Welcome to your

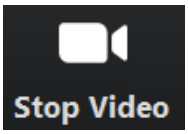
Process Validation

Virtual Training Course

Learn how to implement the Requirements for Process Validation

for the Medical Device and Pharmaceutical Manufacturer

Etiquette



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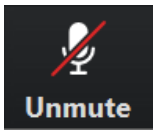
2. Keep microphone off when not speaking please.



3. Aim to contribute a least once during the session.
   - Wait for others to contribute if you have done so already.

Introduction: John Lafferty

- Quality Management in Life Sciences
- Independent Consultant based in Letterkenny
- Quality Systems, Process Validation, Software Validation, Risk Management and Auditing
- Tutor in; Quality Systems, Risk Management, Laboratory Systems Validation, Software Validation, Process Validation and Technical Writing.

Introductions

- Name
- Company
- Job Function
- What you want from the course.

Housekeeping

- Session times:
  - 9:00-10:30 Session 1
  - 11.00-12:30 Session 2
  - 13.30-14:50 Session 3
  - 15:10-16:30 Session 4

All times are in UTC (or UTC + 1 in summertime)

Course Modules

1. Module 1 Regulations and Guidance
2. Module 2 Validation Master Plan
3. Module 3 Validation versus Verification
4. Module 4 Requirements Specification
5. Module 5 Application of Risk Management
6. Module 6 Equipment Specification

Course Modules

7. Module 7 Installation Qualification
8. Module 8 Operational Qualification
9. Module 9 Process Design
10. Module 10 Performance Qualification
11. Module 11 Maintaining the Validated State
12. Module 12 Test Method Validation
13. Module 13 Computerised Equipment Validation

Validation - Regulatory Requirements and Guidelines

In this Session you will Learn

1. Regulations governing Validation
2. Principles of Validation
3. How to complete Validation Planning
4. When to Validate, When to Verify.

Definition of Validation

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

(Guideline on General Principles of Process Validation)

Document the What, How, Who, When, How Much and Why.

A record of;

- What was tested.
- Why these tests were chosen (rationale).
- The conditions under which the samples were manufactured.
- From what materials the samples were manufactured.
- What the state of the equipment was when the samples were manufactured.
- Why those manufacturing conditions were chosen (rationale).
- How many samples were tested.
- What the rationale for that sample size was (rationale).
- What tests were carried out.
- What test methods were used.
- Who performed the testing.
- When the testing was performed.
- What the results were.
- What the acceptance criteria were.
- Where the acceptance criteria came from (rationale).
- Whether or not the results met the acceptance criteria.

Process Validation

- The collection and evaluation of **data**, from the **design stage** through to **commercial production**, which establishes **scientific evidence** that a **process is capable** of consistently delivering quality products.

Process Validation General Principles & Practices FDA Guidance January 2011

Scope of Validation

- Facilities
- Utilities
- Equipment/ Computerised Systems
- Cleaning
- Test Methods
- Processes
- Packaging
- Product

Rule 1:
If it moves
it must be validated.

Rule 2:
If it doesn't move
it must be validated.

Latest Thinking on Validation

- FDA Process Validation Guidance (Guidance for Industry: Process Validation- General Principles and Practices, Jan. 2011) outlines process validation activities in three stages –
- Stage 1: Process Design,
- Stage 2: Process Qualification
- Stage 3: Continued Process Verification.
- 21 CFR 211.180(e) evaluating and determining the need for change in manufacturing or control procedures on an ongoing basis.

Latest Thinking on Validation

- ICH Q8 (Rev 2) recommends an enhanced Quality by Design (QbD) approach that is comprised of a process validation lifecycle with a process verification stage.
- The January 2014 EMA Guidance on Process Validation requires continued process verification during commercial manufacture. This ensures a continued state of process control throughout commercial production.

Continued or Continuous

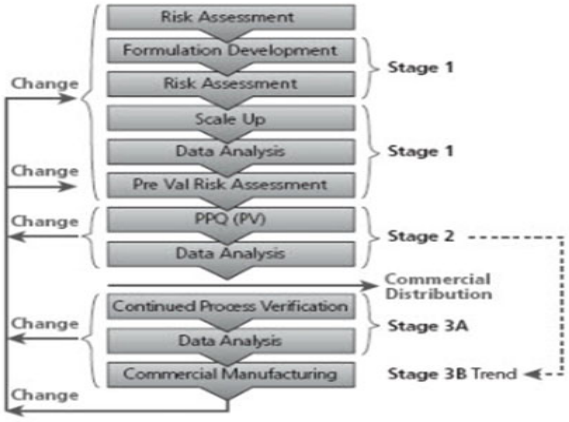
Example of Continuous Verification; Aseptic Filling Class 1 enclosure continuous particle count monitoring.

Example of Continued Verification; Class 7 cleanroom for drug dispenser moulding. Control charts of weekly particle counts.

Based on risk.

"Britain and the USA, two nations separated only by a common language" Winston Churchill.

