FDA Medical Device Industry Coalition

Efficient Validation Strategies and VMPs

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Agenda

- History and Recent Trends
- Why Validate
- 21 CFR 820.75 Process Validation
- Standards and Guidance
- Definitions and Terminology
- Processes Requiring Validation
- Validation Planning
- Validation Sequence
- Process Monitoring, Control and Revalidation

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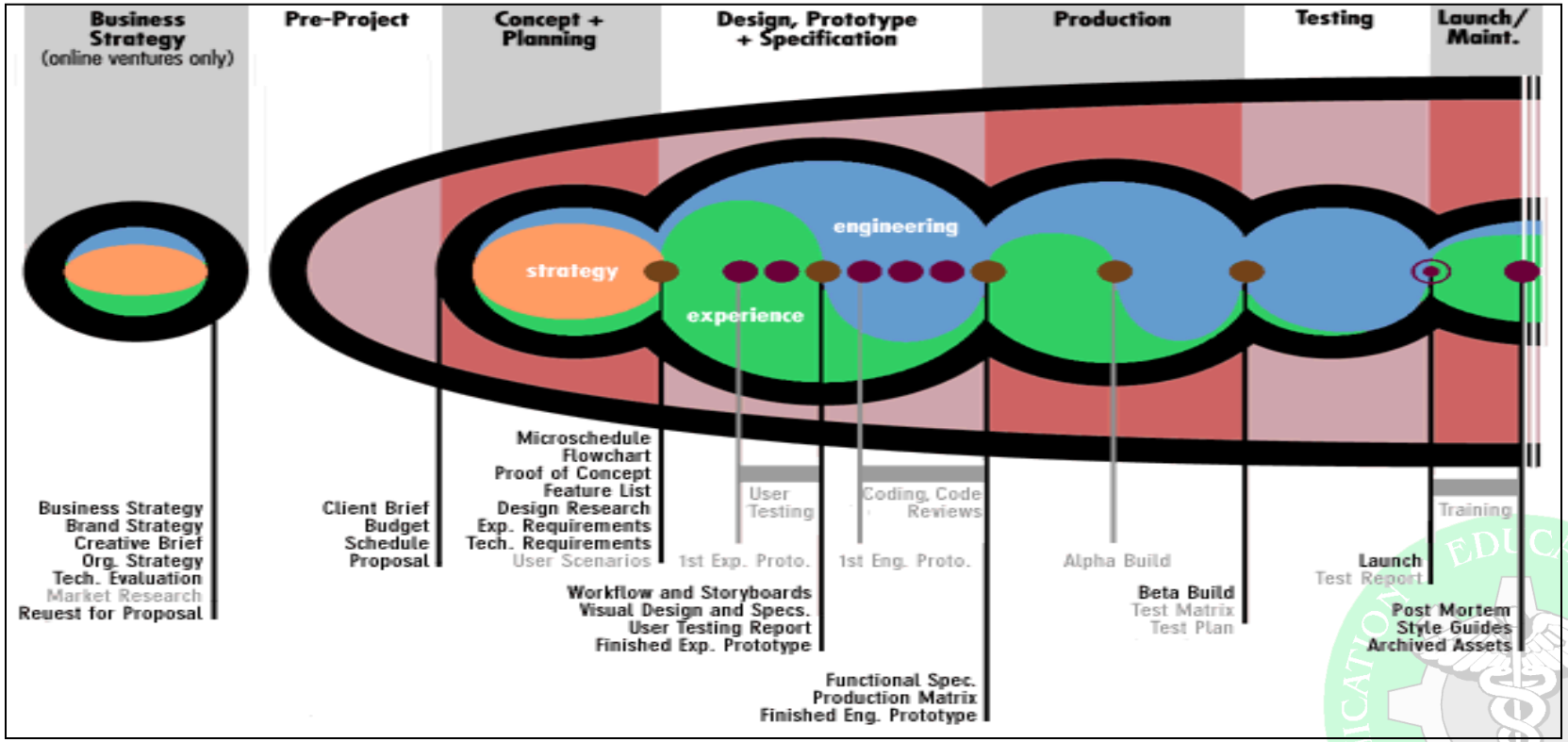
History and Recent Trends

What is a Process?

ANSI/ISO/ASQ 9000

A process is defined as a set of interrelating or interacting activities which transforms inputs to outputs



Process Validation History

In practice…

De facto validations in American Industry since 1950's; Bell Telephone, Aerospace Industry, Chemical and Paper Industry

For Medical Products…

1st documented Process Validation Studies were for sterilization (steam, then EtO) in the pharmaceutical industry during the 1960's.

2015 Trends

- Process Validation, 21 CFR 820.75, moves to 5th Place in Warning Letters

- Production and Process Controls, Subpart G, moves to 2nd Place in Warning Letter Deficiencies

From GMP News- Medical Device Warning Letter Statistics

Why Validate?

Why Validate?

Economic Reasons

- Customer Satisfaction: Non-conforming product can lead to lost customers.
- Product Liability: Product Specifications must be maintained.
- Reduced Production Costs: PV leads to reduced inspections, testing, scrap, and rework. Shifts costs from production to prevention.

Why Validate?

- 1976 GMP, converted to law in 1979, was substantive (i.e., violation was a criminal act). Message was validate.
- 1987 Guideline on General Practices of Process Validation. "This guideline…states principles and practices of general applicability that are not legal requirements but are acceptable to the FDA." Message was how to validate.
- 1999 (Edition 1)/ 2004 (Edition 2) Global Harmonization Task Force- Quality Management Systems- Process Validation Guidance. Message was to define process validation principles and methods such that the resulting product or service can be practically guaranteed.

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21 CFR 820.75 Process Validation

cGMP Requirements 21 CFR 820.75

- Applies to processes where the results 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
- Activities, Results & Equipment validated shall be documented
- Date and signature of individual approving the validation shall be documented

cGMP Requirements 21 CFR 820.75
continued

- Each manufacturer shall ensure that:
  - Written procedures are in place for monitoring and control of process parameters for validated processes
  - Process validation is performed by qualified individuals
  - Monitoring and control methods and data, the date performed and the people associated are 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.

Automated Processes 820.70

Are computers or automated data processing systems used as part of production or the quality system?

Automated Processes 820.70

If yes… then the manufacturer shall validate the computer software for its intended use according to an established protocol.

All software changes shall be validated.

What May Happen if You Don't Validate or Do It Poorly?

