



Advance and Continuous Process Improvement in Healthcare Industries: A Systematic Review

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ABSTRACT

For process improvement in pharmaceutical manufacturing process, there are only some small organizations using models that direct the management and deployment of their improvement initiatives. This is mostly because a lot of these models do not consider the special characteristics of small pharmaceutical industries. It should also be noted that the models which direct improvement implementation for small settings do not present an explicit process with which to organize and guide the internal work of the employees involved in the implementation of the improvement opportunities. In this paper we propose Annual Product Quality Review & Process Capability Study, which takes into account appropriate strategies for this type of organization.

Keywords: APQR, Pharmaceutical Industry, Process Capability.

INTRODUCTION

Continuous improvement is an essential constituent in a modern quality system and it targets at improving efficiency by optimizing a process and eliminating wasted efforts in production. In the current system continuous improvement is difficult, if not impossible. Reducing variability provides a "win-win" opportunity from both public health and industry perspectives, therefore continuous improvement needs to be facilitated.¹

The health care industry has been able to recognize there is a difficulty with system and operational performance. Individual entities and the industry as a whole have expended significant problem-solving efforts throughout the nineties and into the first part of the twenty-first century. Those problem-solving efforts netted significant benefits. However, the net result of organizational, as well as industry, problem-solving efforts were one-time savings or cost deferments at best. The worst-case scenario created a culture that was adverse to further performance improvement activities, since the previous efforts failed to be sustainable activities or resulted in fewer staff to complete the work. The industry and many health care organizations failed to transform their operations and business practices to meet the changing requirements of an industry with many stakeholders. The following approach outlines a path for health care organizations to successfully deploy an organizational transformation strategy to achieve continuous performance improvement.³

Approaches of Process Improvement

Process improvement approaches like for the health care industry, have a long history stemmed deep in the industrial revolution. One of the first documented process improvements was the introduction of the production line by Henry Ford in 1913. Henry Ford was the first

individual to capitalize on continuous flow. Continuous flow serves as a starting point for process improvement in health care, rather than an answer. It was not until the 1950s in a rebuilt Japan that it was realized continuous flow is but one element to an overall process improvement approach. Taiichi Ohno and his regarded apprentice Shigeo Shingo pursued an investigative path that ultimately fathered many continuous improvement methodologies that are still being perfected and utilized today, including Lean and Six Sigma. It is these process improvement methodologies that health care professionals are increasingly turning to in an effort to build an improved and sustainable model for the betterment of their organizations.

Lean concepts were formally developed and ultimately documented at Toyota Motor Corporation through the work of Taiichi Ohno.

While Lean clearly began and continues to succeed as a manufacturing concept, it has been successfully deployed in every industry, including health care. The success of lean deployments comes from two primary drivers.

The first driver is the five principles of lean as documented by James Womack in lean thinking.

1. Specify the value desired by the customer
2. Identify the value stream for each product services providing that value and challenge all of the wasted steps currently necessary to provide that value
3. Make the product (service) flow continuously through the remaining value-added steps
4. Introduce pull between all steps where continuous flow is possible
5. Manage toward perfection so the number of steps and the amount of time and information needed to serve the customer continually fall.



The first principle is often the most challenging principle for health care organizations to grasp. While it is easy for health care organizations to identify the patient as the customer, they must also recognize the internal and affiliated customers when defining value. As a general rule, health care organizations need to recognize not just the patient, but also the physician, care provider, payer organization, ancillary service providers, and others as potential customers. This creates a significant challenge in deploying lean thinking to health care organization.²

Process is defined as “Sequence of interdependent and linked procedures which, at every stage, consume one or more resources (employee time, energy, machines, money) to convert (data, material, parts, etc.) into outputs. These outputs then serve as inputs for the next stage a known goal or end result is reached”.⁴

“Process improvement” means making things improved, not just fighting fires or managing crises. It means keeping aside the customary practice of blaming people for problems or failures. It is a way of looking at how we can do better.⁴

The purpose of process improvement is to eradicate the root causes of performance deficiencies in processes that already exist in the organisation. These performance deficiencies may be causing real problems for the organisation or may be preventing it from working as efficiently and effectively as it could.⁵

However, when industry is busy in true process improvement, it look for to learn what causes things to occur in a process and to use this knowledge to decrease variation, remove activities that contribute variation to the product or service produced, and improve customer satisfaction. A team examines all of the factors affecting the process as below:

- Materials used in the process
- Methods and equipments used to convert the materials into a product or service
- People who perform the work.