The Lifecycle Approach



Not the Evil Twin

- Is necessary
- Is resource hungry
- High Clerical Input
- But has benefits

" I tell my mother I am a doorman in a nightclub, but I really work in Validation"

Benefits of Validation

- Better process understanding.
- Less NCR's, Complaints, CAPA's
- Easier Investigations
- Less rework
- Easier Handover
- Surviving Audits

The Validation Master Plan

Hierarchy of Validation Documents

Document	Purpose	Rationale Contained in Document	Comment
Corporate Validation Procedure	Sets out Company Policy on Fulfilling the Regulations	Rationale: How the Regulations are met.	Very High Level
Site Validation Procedure	Sets out Procedures that are Appliable to the Site.	Rationale: How the Policy is met.	High Level
Master Validation Plan	Applies those Procedures to Various Systems	Rationale: How the Procedures are met.	Applicable to System Types
Validation Plan	States how the Regulations and Procedures will be Applied to a Specific Project.	Rationale: How the Procedures are met.	Key document as it allows you to tailor the Validation to a Specific System & Circumstance
Validation Protocol	States the Activities that will be Performed to meet those Procedures	Rationale: How the Validation Plan is met.	Gives specific activities.
Validation Test Scripts	Sates the detailed Tests to be Performed to fulfil the Protocol	Rationale: How the Protocol is met.	Give specific tests and acceptance criteria.

Validation Master Plan

- VMP – The map to good quality validation!
- Project orientated
  or
- A global document embracing the firms overall validation philosophy.

FDA Quotation

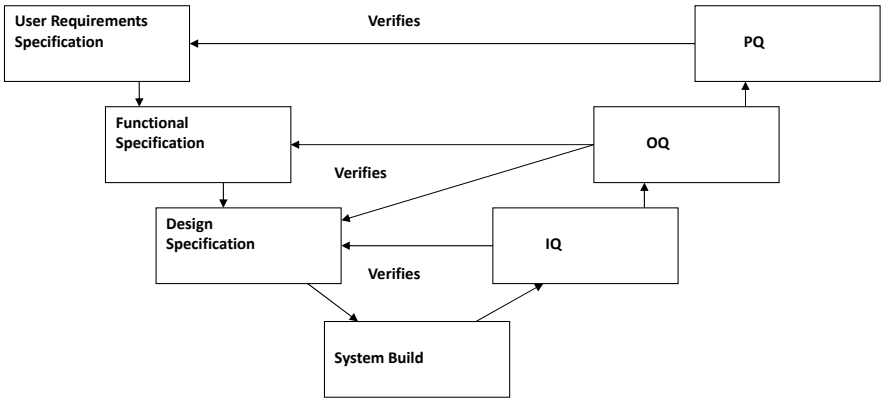
- Planning documentation is a reliable predictor of GMP problems. During the initial phase an FDA audit, it is customary to request the firm's validation plan documents.
  Management reaction to such a request often predicts the quality of the firms documentation. If the firm does not have a formal written validation plan, then it is impossible for the firm to be in a state of validation.
  (Tetzlaff 1992)

Purpose of VMP

- Good validation allows efficient streamlined procedures, programmes and protocols
- Planning facilities consistent decision making that is fundamental for controlling healthcare product development, manufacturing and testing.
- The VMP presents an overview of the entire validation operation, its organisational structure, its content and planning, the core of the VMP is the inventory of items to be validated and the planning schedule.
- The approach to be used.

Sets out the rules of the game!

V Model



VMP Scope

- All validation activities relating to critical technical operations, relevant to process and product within a firm should be included in the VMP. This includes critical manufacturing and control equipment qualification.
- The VMP includes all prospective, concurrent & retrospective validations.

What equipment requires a qualification study?

- Compile an inventory of all equipment in manufacturing, service areas, and testing areas.
- Identify the process steps or test methods that equipment supports
- Categorise the equipment into three groups as follows:

Group III Equipment & Equipment Systems

- Equipment used for a validated process
- Examples include sterilisers, welding equipment, extrusion equipment, ovens for dry sterilisation, HVAC systems, purified water treatment systems

Group II Equipment & Equipment Systems

- Performance of this equipment can be assured through a qualification study alone.
- Examples include compressed air systems where the air does not come into direct product contact, non-sterile barrier packaging equipment, testing jigs.

Group I Equipment & Equipment Systems

- In this group equipment reliability can be assured through routine calibration & PM programmes
- Examples include balances, callipers, pH, meters, viscometers
- Qualification studies are not required to demonstrate equipment operation & reliability.
- Test Method Validation may be required.

Equipment validation versus system validation

- If the equipment is used as a stand alone unit validate as a separate entity.
- If the equipment is used with other equipment, validate the system e.g. packaging line (filler, capper, labeller etc.,) purified water system.

Format & Content continued

- Introduction – include company validation policy, scope, location and schedule.
- Organisational structure.
- List of products/processes/systems
- Extent of validation required (i.e. URS, FAT, DQ, IQ, OQ &/or PQ).
- Planning and scheduling
- Validation approach and exclusions.

Introduction – include company validation policy, general description of the scope of activities covered by VMP, location and schedule including priorities.
Organisational structure – state personnel responsible for VMP, projects and protocols, validation approval process, archiving system and validation training requirements.
List of products/processes/systems to be validated: all validation activities comprised in the VMP should be summarised and compiled in a matrix format. Such a matrix should provide an overview & contain:
All items covered by the VMP that are subject to validation describing the extent of validation required (i.e. URS, FAT, DQ, IQ, OQ &/or PQ). It should include validation of analytical methods used to determine validation status of other process or systems
Planning and scheduling – an estimate of staffing (including training needs), equipment and other specific requirements to complete the validation effort, a time plan of the project with detailed planning of the subprojects.
Change control – The VMP also contains a statement of the company's commitment to controlling critical changes to materials, facilities, equipment or processes including analytical methods.