REGULATORY IMPACT

- 483 Observation
- Warning Letter
- Worse

Warning Letter (June 12, 2015)

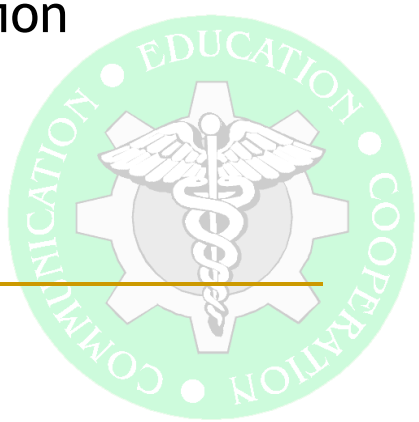
Your firm failed to adequately validate the equipment:

- Installation Qualification (IQ) not approved
- No Operational Qualification (OQ) conducted
- Performance Qualification (PQ) consisted of only (b)(4) lot of production which is inadequate to demonstrate the reproducibility of the production line and only (b)(4) samples from the production lot. Further the PQ documentation for the line verification was incomplete.

Warning Letter (August 12, 2015)

Failure to validate a process whose results cannot be fully verified by subsequent inspection and test as required by 21 CFR 820 .75(a). For example:

- Your firm did not validate the complete range of process parameters used for (b)(4) of the duodenoscope bending section assembly…
- Your firm did not document the statistical rationale for the sample size used in the validation
- …you did not segregate or determine the worst case materials during EO/ECH residual testing as part of the sterilization validation… to determine proper aeration time.



483 Common Themes

- Missing SOP for Process Validation
- Missing Statistical Rationale
- Lack of Consecutive Runs
- Not Following Protocol
- Acceptance Criteria Not Met

They didn't do what they said they would….

Standards and Guidance

Standards

Provide guidance to manufacturers to promote industry consistency.

- **FDA**: US Food and Drug Administration
- **ASTM**: American Society for Testing and Materials
- **ISO**: International Organization for Standards
- **AAMI**: Association for Advancement of Medical Instrumentation

NOTE: If standards are <u>not</u> followed during process validation, the rationale must be provided and approved prior to validation.

Worldwide Validation Guidance

- **Title:** Quality Management Systems – Process Validation Guidance
- **Authoring Group:** SG3
- **Endorsed by:** The Global Harmonization Task Force (*International Medical Device Regulators Forum 2011)*
- **Date:** Edition 2 - January 2004

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Definitions and Terminology

Validation

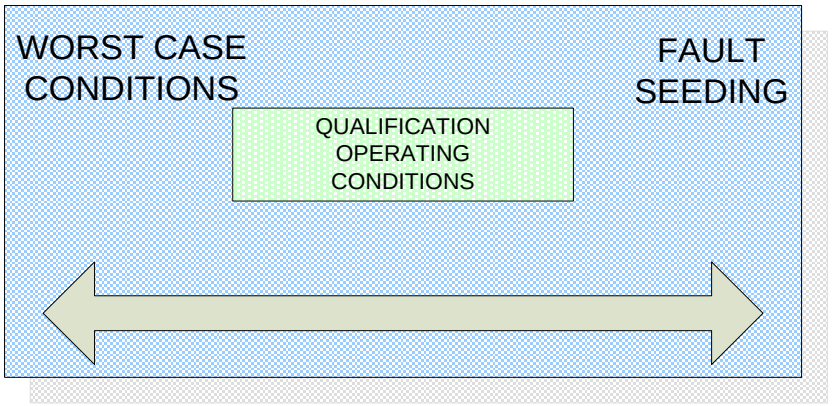
- FDA-Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

- GHTF- Establishing by objective evidence that a process consistently produces a result or product meeting its predetermined requirements.

Worst Case Conditions

- FDA: Worst Case- A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions.

Qualification



- **Definition:** To establish confidence that a process, process equipment, and ancillary equipment are capable of consistently operating within established limits and tolerances.

- More narrowly focused than validation

FDA vs GHTF Terminology

Comparison of Process Validation Terminology

Concept	Relevant Questions	FDA's 1987 Guidance	GHTF 2004 Guidance
Equipment Capability	Is the equipment installed correctly?	Equipment Installation Qualification	Installation Qualification (IQ)
	Does the equipment perform as expected?		
Process Characterization	Are the process factors that influence resulting product quality understood?	Preliminary Considerations	Operational Qualification (OQ)
	Has "worst case" testing been performed to establish process control limits?		
Process Adequacy	Is there consistent process output under normal operating conditions?	Process Performance Qualification / Product Performance Qualification	Performance Qualification (PQ)
	When operating under controlled conditions, does the process deliver product that meets its specifications?		

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Processes Requiring Validation

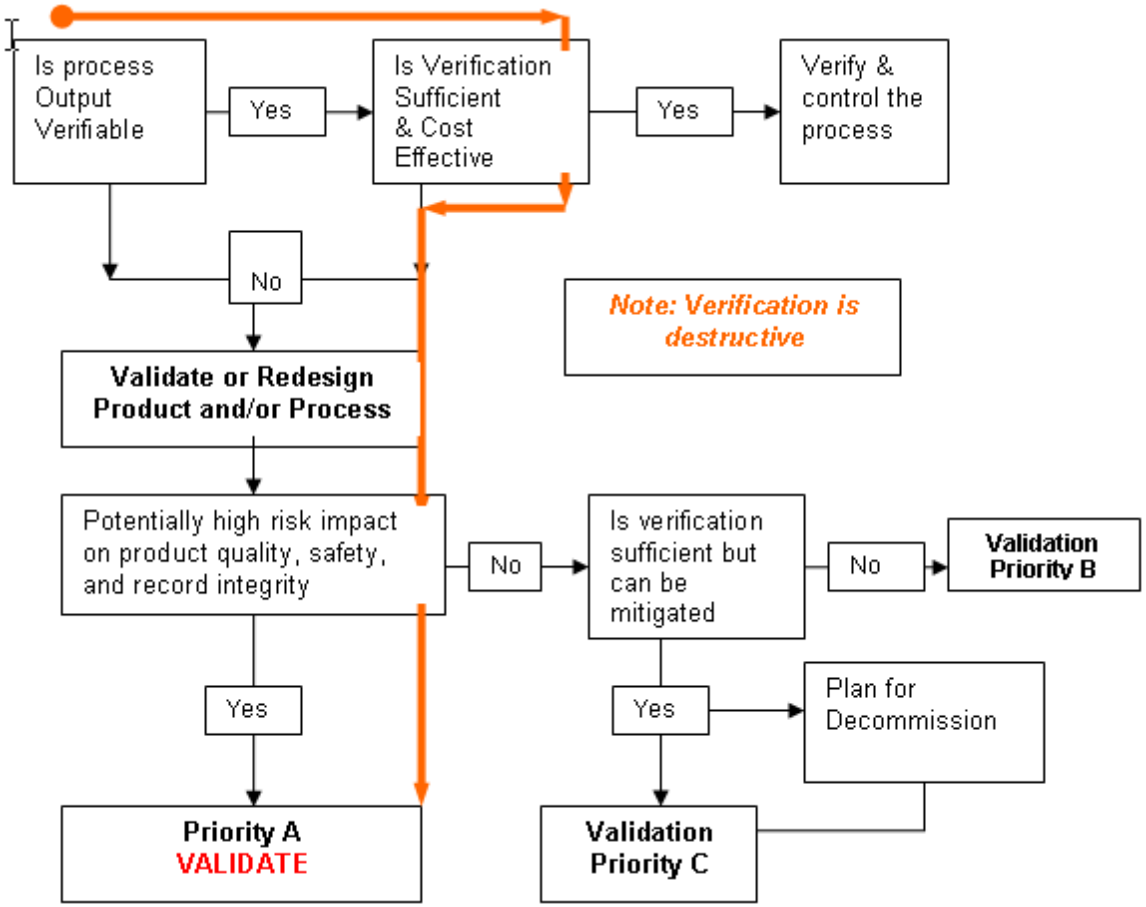
Which Processes Require Validation?