Benefit of process improvement to healthcare industries

A standardized process improvement methodology allows industry to come across at how they perform work. When all of the major candidates are involved in process improvement, they can collectively focus on eliminating waste of money, people, materials, time, and opportunities. The ideal outcome is that jobs can be done cheaper, quicker, easier, and most importantly for pharmaceutical industry is safety of consumers.

A Regulatory structure for Manufacturing Science: A Systems Perspective

Pharmaceutical cGMPs for the 21st Century was proposed to improve and adapt the regulation of pharmaceutical manufacturing and product quality. It provides a summary of the PAT Team's and Manufacturing Science Working Group's combined efforts, accomplishments &

points to consider as the initiative moves into its next phase (implementation and continuous improvement). The FDA Science Board and the Advisory Committee for Pharmaceutical Science (ACPS) discussions provided information on the current state of pharmaceutical manufacturing, challenges faced and opportunities for improvement. Under the ACPS Manufacturing Subcommittee a working group will be formed to identify specific steps required to move towards the desired state. The group will also build up illustrative case studies to support the ICH Q8 document and CPG 7132c.08.

ICH Q8 and illustrative examples should then be a basis to develop the draft comparability guidance to aid continuous improvements.¹

The combined work products of the CGMP Initiative are situated well to provide a comprehensive set of regulatory tools to aid a move towards the desired state. Only companies that attain a high level of process understanding will have the chance to utilize their information to justify a more flexible regulatory path towards continuous improvement.¹

Generally the term **continuous improvement** is broadly used for all improvement efforts including **corrective actions** and the ensuing **preventive actions**. In the regulatory background a distinction between corrective action and continuous improvement is necessary. Necessitate for corrective actions occur when product quality characteristics are in question (e.g., out of specification). Such a situation can require urgent risk assessment and quality decisions to avoid any adverse impact on patients. Innovation is different from continuous improvement as it is not a part of routine production operations and requires significant investment of resources and may require changes in production design and operation.

The simple phrases used in Figure 1 to explain a modern quality system were suggested by the FDA's Quality System Working Group. Some distinguishing characteristics of the three improvement approaches and the contributions of the two groups are summarized in Table 1. A need for similar distinction between improvement approaches was previously suggested in the automotive industry.¹⁻²

Basic Process Improvement Model⁴

The Basic Process Improvement Model is presented on the next page. It has two parts:

A process simplification segment outlining steps 1 through 7 of the process improvement cycle is placed on the left. Teams begin process improvement activities with these steps. Depending on the stability and capability of the process, the team may continue on to step 8, or go directly to step 14. A Plan-Do-Check-Act (PDCA) Cycle consisting of steps 8 through 14 flows from the process simplification segment. Using all 14 steps of the model will increase the team's process knowledge, broaden decision-making options, and enhance the likelihood of



satisfactory long-term results. Let's take a quick look at what's in each of the steps in the model.

well-defined process improvement objective. The objective may be established by the team or come from outside tasking.

