

# **Manufacturing Process Qualification & Validation**



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## **Tutorial**

- **Why to Validate**
- **What to Validate**

## **Program**

- **How to Perform successful  
Validation**

# Regulatory Requirements



- **Required by ISO 13485 – 7.5.2**
- **FDA QSR Subpart 820. 75**
- **The Global Harmonization Task Force (GHTF/SG3/N99-10:2004) Quality Management Systems – Process Validation Guidance**
- **Makes good business sense**

# Purpose of GHTF Guidance Document



- **To assist manufacturers in understanding quality management system requirements for process Validation.**
- **General applicability to manufacturing (including servicing and Installation) process for medical devices.**

# QSR 820.75 Process Validation

- **Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signatures of the individual (s) approving the validation and where appropriate the major equipment validated, shall be documented**

# QSR 820.75 Process Validation, Cont'd

- **Each Manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.**
  - 1. Each manufacturer shall ensure that validated processes are performed by individual(s)**
  - 2. For validated processes, the monitoring and control methods and data, the date performed by qualified individual(s) performing the process or the major equipment used shall be documented.**
- **When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented.**

# Benefits of Validation



- **Thorough understanding of a process**
- **Improves product quality and reliability**
- **FDA Perspective: Large portion of field actions and inspection deficiencies could have been prevented if processes were properly validated.**

# **FDA Inspections – Warning Letters**

- **In 2007, 33% of industry Quality System Warning Letters cited process validation. The reasons:**
  - a) Process Validation procedures weren't established.**
  - b) Did not document val. Activities.**
  - c) Firm failed to review/evaluate processes after changes or process deviations occurred**
  - d) The firm failed to evaluate/validate product functionality and packaging integrity weren't performed.**



# FDA Consent Decree



- **Abbott Signs consent decree with FDA, violations were found in process validation, production and process control. The firm has also agreed to pay \$100,000,000.00 to US treasury with in 10 days after the decree has been entered by the court.**

# Schering-Plough Consent Decree -2002

- **Schering will pay the record \$500 million disgorgement in two equal installments of \$250 million, If the actions are not completed on time, firm will pay \$15,000 a day for every deadline missed.**

# Cost of Quality

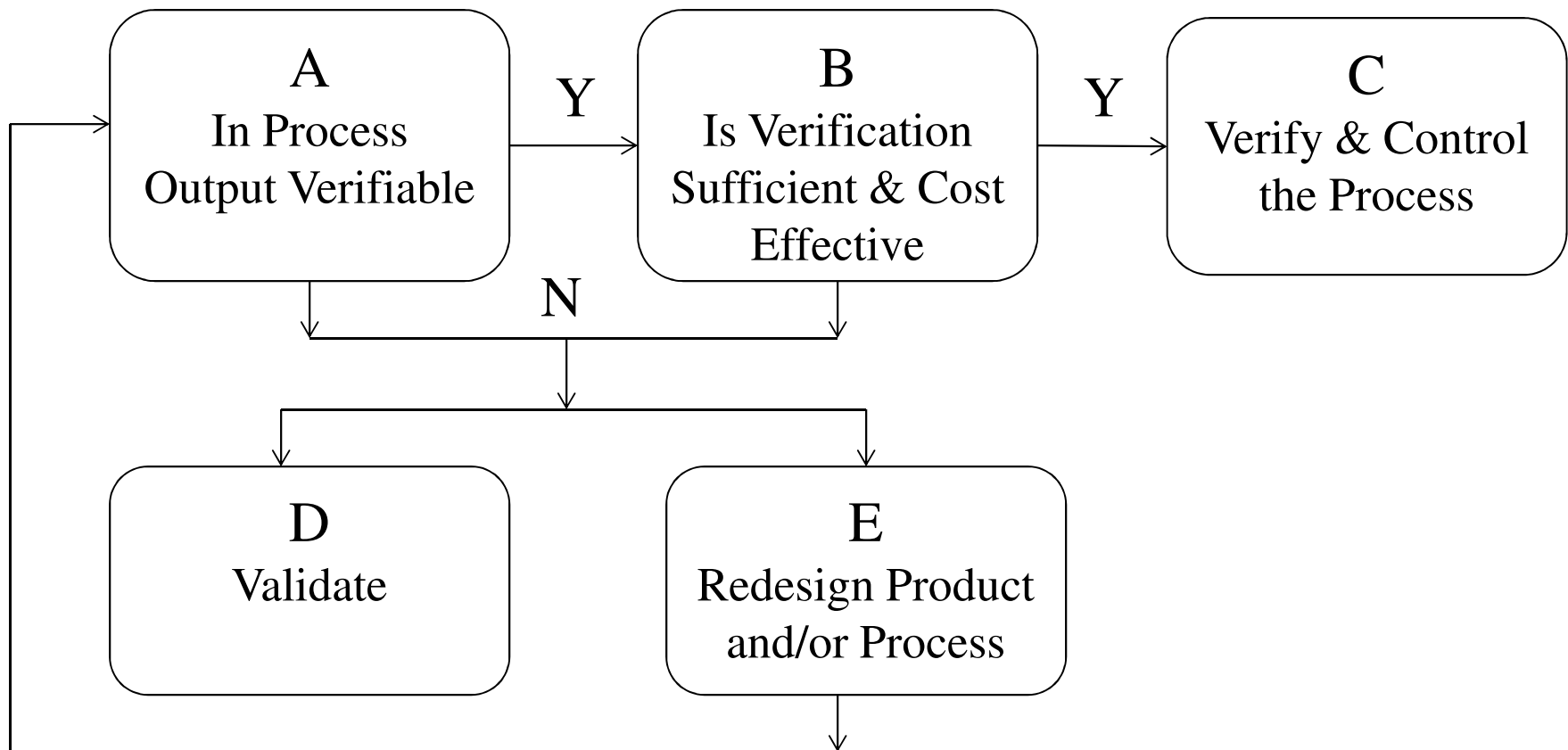
- **Orthopedic Implant maker Zimmer Holdings temporarily recalled and suspended production costed \$70-80 million in lost revenue.**
- **Medtronic CRDM:**
  - a) **Revenue shortfall \$130 million**
  - b) **\$80 million due to inability to fill orders**
  - c) **\$35 million in product returns**
  - d) **\$31 million inventory write-offs**

