed, controlled and improved.
- Entire organization requires commitment specifically from the top level management in order to achieve sustained quality improvement.

Unique Features of Six Sigma

- A clear focus to achieve measurable and quantifiable financial return.
- An increased emphasis on strong and passionate management leadership and support.

- A clear commitment to making decisions on the basis of verifiable data and statistical methods, rather than assumptions and guess work.

Processes that operate with "six sigma quality" over the short term are assumed to produce long term defect levels below 3.4 defects per million opportunities. Organizations need to determine an appropriate sigma level for each of their most important processes and strive to achieve these. As a result of this goal, it is incumbent on management of the organization to prioritize areas of improvement.

Five Phases of Six Sigma Methodology

The Six Sigma methodology is universally recognized and defined as comprising the following five phases: Define, Measure, Analyze, Improve and Control (DMAIC). In some organizations only four phases are used: Measure, Analyze, Improve and Control (MAIC) as shown in Figure 5 and Figure 6.

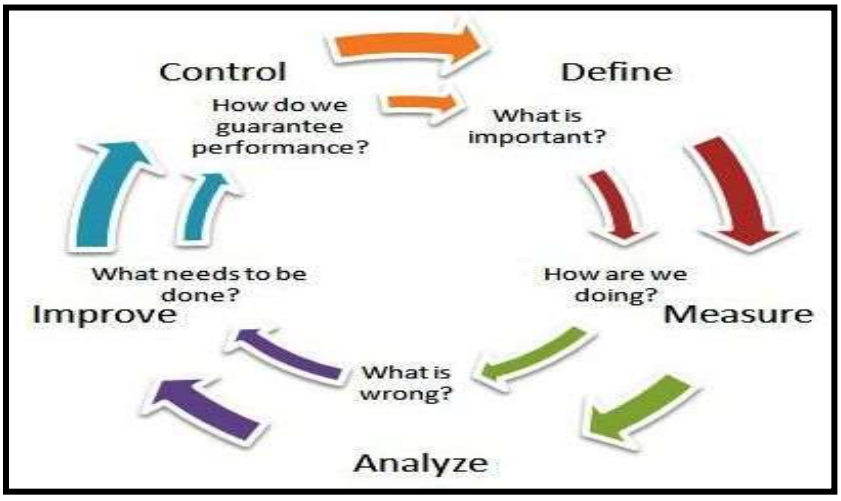

Figure 5: Six sigma Problem solving DMAIC[18]

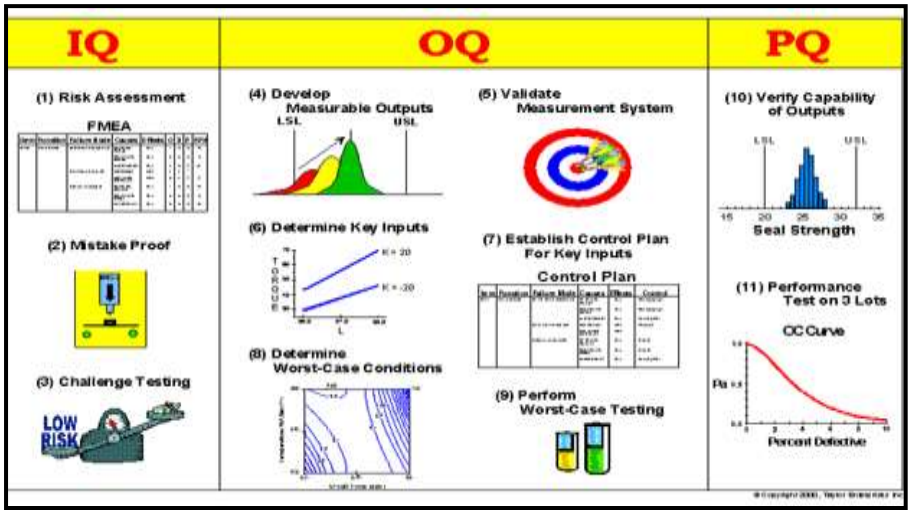

Figure 6: Six sigma Validation IQ-OQ-PQ[19]