Format & Content continued

VMP should state:

- The validation approach (Process Design, Qualification, Verification, PAT)
- Revalidation activities
- Actual status and future planning
- Key acceptance criteria
- Documentation format
- Required SOPs

PAT: Process Analytical Technology (An FDA initiative aimed at reducing process variation throughout the development and product phases).

Validation versus Verification

Definition – Verification

Verification means confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled

Definition – Validation

Validation means establishing documented evidence which provides a high degree of assurance that a SPECIFIC process will consistently produce a product meeting its predetermined specifications and quality attributes.

Decision not to validate

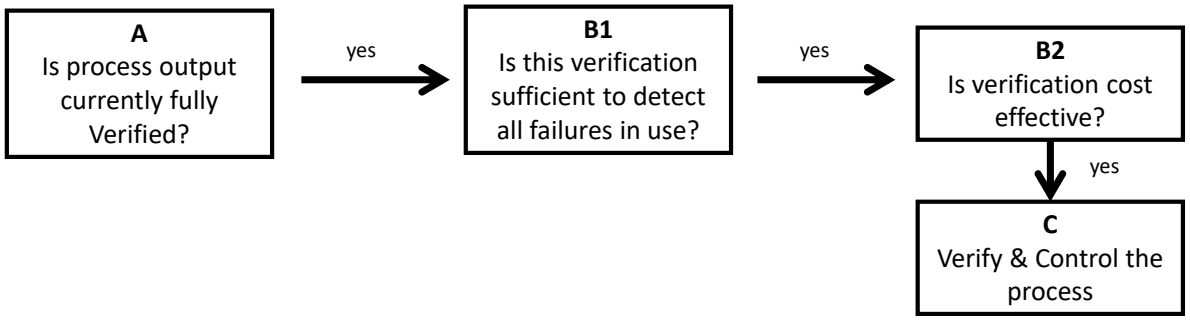
- Where a decision is made not to validate this needs to be fully justified on the basis of lack of risk to the patient.
- The following slides provide guidance for reaching decisions on whether to validate or not.

Process Validation Guidance for Medical Device Manufacturers – edition 2

Process Review

- Carry out Risk Assessment on process
- In-process process monitoring data
- Review process failures, deviations
- Look at risk factor for each process step
- Involve multifunctional experts (engineers, equipment manufacturers)
- Perform FMEA & document the study

Process Verification Decision



If not **validate**.

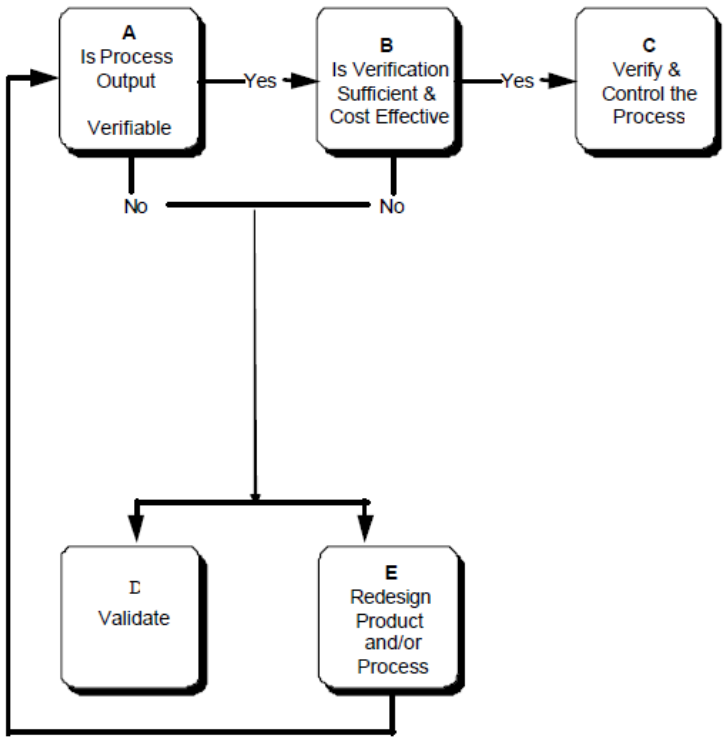


Figure 1: Process validation decision tree

What Processes should be Validated?

- Processes where routine end-product tests have insufficient sensitivity to verify the desired safety & efficacy of the finished product
- Processes where clinical or destructive testing would be required to show that the manufacturing process has produced the desired result or product
  - (e.g. absolute sterility cannot be practically demonstrated without destructive testing of every unit produced.)
- Processes where routine end-product tests do not reveal all variations in safety and efficacy that may occur in the finished product
  - (e.g. visual inspections usually are not capable of detecting defects in structural welds.)
- Processes where capability is unknown, or it is suspected that the process is barely capable of meeting the product specification.