# Most Common Issues Cited by FDA

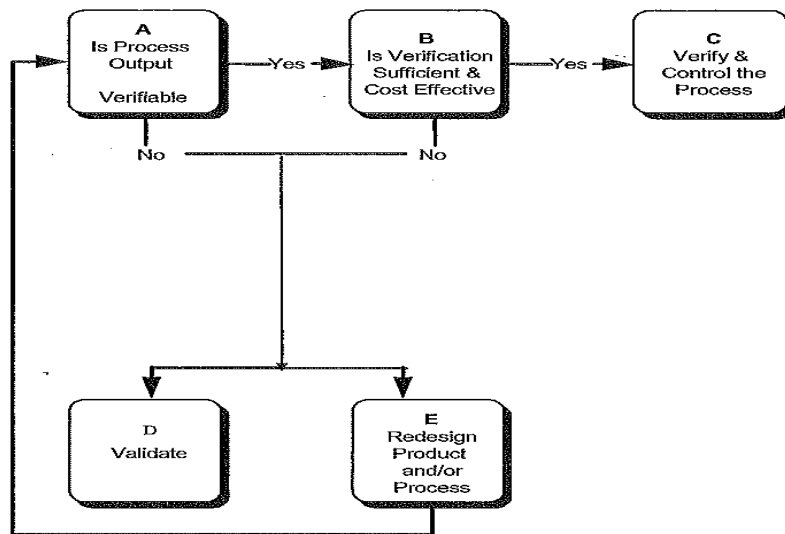
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- **Process Validation**
  - a) Equipment qualification**
  - b) Lack of Validation of Analytical methods.**
  - c) *Ad hoc* manufacturing changes without quality approvals.**
  - d) Lack of written protocols.**
  - e) Short cuts in performing PQ.**

# From GHTF-What to Validate



# What to Validate? Cont'd



- **A. Can the output be verified by subsequent monitoring or measurement?**
- **B. Is verification alone sufficient to eliminate unacceptable risk?**
- **C. If yes, the output should be verified (OQ) and the process should be appropriately controlled**
- **D. If the output of the process is not verifiable, the process must be validated (PQ)**
- **E. Change in manufacturing process may result in need for process validation**

# PROGRAM



## **How to Successfully carrying out Validation**

# Tools & Techniques



- **Understanding the Scope of Validation**
- **How to go about Validation**



# Major Elements of Validation

- **Design Validation 21 CFR Sec 820.30 (g)**  
**Each manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating conditions on initial production lots or batches, or their equivalents. Design Validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate and is documented in DHF**

# Manufacturing Process



- **Process is a unique combination of machines, tools, methods, materials and personnel engaged in Mfg. operation**
- **Capability: is defined as the performance of process itself – demonstrated when the process is being operated in the state of statistical control.**

# Major Elements of Validation

- **Installation Qualification (IQ): Establishing by key objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification of the supplier of the equipment are suitably considered.**

# Major Elements of Validation, Cont'd

- **Operational Qualification (OQ):** Establishing by objective evidence process control limits and action levels which result in product that meets all predetermined requirements. In another word in OQ process parameters should be challenged to assure that they will result in a product that meets all defined requirements under all anticipated conditions.

# Major Elements of Validation, OQ Cont'd

- **OQ Includes:**
  - a) **Process control limits (Time, Temperature, pressure, setup conditions, etc.)**
  - b) **Raw material specs.**
  - c) **Process operating procedures, material requirements training**
  - d) **Short term capability and stability of process, control chart etc.**
  - e) **Potential failure modes, action levels and worst conditions.**

# Major Elements of Validation, Cont'd

- **Process Characterization:**  
**Identifying and quantifying all significant sources of variation, especially variation inherent to the materials and technology as applied to the specific product design**

# Major Elements of Validation, Cont'd

- **Performance Qualification (PQ): Establishing by objective evidence that a process, under anticipated conditions, consistently produces a product which meets all predetermined requirements. In this phase the objective is to demonstrate the process will consistently produce acceptable product under normal operating conditions.**

# Major Elements of Validation, PQ Cont'd

- **PQ considerations include:**
  - a) **Actual product and process parameters and procedures established in OQ**
  - b) **Acceptability of the product**
  - c) **Assurance of process capability as established in OQ**
  - d) **Process Stability and long term process stability**



# Major Elements of Validation, Cont'd

- **Qualification: The activity and analysis performed on equipment, process, or product to demonstrate adherence to predetermined criteria.**

# Major Elements of Validation, Cont'd

- **Worst-Case: A set of process settings and conditions encompassing upper and lower processing limits. These settings pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.**