- Processes whose outputs can NOT be *fully* verified by subsequent inspection or test.
- Processes whose routine end product testing may have insufficient sensitivity to verify the safety and efficacy of finished devices.
- Processes for which validation might be more cost-effective than verification.
- Processes for which validation is performed due to the potential impact on the product. Consider incorporating risk analysis into decision-making.
- Supplier processes for components and/or devices

Processes Requiring Validation

Process		
Test methods	Cleanrooms	Air systems
Water systems	Cleaning, sanitation, degreasing	Calibration
Aseptic processing	Unique filtration processes	Filling operations
Plastic bonding	Plastic injection molding/extrusion	Wave/hand soldering
Utilities	Dipping plastic and rubber	Mixing
Lyophilization	Sterile packaging operations	Sterilization
Formulation methods	Software-controlled processes	Shelf Life

Validation Decision Tree



Which Processes Do Not Require Validation?

- Processes that can be fully verified by subsequent inspection and/or testing.
- Even though validation may not be required, the company may still decide to validate the process.

Examples:

- Output of a machining process which contains a precision-bored hole. The hole can be fully verified by inspection.
- Production-line test procedure for quality characteristic can be conducted 100% in an economical fashion.

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Validation Planning

Validation Timing

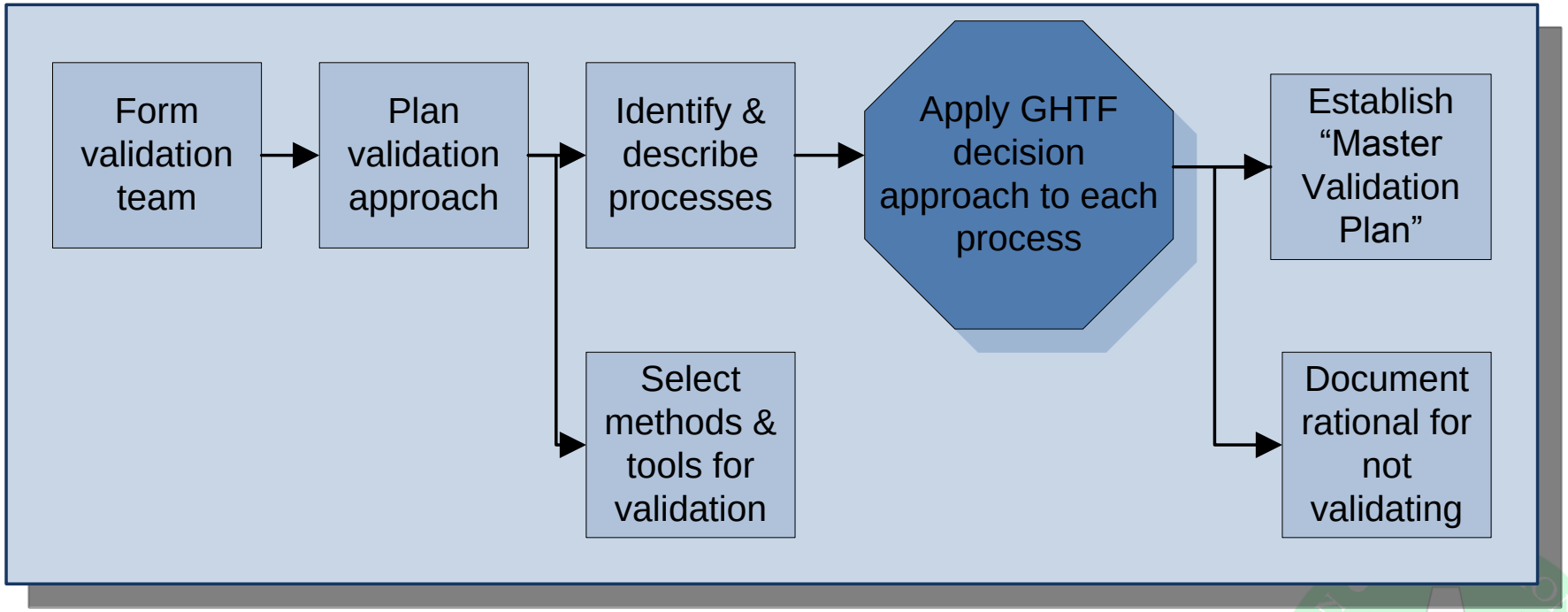
PROSPECTIVE VALIDATION (The Preferred Approach)

- FDA: Prospective Validation-Validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics.

- Prospective validation involves proving that the process does what it is supposed to do by performing an experimental plan, otherwise known as a validation protocol, before the process is actually implemented.