Processes which are Candidates for Validation

- Sterilisation processes
- Clean room conditions
- Aseptic filling processes
- Lyophilisation processes
- Sterile packaging sealing processes
- Heat treating processes
- Plating processes
- Plastic injection molding processes

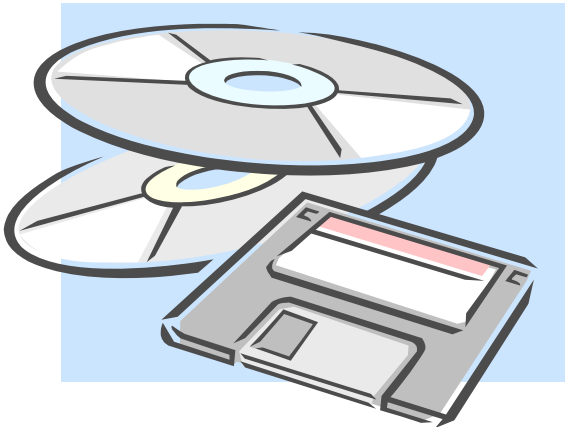
Processes which are Candidates for Verification

- Manual cutting processes
- Colour, turbidity, total pH for solutions
- Manufacture of printed circuit boards
- Manufacturing of wiring harnesses

Processes for which Decision Tree may be Useful

- Cleaning processes e.g. vacuuming to remove particulates
- Human assembly processes
- Filling processes
- Numerical control cutting process
  - e.g. laser cutting

Process Verifiable but…



Verifiable process but uses software for automation – such software must be validated for intended use!

In this Module we Learned

1. Validation Regulations are Quite Concise, the detail is in the Guidance
2. The Importance of Validation Plans
3. Validation Plans set out the Rationale
4. If not (fully) verifying you must validate.

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Requirements Specification

Module 4

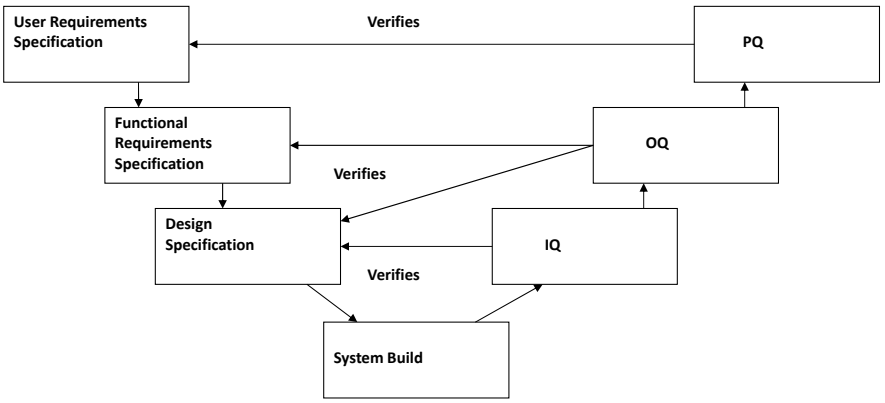
Learn how to Specify Requirements Properly

In this Session you will Learn

1. The V Model Approach to Validation
2. How to complete a URS
3. The Dos and Don’ts of a URS

User Requirements Specification

V Model



Definition – URS

- User Requirements Specification: Defines the requirements of a product, process or piece of equipment at the user level.
- What it will be used for and what is expected from it.

User Requirement Specification (URS)

- The most essential document in the System Development Life cycle / Validation process
- Also important for the remaining phases in the System Development Life Cycle
- Important role in writing the User Manual / Validation Test Plan
- Assists systems personnel in updating system

URS

- When writing the URS use statements that are objective, concise, clear, and testable.
- Use **End User Terminology**
- Each requirement should be numbered to allow traceability.
- Reference SOP's
- Builders / Developers
  - Training/qualifications
  - Training records

Things to consider in the URS:

- Background
- Key Objectives & Benefits
- Main Functions & Interfaces
- Applicable GxP Requirements
- Other Applicable Requirements
- Access and 21 CFR Part 11

URS v FRS v DS

URS	WHAT I WANT	Written by the user. What the user needs but not how that will be done.
FRS	HOW THAT WILL BE ACHIEVED	Written by the provider, this is the proposal of how the need will be fulfilled. Agreed by the user.
DS	WHAT you will RECEIVE	Written by the provider, this defines the detail of what will be delivered.

- Any requirement of the URS that specifies HOW something is to be achieved is known as a Constraint.
- Most URS contain some Constraints.
- Too many Constraints can lead to sub-optimisation.

- For off-the-shelf systems the FRS and DS are combined in one document, the FDS.

DS: Design Specification, this may be in two parts the Software Design Specification (SDS) and the Hardware Design Specification (HDS).
FRS: Functional Requirements Specification.
FDS: Functional Design Specification.
URS: User Requirements Specification.

Writing Requirements

Requirements wording format examples:

The system must ……. (perform a function)	
The system must allow a user to ……	
Only authorised users must be able to …….	
Operators must not be able to ……	
Each user must be assigned ……	

SMART Requirements

S	Specific	Must contain detail.
M	Mandatory or Non-mandatory	If requirements are not show stoppers, then need to state that they are non-mandatory.
A	AND is banned	Requirements must be unique. And or Or in a requirement may mean there are two requirements
R	Realistic	Can we really achieve this? State the requirement and make the statement 'So that means….'
T	Testable	Need to determine how the requirement will be verified or tested during validation.