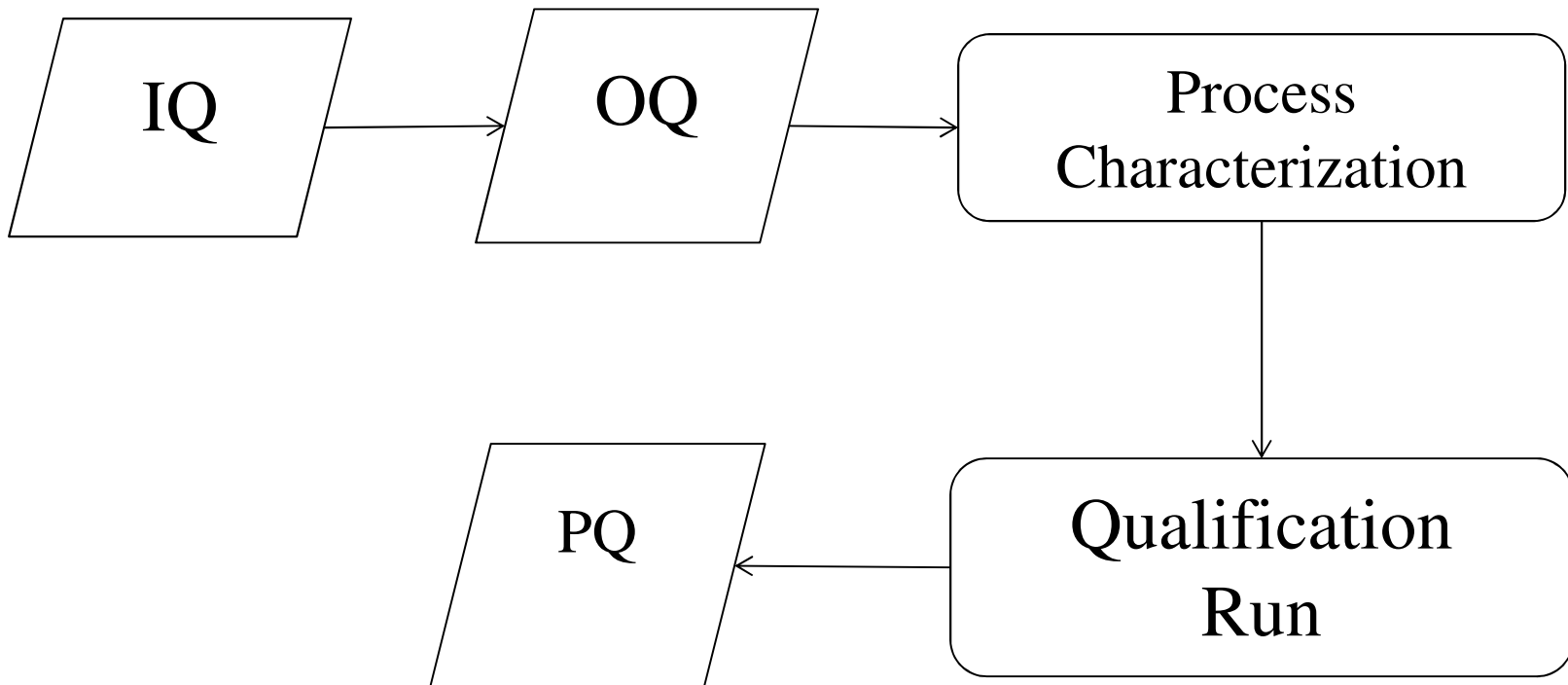
# Major Elements of Validation, Cont'd

- **Protocol: Is a variable document, depending on the nature of the device, the procedure to be used and the purpose of the protocol. The protocols are comprehensive and that the final packages are well documented and easy to follow**

# Major Elements of Validation, Protocol Cont'd

- **Protocol Steps:**
  - a) **Write protocol plan describing all the steps to be taken including sample size.**
  - b) **List characteristics/ features to be verified.**
  - c) **Get approvals from Quality and development team on protocol plan prior to carryout the protocol.**
  - d) **Review the completed protocol to insure that the original intent of the protocol is satisfied.**
  - e) **Go back to the drawing board If protocol fails.**


# Steps for Validation per GHTF Guideline



# For IQ, OQ and PQ

- **Determine what and when to verify/measure**
- **Determine How to verify/measure**
- **Determine how many to verify/measure (Statistical techniques)**
- **Define Accept/ Reject criteria**
- **Define Required documentation including IQ, OQ and PQ records.**

# **Manufacturing Validation**



**Basic Statistical  
methods and Tools**

# Degree of Assurance



- **Degree of Assurance is measured in terms of Confidence Level and Reliability**



# Degree of Assurance cont'd

- **Confidence Level**: It simply means that the more we know about anything the better our chances are of being right. It is a mathematical probability relating to the true value of a parameter to an estimate of that parameter. Only infinitely large sample size can give us 100% confidence that our measurement coincide with the true value.

# Reliability



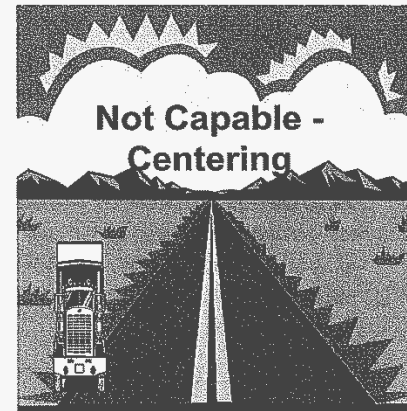
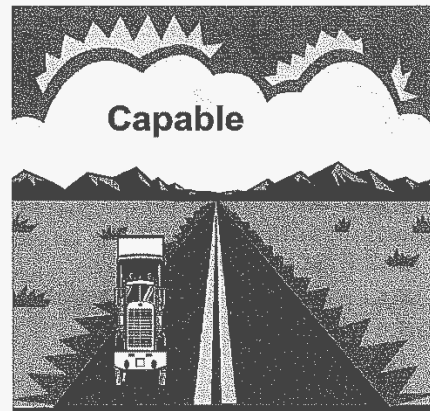
- **Mathematical definition is probability of success.**
- **In our business “Reliability” is our statement of the performance of our process.**