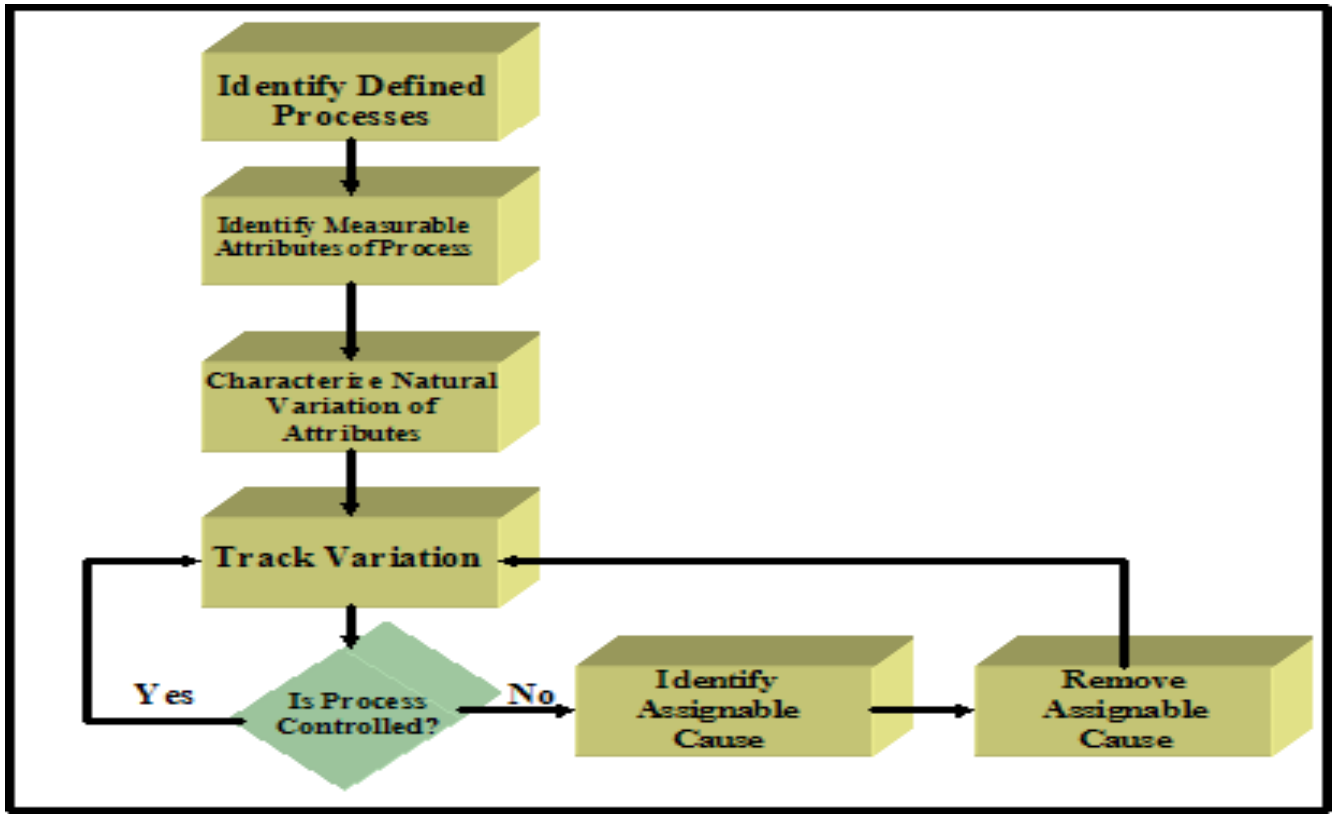
Validation Planning

Establishing the Process Validation Program



AAMI Quality System Compendium, 2004

Validation Planning



Process Validation Master Plan

- Top level document that defines the approach to validation.
- Roadmap for accomplishing related process validations
- Answers how much validation is enough? Why?

Validation Master Plan- Example

Operation/ Process	Description	SOP/WI	Validation Required?	Validation Category & Reference	Comments
N/A	Order Issuance	WI-8.2-1	YES	Category B PR-2016-XXX	ERP System is validated to assure that when an order is received a production schedule is created to specific part numbers, lot numbers and quantities to be produced. A control plan and check sheets for each lot number are generated. It is reviewed, signed and dated prior to issuance to production .
10	Machine	WI-7.5-9	Yes	A	Verifiable process controlled through training and procedures. Acceptability is based on dimensional inspection. IQ, OQ and PQ

VMP Example Cont'd

Operation/ Process	Description	SOP/WI	Validation Required?	Validation Category & Reference	Comments
40	Wash	WI-7.5-XX WI-7.5-XX WI-7.5-XX	Yes	A PR-XXXX	IQ, OQ and PQ to demonstrate cleanliness per ASTM F 2459-05 and ISO 10993-5.
45	DI Water System	Service Agreement with Supplier; WI-7.5-XX	Yes	A PR-XXXX	IQ, OQ and PQ to demonstrate process consistently meets cleaning process and AAMI TIR34:2007 requirements. Ongoing monitoring consists of water sample collection performed by trained personnel and analyzed by an outside laboratory at defined intervals.
70	Final Inspection	SOP-8.2-X	No	N/A	Verifiable manual process controlled through training and procedures.

Validation Process

Generally consists of (3) steps:

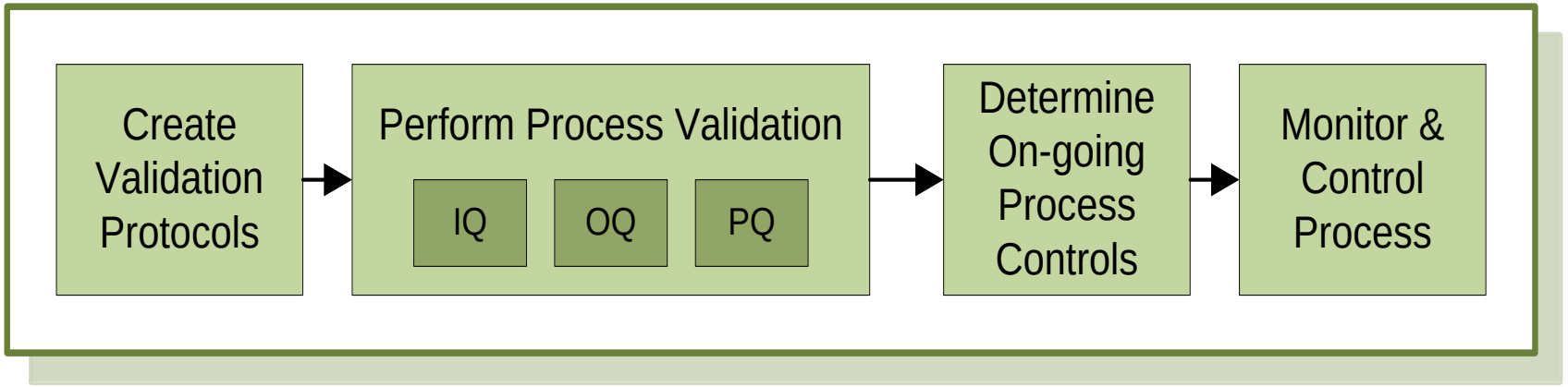
- Installation Qualification
- Operational Qualification
- Performance Qualification