Step 1: Select the process to be improved and establish a

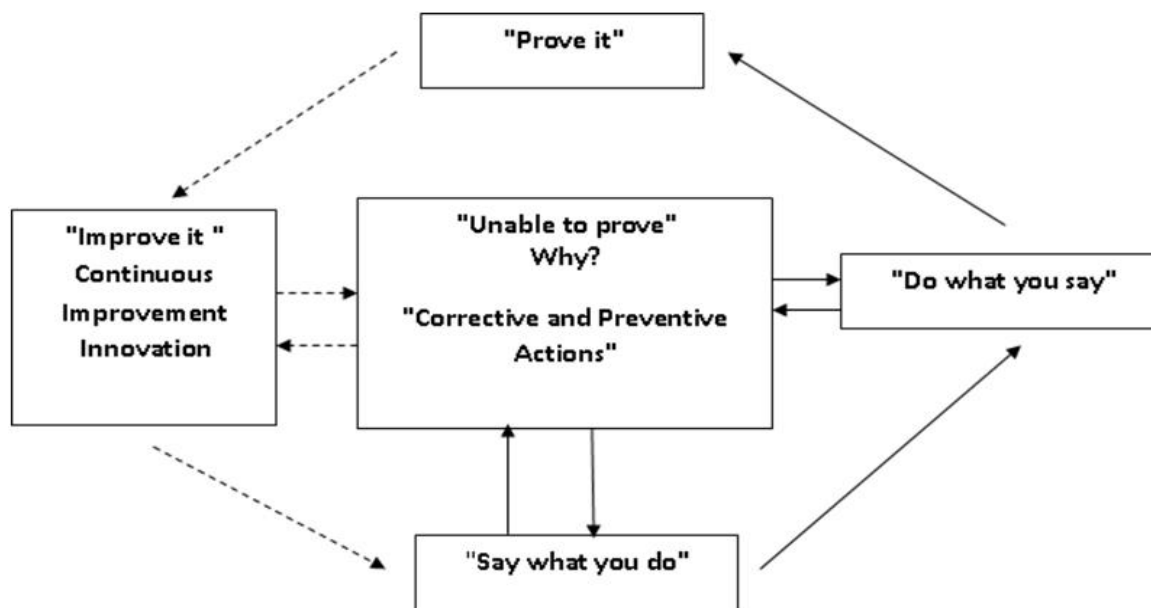


Figure 1: Types of improvement¹

Table 1: Types of improvement and their relation to the objectives of the FDA Initiatives¹

Improvement Approaches		Characteristics and Objectives
Innovation	Primary focus area of the PAT Team. Manufacturing Science WG is contributing to harmonization of the PAT framework in ICH.	Primary focus area of the PAT Team. Manufacturing Science WG is contributing to harmonization of the PAT framework in ICH.
Continuous Improvement	PAT Framework provides many options and opportunities including research data collection in production. Manufacturing Science WG creating regulatory flexibility through ICH Q8.	Product is in specification Acceptance criteria variable/continuous data Evolutionary, incremental process optimization, continuous, daily activity carried out by plant and quality staff CGMP Initiative Objective #1-5.
Corrective Actions	PAT opens the door for new tools for root cause Investigations and data Collection in production. Manufacturing Science provides the foundation for more effective approaches.	Product is out of specification (OOS) or Procedural deviations "Crisis" - immediate action needed Required by regulators CGMP Initiative Objectives: #1-5.

Step 2: Organize a team to improve the process. This involves selecting the "right" people to serve on the team; identifying the resources available for the improvement effort, such as people, time, money and materials setting reporting requirements; and determining the team's level of authority. These elements may be formalized in a written charter.

Step 3: Define the current process using a flowchart. This tool is used to generate a step-by-step map of the activities, actions, and decisions which occur between the starting and stopping points of the process.

Step 4: Simplify the process by removing redundant or unnecessary activities. People may have seen the process on paper in its entirety for the first time in Step 3. This can be a real eye-opener which prepares them to take these first steps in improving the process.

Step 5: Develop a plan for collecting data and collect baseline data. These data will be used as the yardstick for comparison later in the model. This begins the evaluation of the process against the process improvement objective established in Step 1. The flowchart in Step 3 helps the team determine who should collect data and where in the process data should be collected.

Step 6: Assess whether the process is stable. The team creates a control chart or run chart out of the data collected in Step 5 to gain a better understanding of what is happening in the process. The follow-on actions of the team are dictated by whether special cause of variation is found in the process.

Step 7: Assess whether the process is capable. The team plots a histogram to compare the data collected in Step 5 against the process improvement objective established in Step 1. Usually the process simplification actions in Step 4

are not enough to make the process capable of meeting the objective and the team will have to continue on to Step 8 in search of root causes. Even if the data indicate that the process is meeting the objective, the team should consider whether it is feasible to improve the process further before going on to Step 14.

Step 8: Identify the root causes which prevent the process from meeting the objective. The team begins the Plan-Do-Check-Act Cycle here, using the cause-and-effect diagram or brainstorming tools to generate possible reasons why the process fails to meet the desired objective.

Step 9: Develop a plan for implementing a change based on the possible reasons for the process's inability to meet the objective set for it. These root causes were identified in Step 8. The planned improvement involves revising the steps in the simplified flowchart created after changes were made in Step 4.