# Sample size for various Confidence/ Reliability

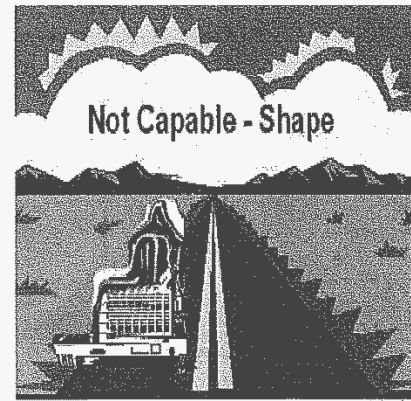
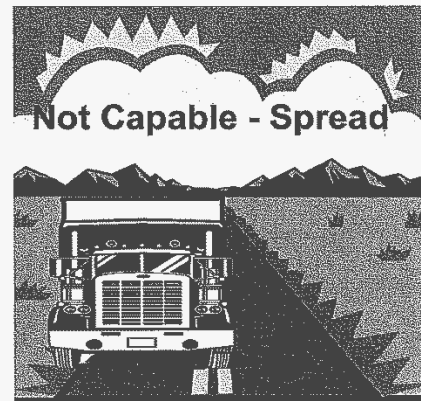
<b>Risk Level</b>	<b>Confidence Level</b>	<b>Reliability</b>	<b>Attribute Sample Size</b>
<b>Low</b>	<b>95</b>	<b>60-70</b>	<b>9</b>
<b>Medium</b>	<b>95</b>	<b>80</b>	<b>14</b>
<b>Medium/ High</b>	<b>95</b>	<b>90</b>	<b>29</b>
<b>High</b>	<b>95</b>	<b>95</b>	<b>59</b>
<b>Very High</b>	<b>95</b>	<b>99</b>	<b>299</b>

**Note: All Sample sizes requires 0 Non conformances to achieve the confidence/ reliability indicated**

# Process Capability



How do we measure capability?



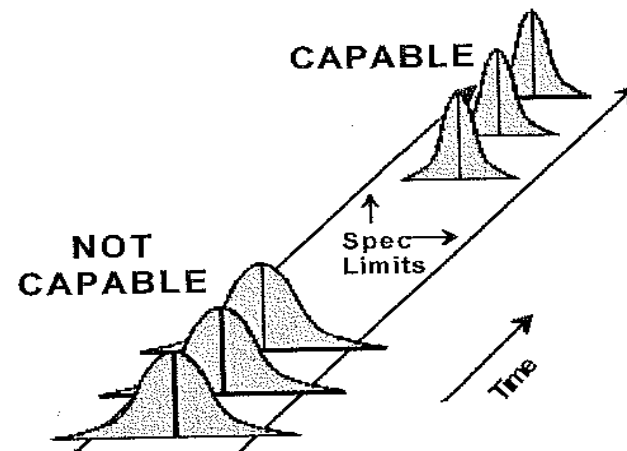
# Process Capability, Cont'd

- **Capability**: is defined as the performance of process itself – demonstrated when the process is being operated in the state of statistical control. Capability can be determined only after the process is in Statistical Control. A stable process in statistical control does not have any special causes remain. Common causes are inherent in the process.

# Control Vs. Capability

- **Control is concerned with process variation relative to stability and predictability – only common causes present**
- **Capability is concerned with the ability of the stable process to meet specifications/ expectations**

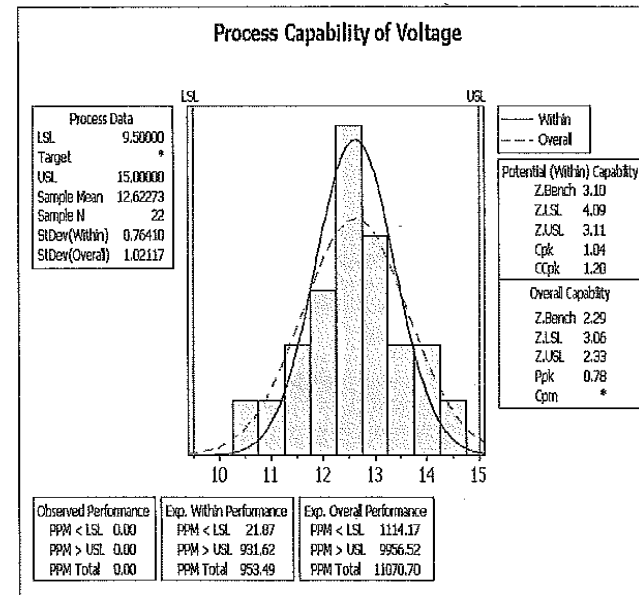
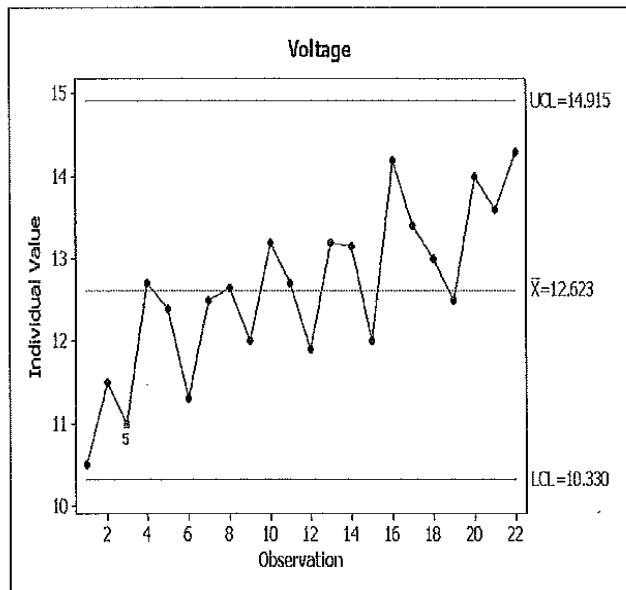
# Process Capability



A **capability study** is used to determine whether a process is stable and capable. It involves collecting samples over a period of time. The average and standard deviation of each time period is estimated and these estimates plotted in the form of a **control chart**. These **control charts** are used to determine if the process is stable. If it is, the data can be combined into a single histogram to determine its capability. To help determine if the process is capable, several capability indices are used to measure how well the histogram fits within the specification limits. One index called  $C_p$  is used to evaluate the variation. Another index  $C_{pk}$  is used to evaluate the centering of the process. Together these two indices are used to decide whether the process meets its requirements. The values required to pass depend on the severity of the defect (major, minor, critical) that the manufacturer considers acceptable.