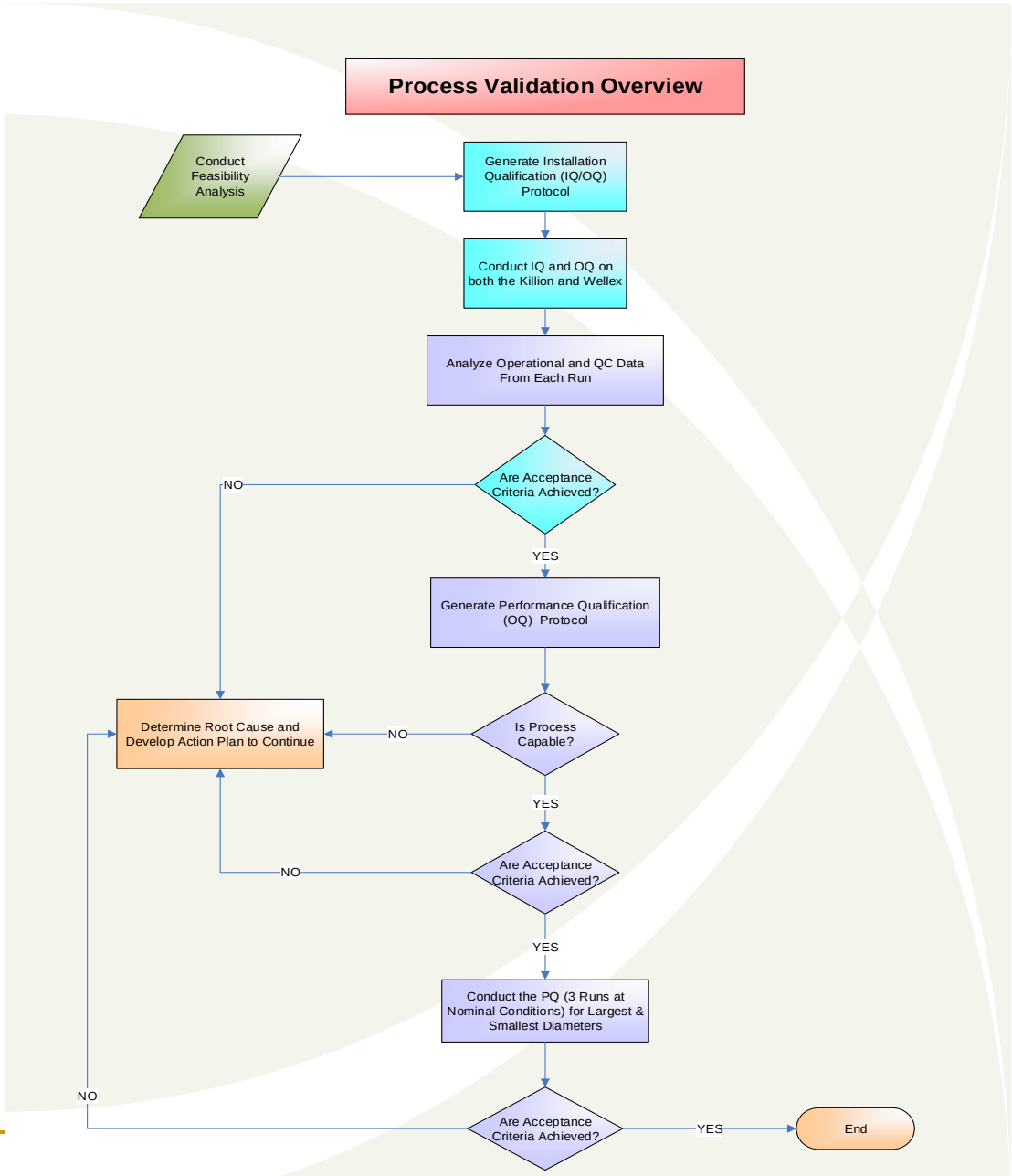
- Elements of each qualification will vary-depending on the process. Use standard templates for efficiency and to minimize the possibility of omissions.

Note: Usually process validation coexists with, and supplements in-process and end product testing.

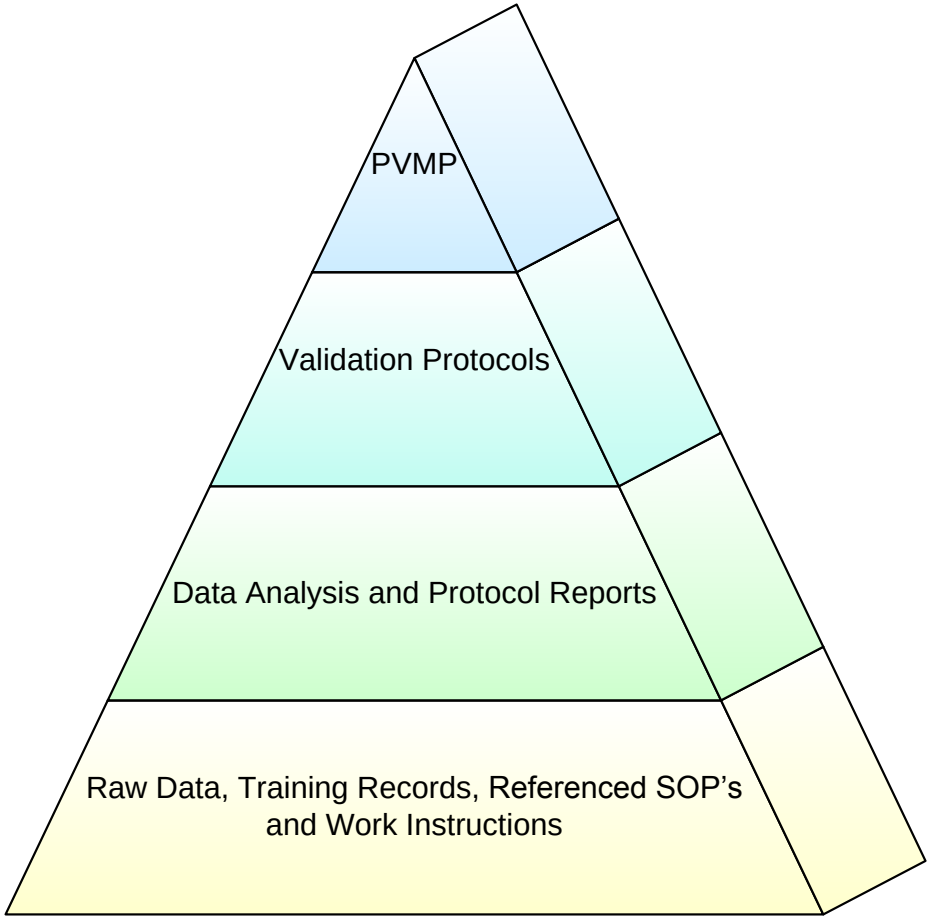
Process Validation Flowchart

Individual Process Validation Steps




Process Validation Overview
Conduct Feasibility Analysis
Generate Installation Qualification (IQ/OQ) Protocol
Conduct IQ and OQ on both the Killion and Wellex
Analyze Operational and QC Data From Each Run
Are Acceptance Criteria Achieved?
NO
YES
Generate Performance Qualification (OQ) Protocol
Determine Root Cause and Develop Action Plan to Continue
NO
Is Process Capable?
YES
NO
Are Acceptance Criteria Achieved?
YES
Conduct the PQ (3 Runs at Nominal Conditions) for Largest & Smallest Diameters
NO
Are Acceptance Criteria Achieved?
YES
End

Validation Documentation



Validation Documentation Structure

What Should Be in the Protocol?