Step 10: Modify the data collection plan developed in Step 5, if necessary.

Step 11: Test the changed process and collect data.

Step 12: Assess whether the changed process is stable. As in Step 6, the team uses a control chart or run chart to determine process stability. If the process is stable, the team can move on to Step 13. If not, the team must return the process to its former state and plan another change.

Step 13: Assess whether the change improved the process. Using the data collected in

Step 11 and a histogram, the team determines whether the process is closer to meeting the process improvement objective established in Step 1. If the objective is met, the team can progress to Step 14; if not, the team must decide whether to keep or discard the change.

Step 14: Determine whether additional process improvements are feasible. The team is faced with this decision following process simplification in Step 7 and again after initiating an improvement in Steps 8 through 13. In Step 14, the team has the choice of embarking on continuous process improvement by re-entering the model at Step 9 or simply monitoring the performance of the process until further improvement is feasible.

Table 2: Contribution for APQR from various regulatory bodies⁶

Regulatory Body	Contribution for APQR
European Union (Eudralex)	The additional text "Product Quality Review" for Chapter 1 to the EU GMP Guide has been adopted by the Ad hoc GMP inspectors Working group at their first meeting in July 2003. The proposal of Product Quality Review arises from the experience of Member States' inspectorates where quality problems with products on the market leading to recall could have been anticipated if the manufacturer/marketing authorization holder had operated a system for formally reviewing process consistency and trends.
US Food and Drug Administration (FDA)	The code of federal regulations (CFR) of Food and Drug Administration in their 21 CFR – Parts 210 & 211 dictated the requirements of reviewing the products annually. It is clearly stated under Subpart J - Records and Reports 211.180(e) that written records required by the part shall be maintained so that data can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.
International Conference on Harmonization (ICH)	ICH Q7A GMP Guide for Active Pharmaceutical Ingredients requires manufacturers to conduct annual quality review of the active pharmaceutical ingredients in order to know the consistency on the quality of products manufactured throughout the year.

Annual Product Quality Review (APQR) & Process Capability as challenging tools for process improvement

- **APQR**

Product Quality Review is usual periodic or rolling quality reviews of all licensed medicinal products, including export only products, which are conducted with the objective of verifying the consistency of the active process, the fitness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. APQR is an effective quality improvement tool to increase the uniformity of the process and the overall quality of the product. The APQR will arrest a broader view of product data, capturing trends and will

help conclude the need for revalidation and changes, if any.³

Annual product quality review (APQR) is a natural progression of GMP quality system implementation by manufacturers and this requirement is also not new to begin with, however it (product quality review) is just that the requirement is now clearly specified in the PIC/S Guide to Good Manufacturing Practice for Medicinal Products. It is believed that manufacturers might have done some sort of informal review of their manufacturing processes over the years, but it has not been documented or announced.

Process of APQR⁶

Method: Product Quality Review is carried out for any products manufactured in the previous year. Steps of APQR Study are as follows:



❖ **A Review of Starting Materials and Product**

It includes

- Summary of all batches of starting and packaging materials received in a year and their approval status.
- Summary of the suppliers/manufacturers of the materials.
- Summary of details related to any significant deviations observed such as rejection of vendor lots.

❖ **A Review Finished Product Results**

It includes

- Compilation of finished product test results such as description/appearance, identification and assay.

❖ **A review of all batches that failed to meet established specifications and their investigation**

It includes

- Summary of the number of failed batches/products. The list will identify the batches that failed specifications and the root cause for this failure, if identified.
- Summary of the reasons for failure.
- Summary of the completed investigation reports and corrective actions taken.

❖ **A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken**

It includes

- Summary of all deviations or non-conformance, together with causes of the non-conformance, sorted based on data trending.
- Compilation (using trend analysis) of corrective and preventive actions (CAPA) taken.

❖ **A review of all changes carried out to the processes or analytical methods**

It Includes

- Summary of the changes, if any, made to the process e.g. change of mixing time, blending time, order of addition of ingredient.
- Summary of the changes made to the analytical methods, e.g. change of solvents, buffers, reagents, pH, change in composition of mobile phase, change in HPLC/GC method parameters i.e. flow rate, temperature, wavelength, run time, and change of HPLC/GC column etc.