# Stability & Capability

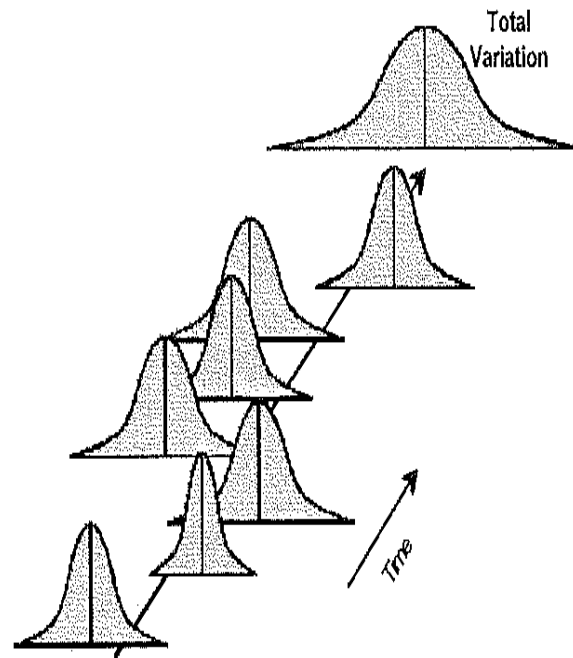
- Would a capability analysis of this process make sense?