Requirement Examples

	POOR	GOOD
Specific	1.1 The system must alert the user to low temperature situations.	1.1 The system must alert the user by means of an audible alarm if the temperature falls below 5.0 °C.
Mandatory/ Non-Mandatory	2.1 The system should be capable of being viewed on as many browsers as possible.	2.1 … must be ... browsers A,B and C (Mandatory) 2.2 .. should be ..browsers X,Y and Z (Non-mandatory)
AND is banned	3.1 Each user must have a unique username and password.	3.1 Each user must be assigned a unique username. 3.2 Each user must have the ability to create their own password.
Realistic	4.1 The system must measure the temperature in the cleanroom with the range of 15 to 35 °C 'So that means' – The system need not measure if the temperature drops to	4.1 The system must be capable of measuring temperatures with the cleanroom up to +80°C 4.2 The system must be capable of measuring temperatures with the cleanroom of as low a - 40°
Testable	5.1 The system must out-perform the system that it replaced.	5.1 The system must be capable processing 800K records a year.

5 Don’ts of the URS

- **Don’t use time-based metrics.** Today, performance metrics are almost always written as a time-dependent measurement. For example, “100 products per minute.” This approach is too vague and does not take into account product yield and quality.
- **Don’t use broad, sweeping statements.** For example, “must be 21 CFR Part 11 compliant.” Be specific about the elements within the compliance. What part of 21 CFR Part 11 needs to be compliant? Which records do you need to comply with?
- **Don’t cover functional requirement specifications (FRS) in the URS.** The overall intention of the URS is to describe what the equipment is supposed to do. How it performs is not a function of the URS.
- **Don’t place multiple requirements in a single section.** This makes it hard to test and validate each independent requirement. Each requirement should be numbered and stand on its own.
- **Don’t duplicate requirements in multiple sections.** You don’t want the same requirements repeated in five different sections of the document. This causes unnecessary work. Rather, collect the requirements in a general section and test them once.

In this Session we Learned

1. The V Model Approach Builds in Quality
2. The Importance of Wording Requirement
3. How to write Requirements Statements

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Risk Assessment

Module 5

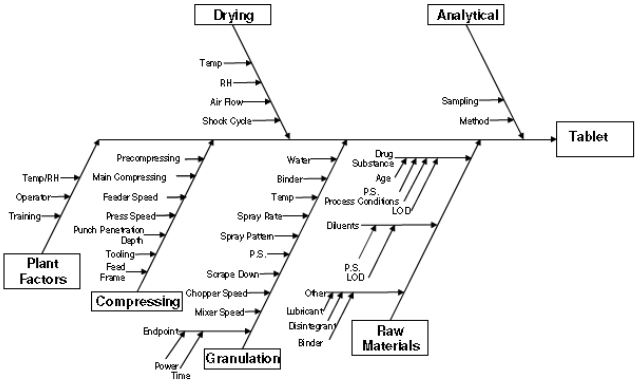
Learn how to Apply Risk Assessment to Equipment and Process Validation

In this Session you will Learn

1. How to apply Risk Assessment
2. How to compete a PHA
3. The Role of the FMEA

PHA: Preliminary Hazard Analysis

Sources of Variation



Concept of Risk

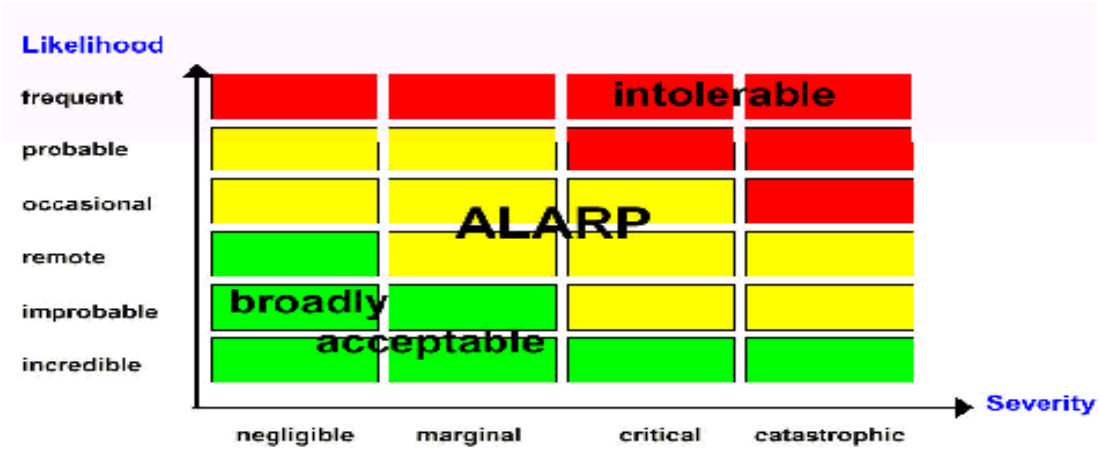
Two components:

- The probability of the risk occurring i.e. how often it will occur
- The consequences of that risk i.e. how severe it might be

Risk in the Healthcare Sector

Risk to whom?
Patient
Company
Risk Source?
Chance of a failure occurring
Effect of the failure on product quality
Chance of a failure going undetected

Risk Graph Worldwide (Non - EU/EFTA)