❖ **A review of quality-related product returns, complaints and recalls and the investigations performed at the time**

It includes

- Summary of batches returned due to potential quality defects, together with the reasons.
- Summary of market complaints received in a year, together with the nature of complaints.
- Summary of batches recalled, together with the reasons.

❖ **A review of post-marketing commitments for new marketing authorizations and variations to marketing authorizations**

It includes

- Summary of any changes, in terms of the specification, registered with drug regulatory authority, including overseas drug regulatory authorities.
- State any post-marketing commitments and review the status of these commitments.

❖ **The qualification status of relevant critical equipment and utilities**

It includes

- Qualification status of Sifter, Mixer, Octagonal blender, Sachet filling machine, HVAC system, Water.
- Qualification status of QC instruments.

❖ **Analysis of Data**

Data is analyzed by Control Chats & Process Capability.

How to Recognize Trends, Interpret Data, and Draw Conclusions From the Data⁶

1) The data generated from the batch or product shall be trended using the suitable statistical techniques such as time series plots, control charts, etc to draw the conclusions, if any. This will help the manufacturer to take any corrective or preventive action, should manufacturer find the process to be out of control.

2) The data should be trended and analyzed to determine if

(i) The process is in control.

(ii) The process is capable. Control limits should be established through trending. The appropriateness of current specifications for both starting materials and finished product should also be determined. In addition, it is important to highlight any trends observed and to identify product and process improvements. Improvement plans and actions should be initiated and taken if the process is found to be out of control or has low capability indices.

The data may be analyzed using the following techniques

a) Control Charts

Processes should be demonstrated to be in control, and one of the ways to demonstrate this is the use of charting techniques commonly known as the Shewhart Control Charts. The use of such charts (example: X-bar charts, R-charts and Moving Range charts etc.) enables the manufacturer to determine upper and lower control limits, and identify trends (examples: upward trend of data, shift in mean etc.) so that appropriate actions may be taken before out-of specification occurs.

b) Process Capability Study

Process Capability & Other types of statistical techniques may also be used, when appropriate in the Product Quality Review. Information derived from such statistical analysis should be interpreted and conclusions drawn, so as to ensure that processes are in control and capable.

Process Capability

In process improvement efforts, the process capability index or process capability ratio is a statistical measure of the ability of a process to produce output within specification limits which is called as Process Capability.⁷ The concept of process capability only holds meaning for processes that are in a condition of statistical control. Process capability indices measure how much "natural variation" a process experiences comparative to its specification limits and allows unlike processes to be compared with respect to how well an organization controls them.⁷⁻⁸

Process capability is also the ability of the combination of people, machine, methods, material, and measurements to produce a product that will consistently meet the design requirements or customer expectation.⁸

Process Capability Study

Process Capability study is a systematic procedure for determining the capacity of a process. This process capability study may contain studies to improve the process and in turn the capability of the process. Process capability studies are usually performed as a element of a process optimization effort.⁸

Process capability indices (PCIs), Cp, Cpk, Cpl & Cpu have been developed in certain manufacturing industry as capability measures based on various criteria, including process uniformity, process going away from a target, process yield, and process loss. It is noted in certain recent quality assurance and capability analysis works that the three indices Cp, Cpk, Cpl provide the same lower bounds on the process yield.⁸⁻⁹

Need of Process Capability Analysis⁹

- Process capability measurements allow to summarize process capability in terms of meaningful percentages and metrics.

- To predict the extent to which the process will be able to hold tolerance or customer requirements. Based on the law of probability, organisation can compute how often the process will meet the specification or the expectation of its customers.
- Organisation may learn that bringing the process under statistical control requires fundamental changes - even redesigning and implementing a new process that eliminates the sources of variability now at work.
- It helps organisation to choose from among competing processes, the most appropriate one for meeting customers' expectation.
- Knowing the capability of the processes, organisation can specify better the quality performance requirements for new machines, parts and processes.

Measures of Process Capability - Process Capability Indices

Cp, Cpl, Cpu, and Cpk are the four most universal measures of process capability.

- Process capability indices measure the degree to which process produces yield that meets the customer's specification.
- Process capability indices can be used efficiently to summarize process capability information in a suitable unit less system.
- Cpk and Cp are quantitative expressions that represent the variability of process (its natural limits) relative to its specification limits (customer requirement).