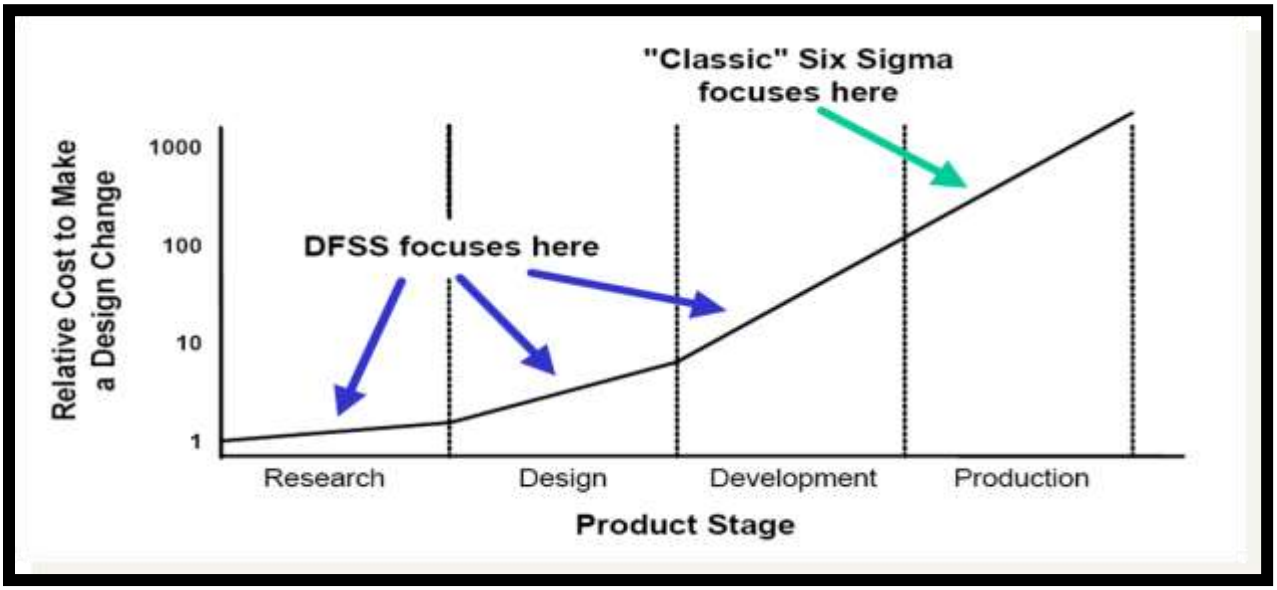

Figure 7: DFSS and Six Sigma[11]

The DMAIC methodology breaks down as follows:

Define: Define the project goals and customer (internal/external) deliverables.

Measure: Measure the process to determine current performance. The problem must be quantified.

Analyze: Analyze and determine the root causes of any defects.

Improve: Improve the process by eliminating defect root causes.

Control: Control future process performance.

The **second** focuses on process design using Design for Six Sigma (DFSS) approach. DFSS typically requires IDOV:

Identify: process goals in terms of critical parameters, industry & competitor benchmarks.

Design: involves enumeration of potential solutions and selection of the best.

Optimize: performance by using advanced statistical modeling and simulation techniques and design refinements.

Validate: that design works in accordance to the process goals.

An important aspect of the six sigma program is total process characterization, which involves optimizing all manufacturing processes to a very high Cp and Cpk value. The quality goal should not be zero defects, by default an impossibility and simply unreasonable. Rather, the organization should set a value, such as 0.002 parts-per-million defective (plus or minus six sigma), 3.4 parts-per-million defective (4.5 sigma shifted) or some other challenging but achievable value. A Six Sigma quality goal strives for a stringent but achievable Cp and Cpk value equal to 2.0.This value would bring considerable profit to an organization. Motorola, for example, established a quality

goal of 3.4 parts-per million defective (Cp=2.0, Cpk=1.5).It usually takes a team working a few hours a week for a few months to characterize a machine or process.

CONCLUSION

Organization should characterize all processes in a manufacturing site by proper utilization of its resources, time and money. Six Sigma and process capability is necessary to keep the program focused, scheduled and running in a timely manner and to minimize the variation to long term defect levels below 3.4 defects per million opportunities.

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