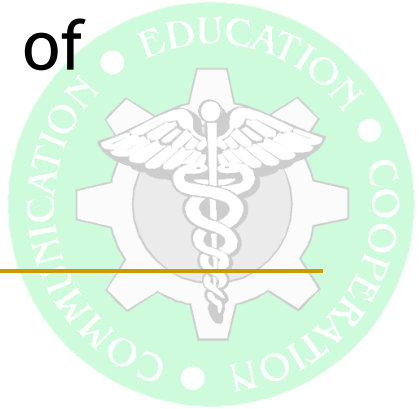
- Purpose
- Scope
- Sample Size with statistical rationale for selection
- Reference Documents
- Method
- Acceptance Criteria

What This Means:

- Process and product specification should be determined before starting validation.
- Validations must be in writing.
- Confidence level should be based on criticality.
- For product performance qualification, at least three (3) sequential groups of product are evaluated.

Agree on Analysis Techniques Up Front

- How good is your evaluation?
- What test for distribution assumptions is appropriate?
- Will you have access to the required number of samples?
- What assumptions are being made about the process or the data?
- Agree on process criticality and determine appropriate α value.
- Will samples/material be “representative” of production?



Tools Used to Identify Key Process Variables Based on Risk

- Fishbone Diagram
- Process Flow Chart
- Hazard Analysis
- Fault Tree Analysis
- Failure Modes, Effects and Critical Analysis
- Screening Designs of Fractional Factorial Experiments

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Validation Sequence IQ/OQ/PQ

Installation Qualification (IQ) Definitions

- FDA

  Establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances.

- GHTF

  Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendation of the supplier of the equipment are suitably considered

Items Generally Included in an IQ

- Utility requirements
- Safety features
- Environmental conditions required
- Equipment identity, serial numbers, location, model numbers
- Calibration
- Preventative Maintenance

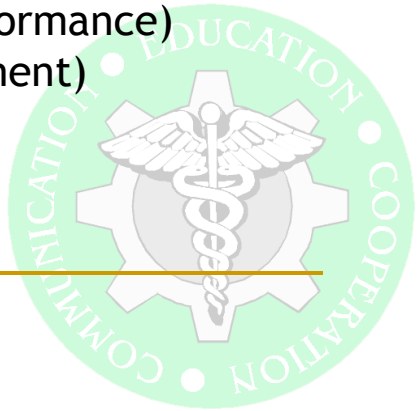
IQ- How to Perform

- Verify equipment configuration and schematics exists
- Verify any custom fixtures meet print(s)
- Verify ancillary systems (air , water) are connected and operate as specified
- Measure the equipment/systems to determine if they meet design specification tolerances.
- Establish preventative maintenance procedures, and repair lists.
- Develop and implement calibration methods and procedures, if required.
- Document all results

Operational Qualification (OQ)

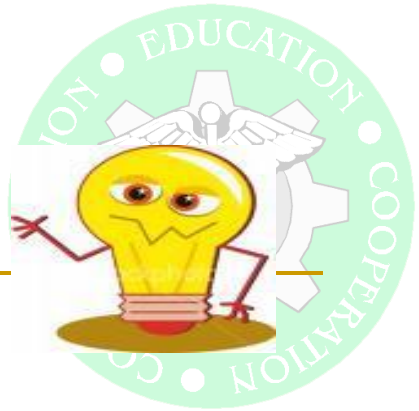
- Demonstrate it works over anticipated range and worst case conditions
- In this phase, process parameters should be challenged to assure they will result in a product that meets requirements under all anticipated conditions of manufacturing. Also, action level(s) should be developed to monitor routine production.

- OQ Considerations include:
  - Should simulate actual production conditions and worst cases
  - Process control limits (time, temperature, pressure, setup conditions, etc.)
  - Software parameters
  - Raw material specs
  - Process operating procedures
  - Material handling requirements
  - Process change control
  - Training
  - Short term stability and capability of process (think process performance)
  - Potential failure modes, action levels (think FMEA, risk management)



Items Generally Included in an OQ

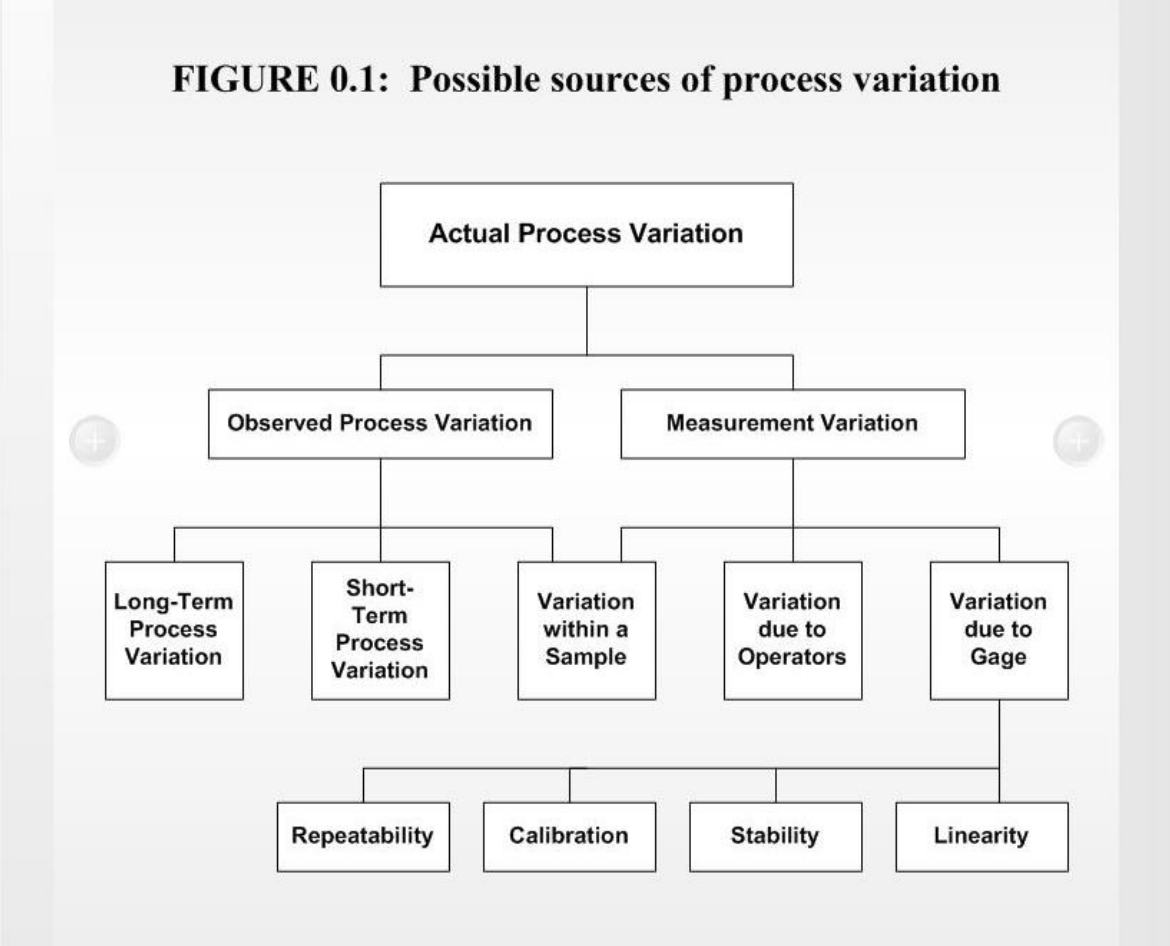
- Process capability study
- Design of Experiments
- Gage R&R
- Test method validation
- Verification and testing of circuit breakers and fuses for proper operation.
- Exercise of all moving parts of the equipment to assure that they perform properly.
- Exercise of any sensors or control elements to make certain they perform properly.
- Confirmation of the safety shielding or other safety devices to assure that they perform properly and that they prevent the danger they are designed to eliminate.
- Verification and testing of electrical connections for possibility of power surge or loss of power.