Following are the graphical details and equation quantifying process capability;

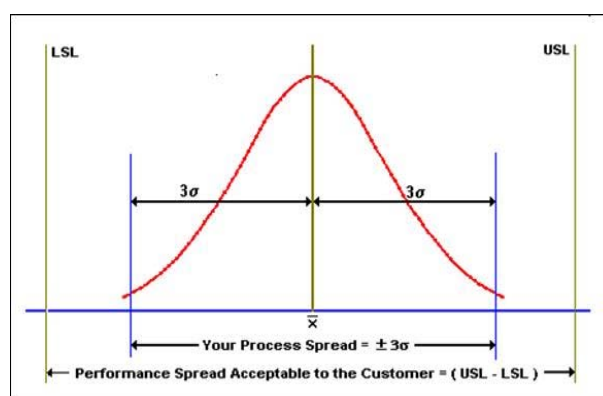


Figure 2: Histogram of capable process⁹

Where, USL = Upper Specification Limit, LSL=Lower Specification Limit, X-Bar = Mean of the Process, s= Standard Deviation of the Process

Cp: Estimated Equation - $(USL - LSL) / 6s$

Usage- Process Capability for two-sided specification limit, irrespective of process centre.

Cpu: Estimated Equation - $(USL - \bar{X}) / 3s$

Usage - Process Capability relative to upper specification limit.

Cpl: Estimated Equation - $(\bar{X} - LSL) / 3s$

Usage - Process Capability relative to lower specification limit.

Cpk: Estimated Equation - Min. of (Cpu, Cpl) or Distance between mean of the process and the closest spec. limit / 0.5 of the process variability.

Usage - Process Capability for two – sided specification limit accounting for process centring.

Notes

1. If \bar{X} is at target, then $C_p = C_{pk}$.
2. C_{pk} will always be equal to or less than C_p

Process Capability and Defect Rate

Using process capability indices it is easy to stop thinking about how much of product is falling outside specification. The conversion curve presented here can be a helpful tool for interpreting C_{pk} with its equivalent defect levels. The defect levels or parts per million non-conforming were calculated for different C_{pk} values using the Z scores and the percentage area under the standard normal curve using normal deviate tables.

The figure below presents the non-conforming parts per million (ppm) for a process corresponding to C_{pk} values if the process mean were at target.

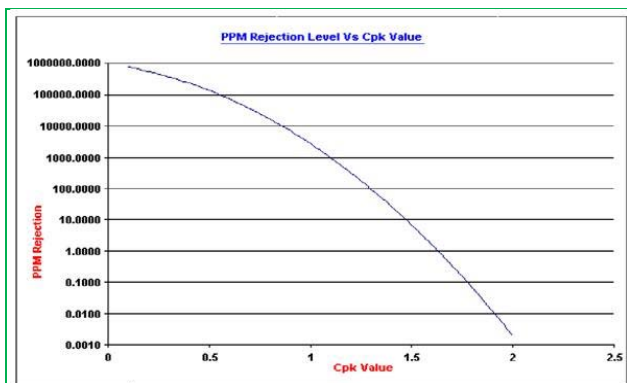


Figure 3: Cpk conversion curve for process with mean at target⁹

Explanation: A process with C_{pk} of 2.0 (± 6 sigma capability), i.e. the process mean is 6 sigma away from the nearest specification can be expected to have no more than 0.002 nonconforming parts per million. This process is so good that even if the process means shifts by as much as ± 1.5 sigma the process will produce not more than 3.4 non-conforming ppm.¹³

Natural Variability versus Specifications for Process Capability

There are three components of process capability

1. Design specification or customer expectation (Upper Specification Limit, Lower Specification Limit)
2. The centering of the natural process variation (\bar{X} -Bar)
3. Spread of the process variations
4. A minimum of four possible outcomes can arise when the natural process variability is compared with the design specifications or customer expectations

• **Case 1: $C_{pk} > 1.33$ (A Highly Capable Process)**

This process should produce less than 64 non-conforming ppm.