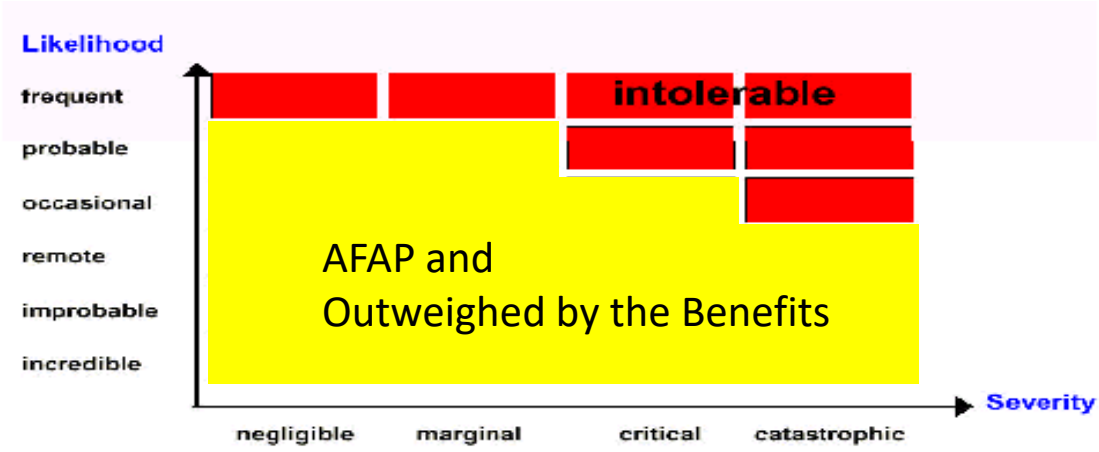
Risk Categories outside the EU/EFTA

Intolerable
As low as reasonably practicable (technical & economic considerations)
Broadly acceptable

Risk Categories in the EU/EFTA

- ~~Broadly acceptable~~
- ~~As low as reasonably practicable (technical & economic considerations)~~
- As Far As Possible (AFAP) (technical considerations only)
- Intolerable (Not Outweighed by the Benefits)

Risk Graph MDR
(Medical Devices Regulation)



MDR: Medical Devices Regulation

Risk Acceptability (EU/EFTA)

- Risk should only be accepted if it is outweighed by benefit!
- Most companies apply the EU/EFTA requirements to all products.

Risk Assessment

Carry out a detailed review of each product or process step:

- Equipment by equipment
- Line by line
- Control system by control system
- In all states (operating, testing, cleaning & maintaining)
- Identify causes of failure and the effect such a failure would have on a product and on the patient, user or bystander.

Some Risk Analysis Techniques:
Failure Mode and Effect Analysis (FMEA)
Fault Tree Analysis (FTA)
Hazard and Operability Study (HAZOP)

FMEA Calculate Risk - Risk Priority Number

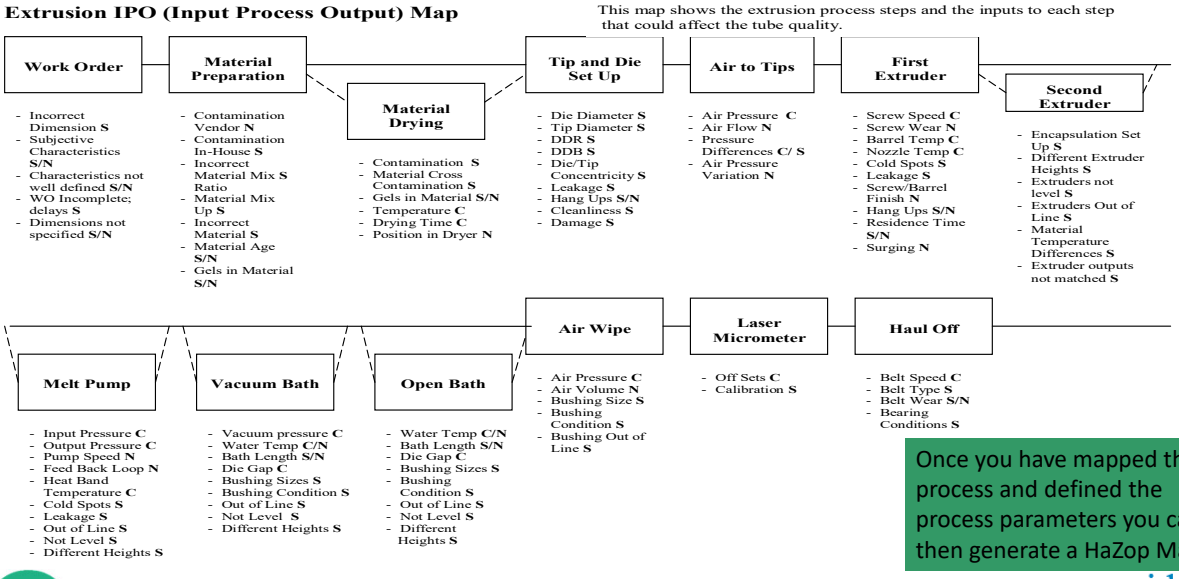
For each potential risk

- Allocate a severity factor (S) 1-10
- Allocate an occurrence factor (O) 1-10
- Allocate a detection factor (D) 1-10

Calculate the Risk Priority Number

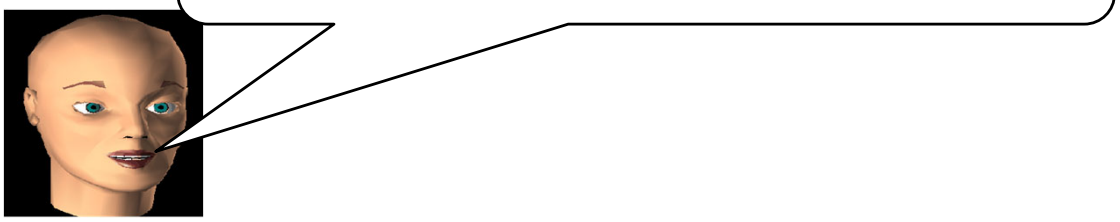
RPN = S x O x D

Map the Process



No process step is too small to be significant.