Measurement/Gage Qualification

- REPEATABILITY
  - Variation in measurements obtained with one gage when used several times by one operator while measuring a characteristic on one part.
- REPRODUCIBILITY
  - Variation in the average of the measurements made by different operators using the same gage when measuring a characteristic on one part.
- EXAMPLES
  - GM
  - Chrysler
  - Ford
  - Barrentine

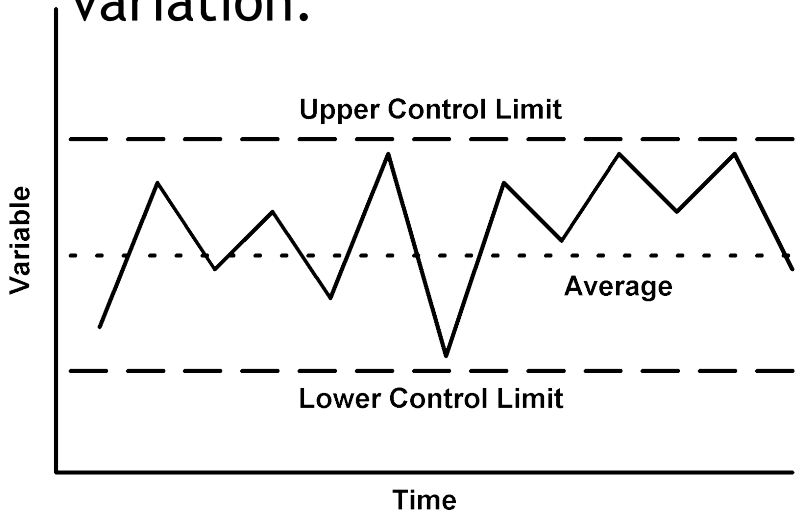
Sources of Variation

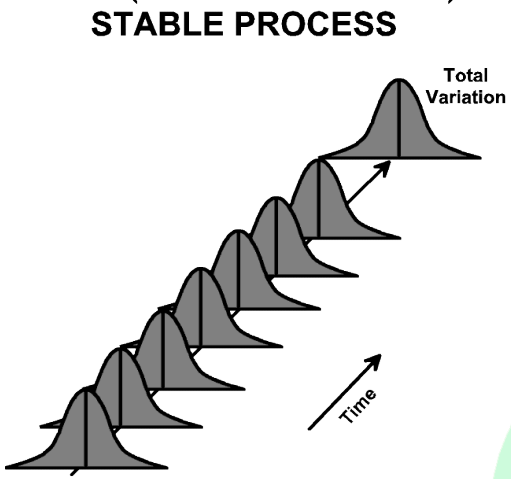


Statistical Process Control (SPC)Terminology

USL/LSL – Upper/Lower Specification Limit.

Process Stability – Achieved when the measurable outputs of a process have constant means and constant variance over time. The process should not have any special (non-random) causes of variation.

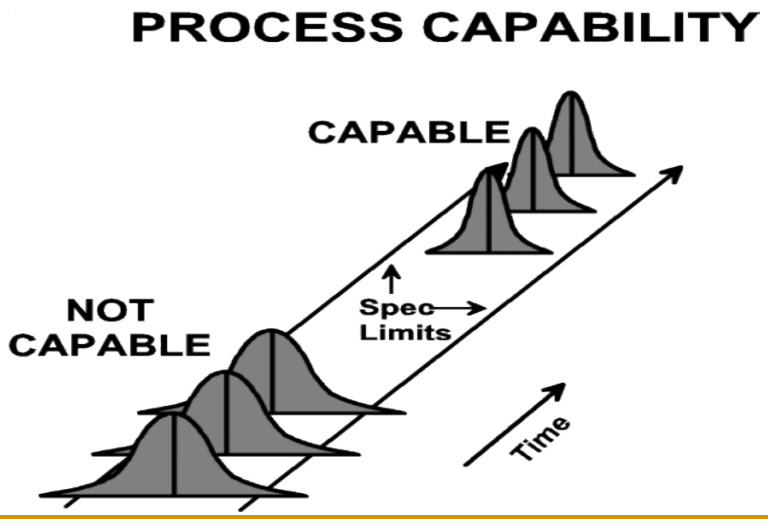




If Stable Then Assess Capability

Process Capability – The ability to produce products/services that meet specifications defined by the customer's needs, or a measure of the inherent uniformity of the process and the ability to direct the process to a defined target.

An unstable process is unpredictable. Process stability must be ensured before analyzing process capability.



Process Capability Performed During OQ

- PROCESS CAPABILITY- The statistical measure of the common cause variation of a process under controlled conditions (short term).

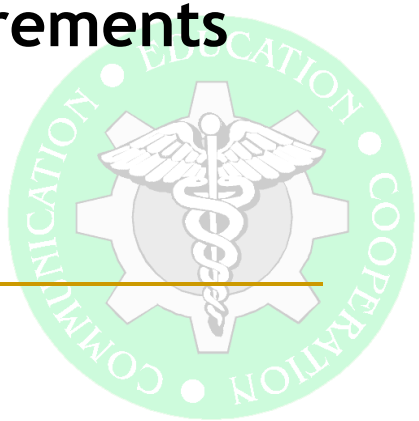
- PROCESS CAPABILITY STUDY – A process capability study is a desirable element for validations involving measurable process outputs. It is a statistical method to determine the capability of a process is in a state of control. These studies can provide the basis for establishing evidence that a process is validated.