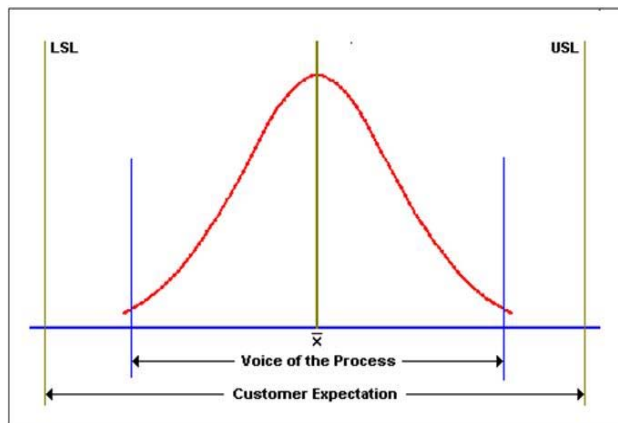


Figure 4: Histogram of highly capable process⁹

This process will generate conforming products as long as it remains in statistical control. The process owner can assert that the customer should experience least difficulty and greater consistency with this product. This should convert into higher profits.

• **Case 2: $C_{pk} = 1$ to 1.33 (A Barely Capable Process)**

This process will produce greater than 64 ppm but less than 2700 non-conforming ppm.

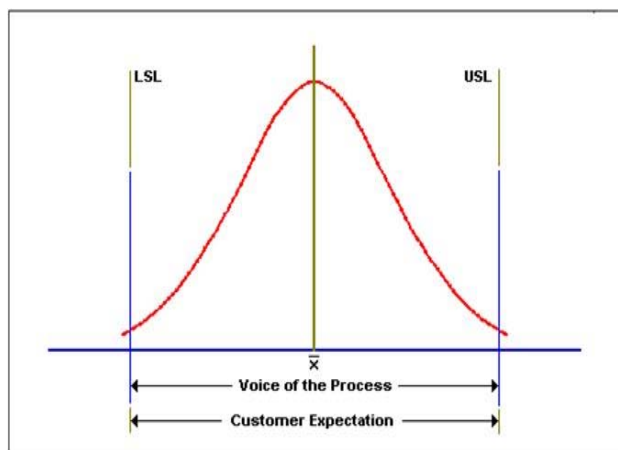


Figure 5: Histogram of barely capable process⁹

This process has a width just about equal to specification width. It should be noted that if the process mean moves to the left or the right, a significant portion of product will begin falling outside one of the specification limits. This process must be closely monitored.¹³

Case 3: Cpk < 1 (The Process is not Capable)

This process will produce more than 2700 non-conforming ppm.

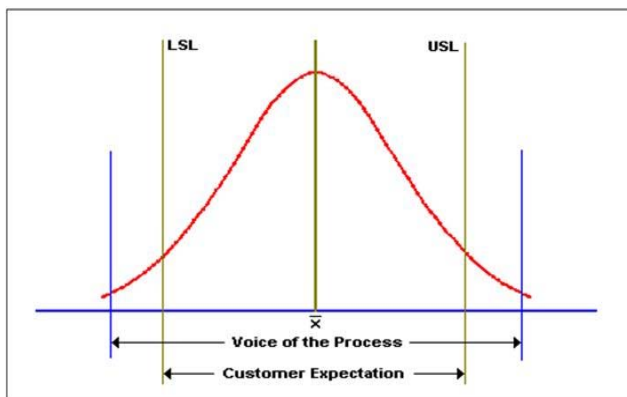


Figure 6: Histogram of incapable process⁹

It is impossible for the current process to meet specifications even when it is in statistical control. If the specifications are realistic, an effort must be immediately made to improve the process (i.e. reduce variation) to the point where it is capable of producing consistently within specifications.⁹

CONCLUSION

In the real world, very few processes completely satisfy all the conditions and assumptions required for Improvement in Process. APQR & Process Capability Study is an effective tool to assess process performance & to improve process by respective corrective & preventative actions. APQR the manufacturer and marketing authorization holder, (where different) should evaluate the results of this review and an assessment can be made whether corrective and preventive actions (CAPA) or any revalidation can be undertaken. Reasons for such corrective actions can be completed in a timely and effective manner. Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties

that defines their respective responsibilities in producing the quality review. As far as Process Capability Concerns many new complicated capability indices can be calculated however, the key to effectual use of process capability measures continues to be the level of user understanding of what these measures really represent. Finally, in order to achieve continuous improvement, one must always attempt to refine the "Voice of the Process" to match and then to surpass the "Expectations of the Customer".

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