- We need to demonstrate stability before we can discuss capability

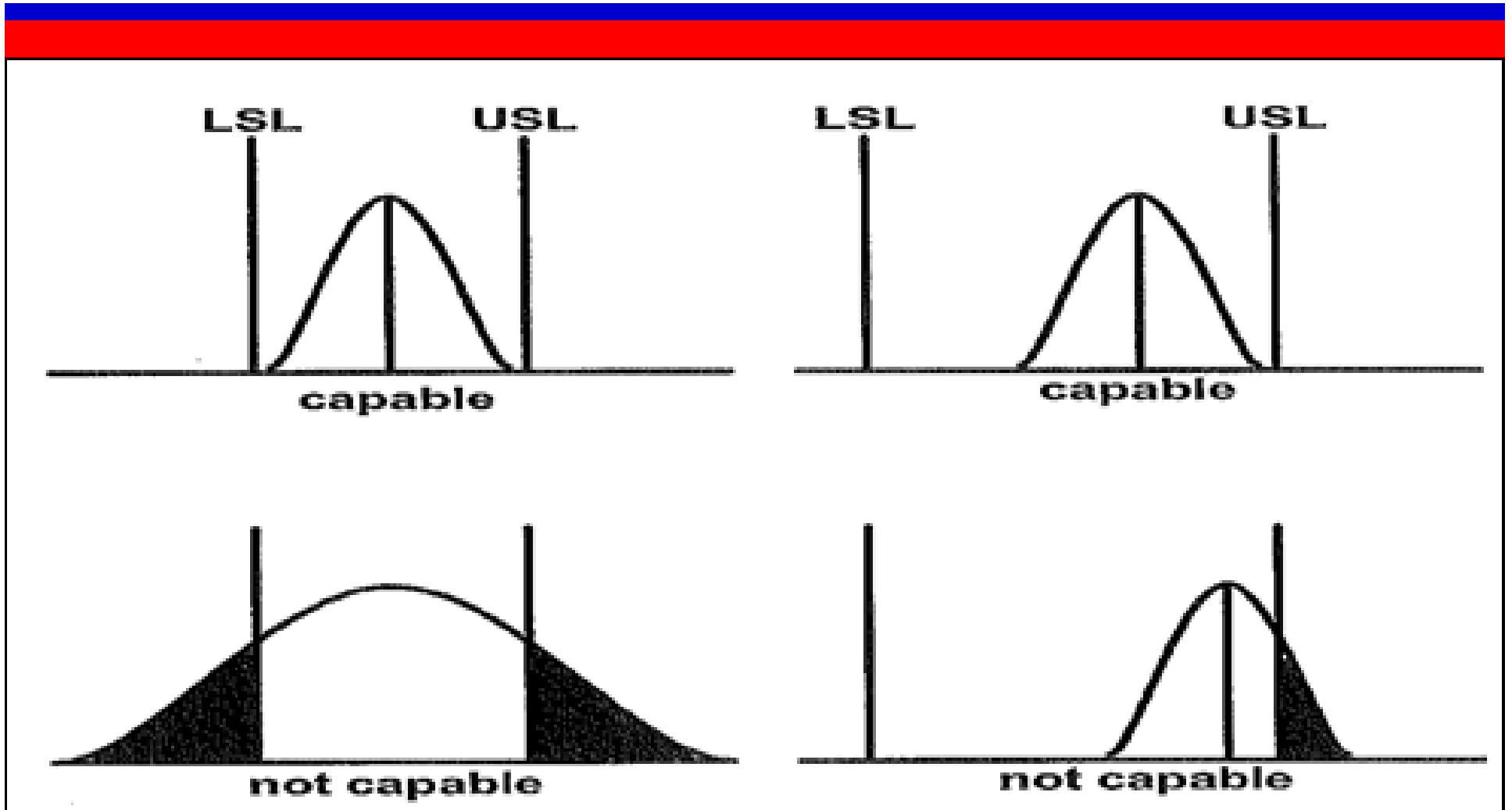


# Unstable Process

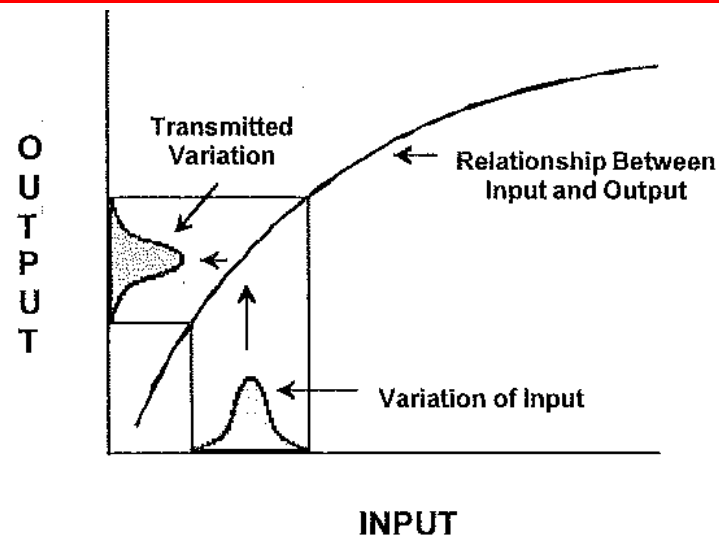


Instead, stable processes are desired as shown in figure 5. Stable processes produce a consistent level of performance. The total variation is reduced. The process is more predictable.

# Process Variation Examples



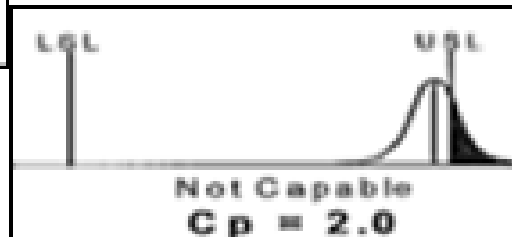
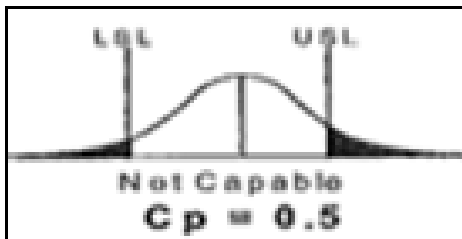
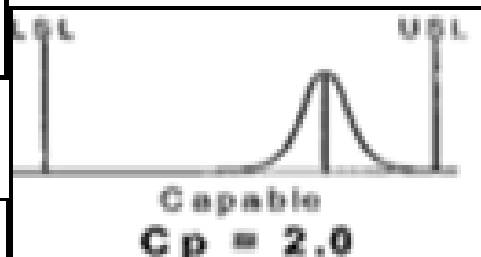
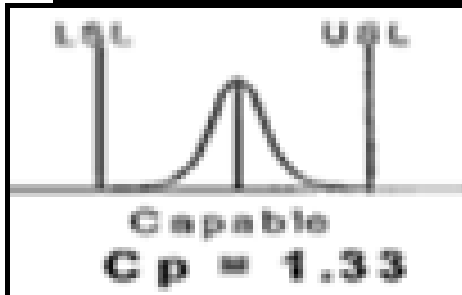
# Transmission of Variation



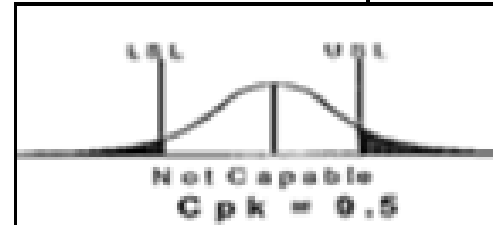
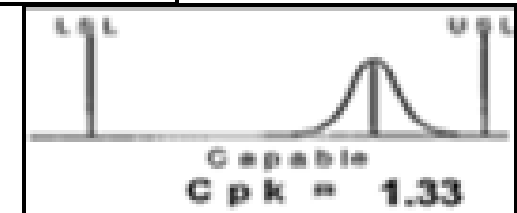
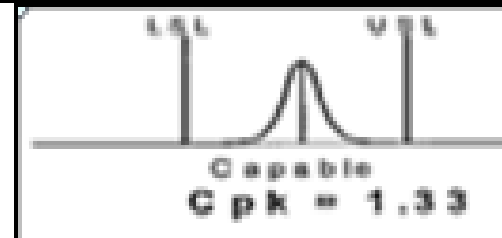
Reducing variation requires identifying the key input variables affecting the outputs, designing the process to take advantage of relative input sensitivities (the relationships between cylinder radius, stroke length, motor speed and output) and establishing controls on input variation (wear, motor speed, temperature/viscosity, etc.) to ensure that the outputs conform to their established specifications. In general one should, identify the key input variables, understand the effect of these inputs on the output, understand how the inputs behave and finally, use this information to establish targets (nominals) and tolerances (windows) for the inputs. Various techniques can be used.