Look for the Human Element



Do the Math!

Occurrence	Severity	RPN	Probability of Occurrence	Effect	Quantity/ Year	Outcome	Quantity/ Year	Outcome
5	5	25	0.0025	Device does not work	10,000	25 Devices Fail per Year	500,000	1250 Devices fail per year
2	10	20	0.00005	Death or Serious Injury	10,000	One possible death every two years	500,000	25 deaths a year.

One of the major flaws with risk management practice.

Risk Management

- Determine additional controls to reduce risk
- Build in safety and quality (inherent features)
- Use Severity to decide on sample size.

In this Session we Learned

1. The Importance of the PHA
2. How complete a PHA
3. How to Transition from a PHA to an FMEA

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Equipment Specification & DQ

Module 6

Learn how to Achieve Good Equipment Design

In this Session you will Learn

1. The function of the FRS and FDS
2. How to Ensure Good Equipment Design
3. How to Preform Design Qualification

Equipment Specification

Definition – FRS

- Functional Requirements Specification: Defines the requirements of a product, process or piece of equipment at the functional level.
- How it operates to achieve the required outputs.

Definition – DS

- Design Specification: Defines the make up, components or construction of a product, process or piece of equipment.
- What it is comprised of.

Functional Design Specification (FDS)

- A formal statement of services to be provided by the system
- May replace the less detailed Requirements specification if the project is small, or supplement the requirements specification for a large project
- Acts as a contract between the supplier and the customer, and should be understandable by both customer and supplier technical staff

FRS or FDS

- **Overview**
  - High level description
  - Reference regulations
  - Assumptions / limitations
  - Non-conformances with URS if applicable
- **Functional Requirements**
  - Identify how the requirement specifications will be implemented
  - Product Characteristics
  - Include performance requirements – yield, capacity, throughput etc.
  - Safety
- **Traceability to URS**

FRS/FDS

- **Interfaces and Software**
  - User – admin / operator / etc.
  - Interface / peripheral types
  - Equipment / other systems
  - Data type / format / ranges / timing / rates / protocols
  - Error handling, recovery, reporting
  - Security
- **Non functional Requirements**
  - Availability – reliability / redundancy / error checking / stand-by operation
  - Maintainability – expansion possibilities / spare capacity / likely changes.

Hardware Design Specification HDS

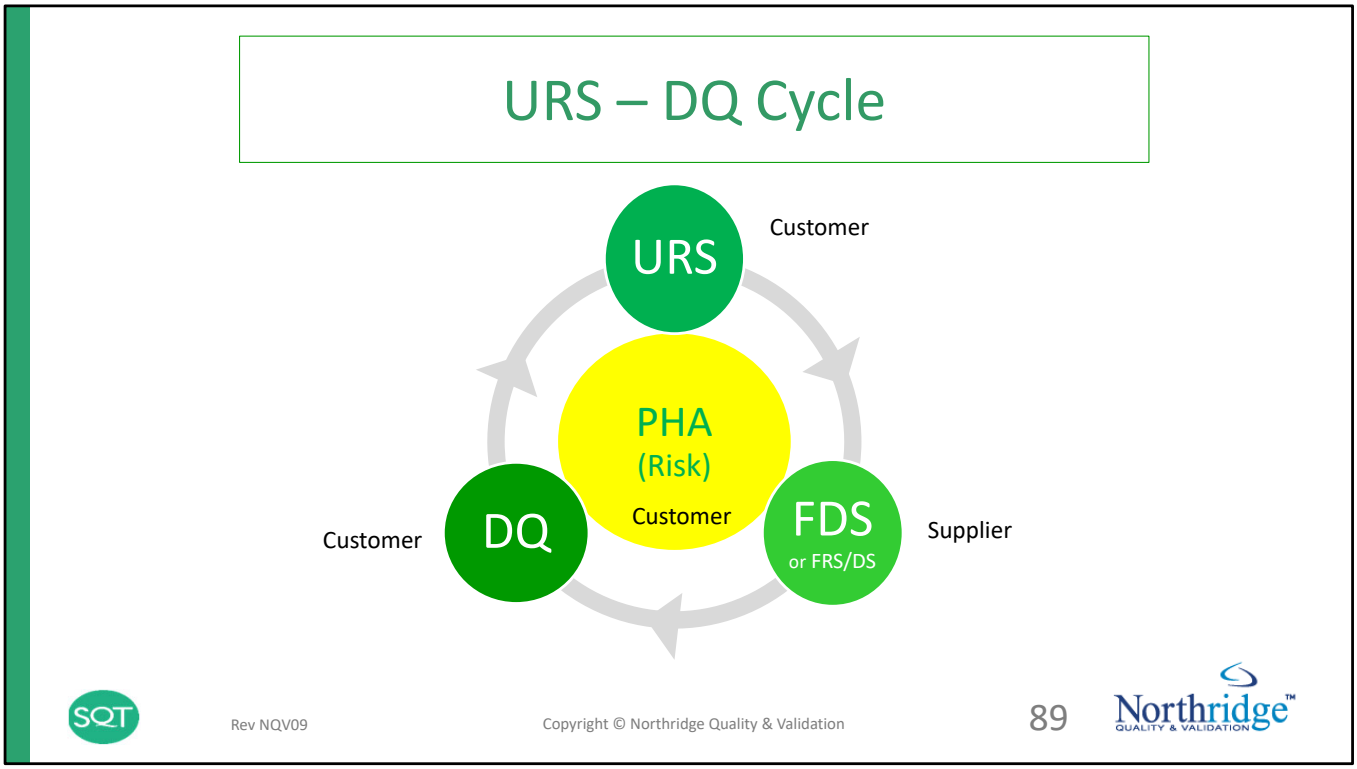
- Configuration
- Environment
- Electrical supplies
- Layout / location diagrams
- Drawings
- Component list
- Standards references