Process Capability Studies

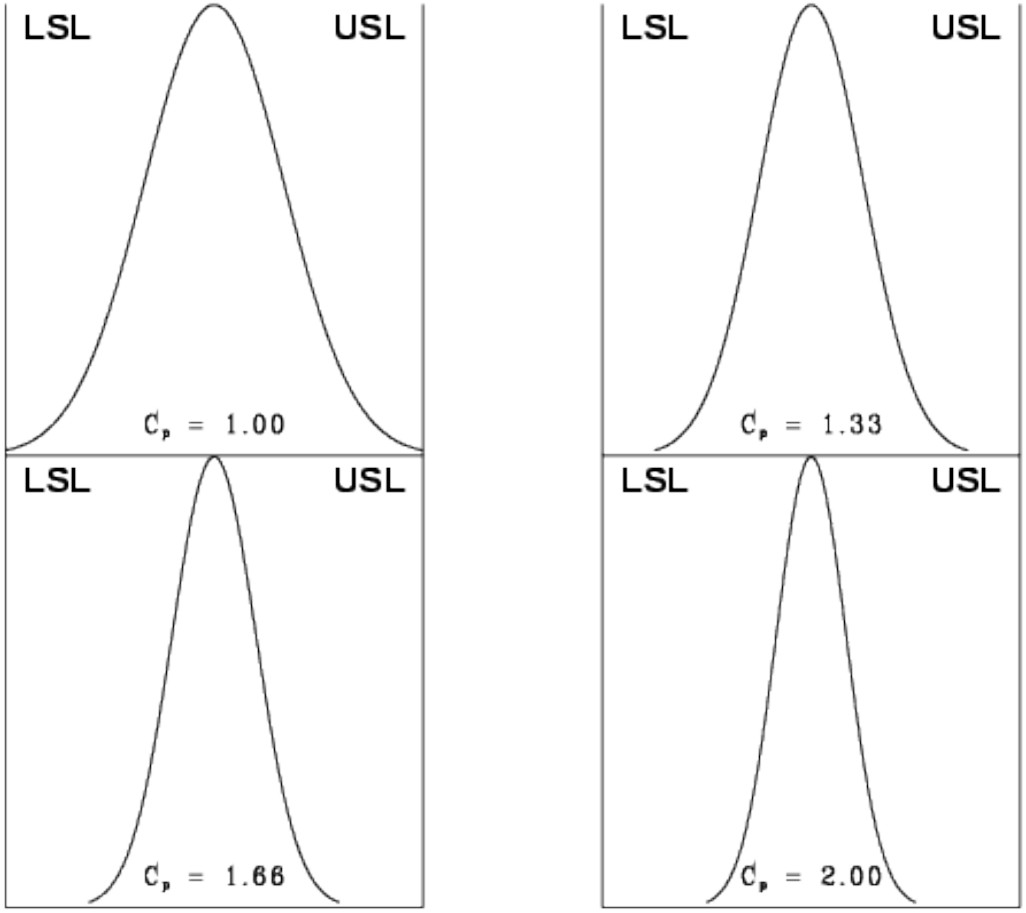
- **Assumptions**
  - Statistical Stability
  - Normal Distribution
  - Specifications Based on Customer Requirements
  - Accept index/ration as “true” number

- **Many types of Indices (always look at >1)**
  - Cp and Pp-Process Variation Only
  - CPU, CPL, Cpk, Ppk-Process Variation & Centering
  - CR and PR-Process Variation Ratio Only

- **Goal: To align process with customer requirements**
  - Continually reduce variation and minimize loss



Graphical Interpretation of Process Capability



Interpretation of Process Capability

Higher process capability index results in a more capable process.

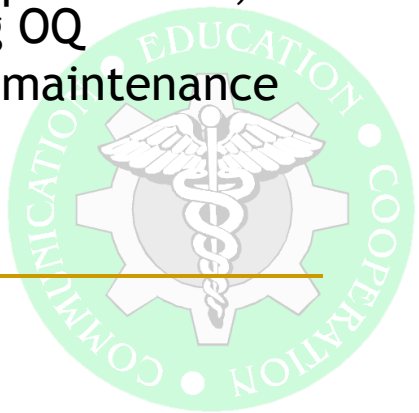
The following table lists expected defects for various process capability indices:

Process Capability Index (C_{pk})	Estimated Defects per Million
0.67	45,500
1.00	2,700
1.33	63
1.67	1

Performance Qualification (PQ)

- In this phase, the key objective is to demonstrate the qualified process will consistently produce acceptable product under normal operating conditions.

- PQ Considerations include:
  - Actual product and process parameters, procedures established in OQ
  - Acceptability of product
  - Raw materials variation
  - Operator and shift variation
  - Assurance of process capability established in OQ
  - Process repeatability and long-term process stability
  - Challenges to process simulating conditions during actual production, including range of operating conditions established during OQ
  - Development of attributes for continuous monitoring and maintenance of process



FINAL REPORT

- At the conclusion of all validation activities, prepare a final report.
- Summarize and reference all protocols and results.
- Derive conclusions regarding the validation status of the process.
- Validation team should review and approve, as well as appropriate management. Update the VMP.

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Process Monitoring, Control and Revalidation

Validation Results Are not Meaningful If…

- Measurement Systems are not appropriate for the Job
  - Repeatable and reproducible
- Process is not capable and stable
- Maintenance is not established and deployed
- Monitoring is not established to verify process performs as validated
- Changes are not revalidated as planned

Ongoing Controls

- Attributes for monitoring process should be developed during OQ/PQ.
- Use SPC for routine monitoring of process output(s). Use tools like:
  - Control charts, histograms, check sheets, Pareto charts, scatter diagrams, etc.
  - Sampling plans
  - Control plans
- Also look at other Quality Management System trends, consider:
  - Nonconforming material trends
  - Customer feedback/complaint trends
  - Material Testing/Verification
- When negative trends occur, investigate the cause and consider corrective/preventive action to correct. If necessary, also consider revalidation.

Revalidation

- Per the FDA, A system which requires revalidation with a change to:
  - Packaging
  - Formulation
  - Equipment
  - Sterilization
  - Process
  - Water System

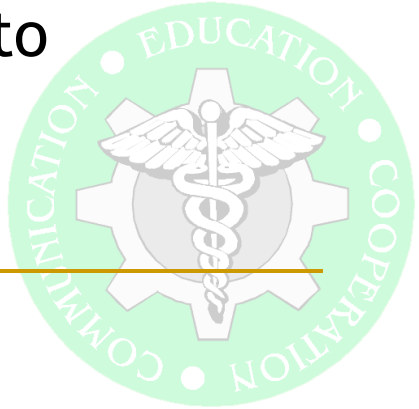
  which could impact product effectiveness or product characteristics AND with a change to product characteristics

Revalidation continued

- Revalidate when…

  Any significant change in product specifications, process parameters, equipment type, function or location, control system, raw materials, manufacturing materials, major repairs to process equipment, etc.

- Scheduled, planned or otherwise anticipated recurring validations to demonstrate continuing compliance of validated process or operation to meet its intended specifications (e.g., sterilization).



Take Away Message

Validation is the tool to meet high product quality consistently…it's your reputation