# Process Capability Indices

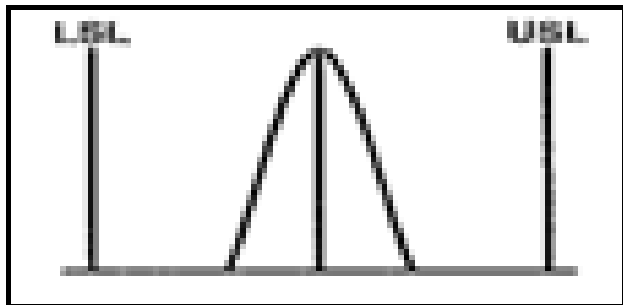
$$C_p = \frac{USL - LSL}{6\sigma} = \frac{\text{total tolerance}}{\text{process capability}}$$



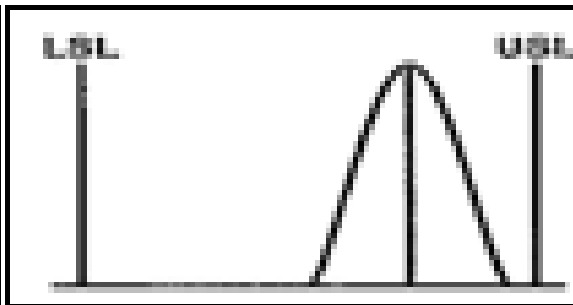
$$C_{pk} = \frac{USL - \mu}{3\sigma} \text{ or } \frac{\mu - LSL}{3\sigma}, \text{ whichever is smaller}$$



# Relationship between Cp and Cpk



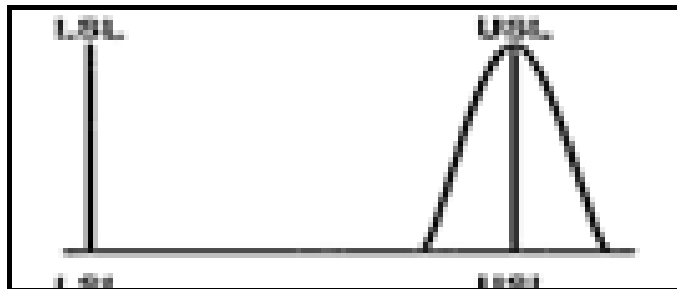
**Cp = 1.5, Cpk = 1.5**



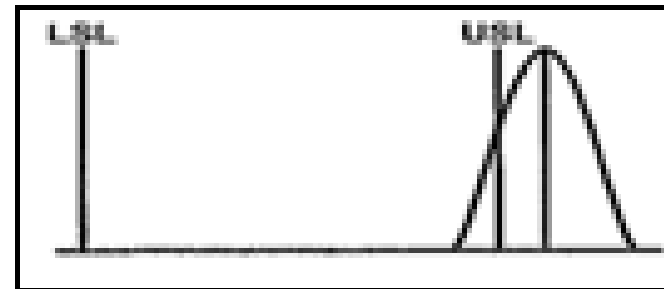
**Cp = 1.5, Cpk = 1**



**Cp = 1.5, Cpk < 1**



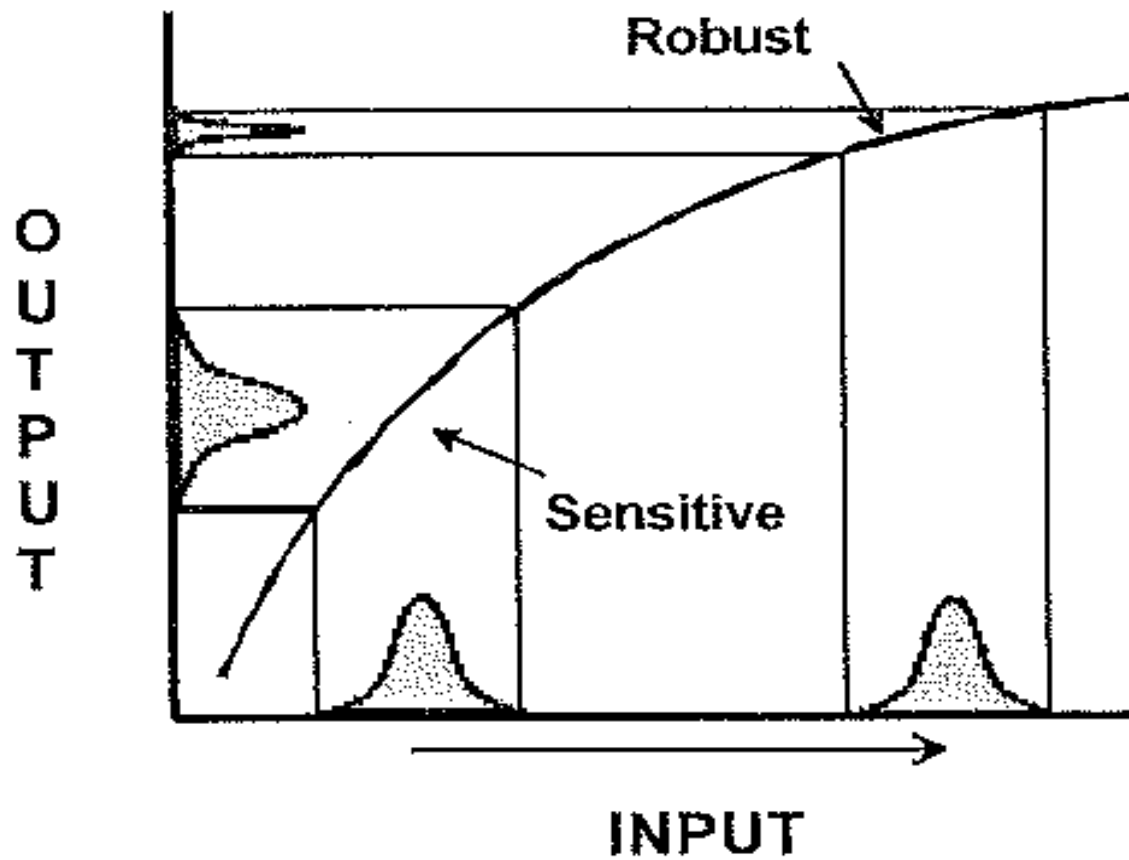
**Cp = 1.5, Cpk = 0**



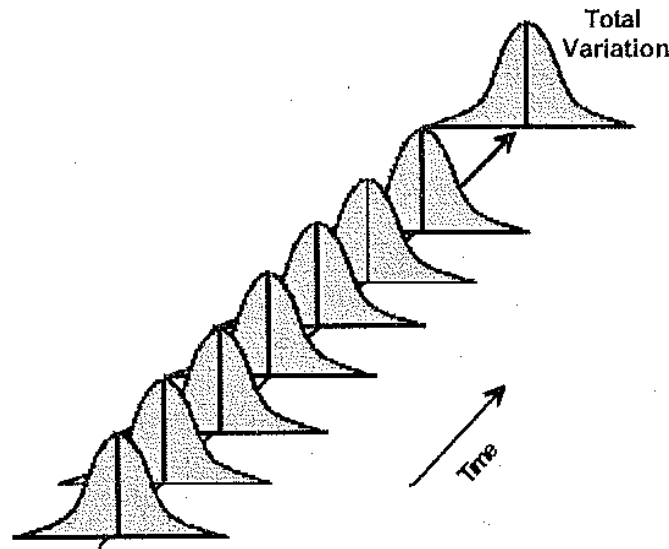
**Cp = 1.5, Cpk < 0**

**Cp = Cpk when process mean is at the nominal  
Cp > Cpk otherwise**

# Robust Design



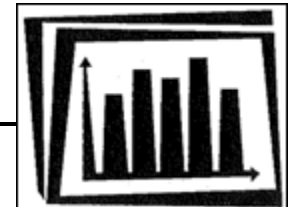
# Stable & Capable Process



However, stability is not the only thing required. Once a consistent performance has been achieved, the remaining variation must be made to safely fit within the upper and lower specification limits. Such a process is then said to be stable and capable. Such a process can be relied on to consistently produce good product as illustrated in figure 6.

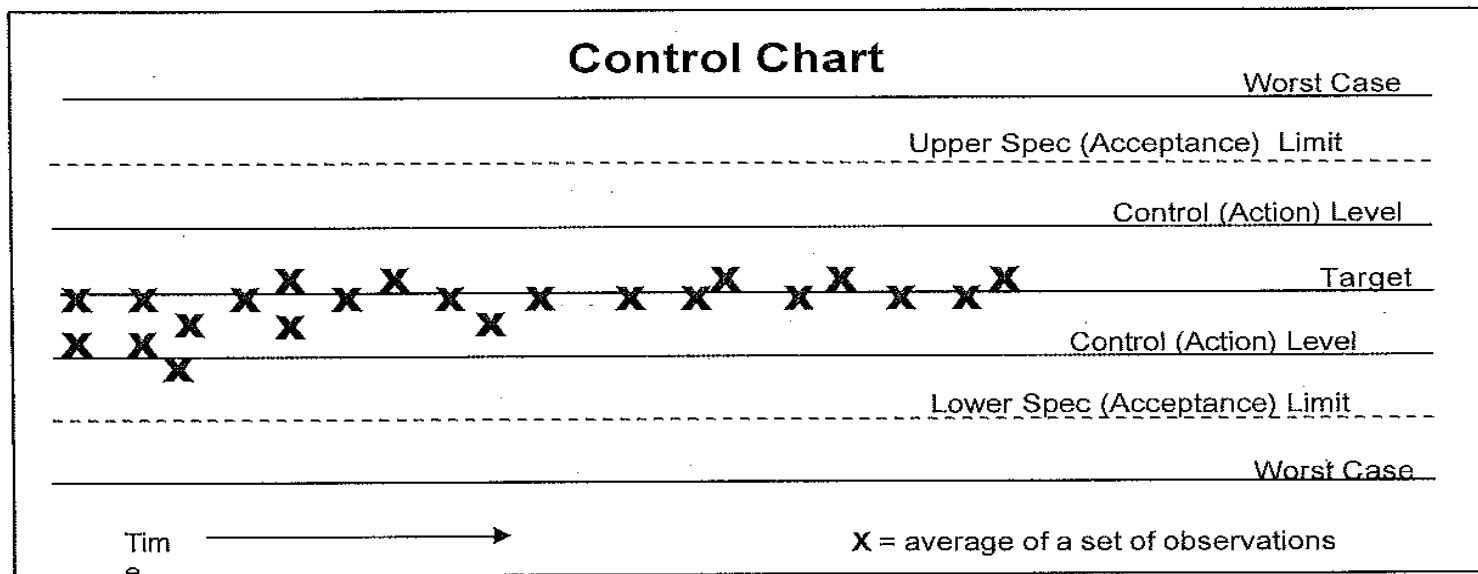
# Process Monitoring and Controls

- **If a problem develops or change are made, immediate revalidation shall be addressed and documented**
  - **Statistical Process Control (SPC) is not a substitute for a complete process validation program**
    - » **Refer to FMEA for potential risks of process failure and effectiveness of proposed controls**
    - » **Process monitoring and analysis requirements shall be established**
    - » **Process monitoring requirements shall be documented in OQ and PQ reports**
- Validated state means stable and capable





# Monitoring & Control



By monitoring the results of changes of inputs through control charting, the resultant variation in output can be determined and inherent variation of the process identified. Ultimately, control charting may be used to continuously monitor the process and assure a state of validated control. Control or action levels can be determined to adjust the process and maintain the process within the control limits.

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**Thank You**