Software Design Specification (SDS)

- Each software sub-system (module) may require a Software Module Design Specification
- Enough detail for coding of the module to proceed
- May require updating with implementation details

Design Qualification (DQ)

- A very important step within qualification is determining if the equipment design fulfils the user requirements. This process is called **Design Qualification.**
- A DQ report is produced stating how the design as stated in the FS, FDS or DS meets the user requirements as stated in the URS.



PHA: Preliminary Hazard Analysis.
It is important to conduct high-level risk analysis early in the project so that quality can be built into the system design.

Writing Requirements and fulfilling them can be an iterative process.

Custom (Bespoke) Systems:

1. The customer writes the URS.
2. The customer performs a Preliminary Hazard Analysis updates the URS.
3. The supplier writes the FRS – The proposal/concept.
4. The customer performs the DQ and asks the supplier to update the FRS and if necessary updates the URS.
5. Once the DQ has passed the supplier develops the HDS and SDS.
6. The customer performs the DQ and if necessary asks the supplier to update the HDS and SDS.
7. Once the DQ has passed the supplier builds the equipment.

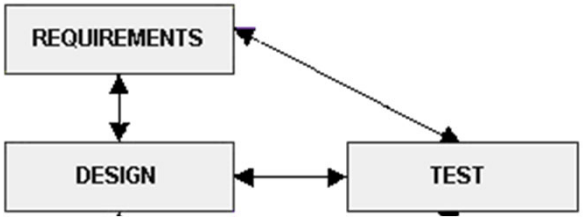
Off-the-shelf systems:

The supplier writes the FDS independently of the individual customer.

1. The customer writes the URS.
2. The customer performs a Preliminary Hazard Analysis updates the URS.
3. The customer performs the DQ and asks the supplier for modifications (or chooses another system) and updates the URS if necessary.
4. Once the DQ has passed the supplier develops the HDS and SDS.
5. Once the DQ has passed the equipment may be purchased.

Requirements Traceability Matrix (RTM)

(Trace Matrix)



Requirements Traceability Matrix Example

URS Number	URS Requirement	FDS Reference	Software Design Specification	Installation Qualification Test Reference	Operational Qualification Test Reference	Performance Qualification Test Reference	Approval
	ABCD-URS-090	**ABCD-FDS-079**	**ABCD-SDS-050**	**VAL-QA-73**	**VAL-QA-75**	**VAL-QA-75**	**Sign and Date**
1.1	The system must assemble Part number XXXXX in accordance with Drawing XXXXX Rev C.	2.1	Sect 2/App F	N/A	2.21	5.1	
				N/A	2.22	5.1	
				N/A	2.23	5.1	
1.2	The system must pressure test the completed assembly to within a range of 10 to 50 psi.	2.9	Sect 1/App B	1.9	2.25	N/A	
1.3	No leakage >0.02 ml/min is permissible within 2 minutes.		Sect 2/App G	No testing required; tested at 1.9 and 2.25 above		5.1	

In this Session we Learned

1. The Importance of DQ.
2. For Custom Equipment – FRS, HDS, SDS.
3. OTS Equipment – FDS; often the Manual.
4. Keep the Trace Matrix Up to Date.

Welcome to your
Process Validation Virtual Training Course
Installation Qualification - IQ
Module 7

Learn how to Preform an IQ.

In this Session you will Learn

1. The Role of the IQ.
2. How to Perform an IQ.
3. To avoid Checklists during IQ.

Definition – Installation Qualification

- Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufactures approved specification and that the recommendations of the supplier of the equipment are suitably considered

Installation Qualification Studies

- The IQ process captures the installation of the equipment in a way that allows for efficient implementation of the calibration and PM programmes and facilitates effective equipment change over time

IQ Protocol Format

- Equipment Description – Include equipment capacity and safety features
- Engineering Documentation - Include specifications, spare parts lists, drawing etc. Identify where manuals are located
- Equipment List – Complete an equipment list based on information from purchase orders and machine specifications. Document equipment identification number, location, manufacturer and instruments requiring calibration.

IQ Protocol Format

- Procedure List – List all applicable SOPs including cleaning, operating and preventative maintenance routine. Ensure training records are documented for personnel operating, cleaning or maintaining the equipment.
- Utilities List – Complete a list of utilities supplied to the equipment based on equipment specifications and installed systems. Verify that utilities meet equipment specifications.

IQ Protocol Format

- Software IQ – Ensure adherence to vendor installation instructions, confirm correct version is installed and record version name and number.
- Materials in contact with product – list and confirm that product contact materials are acceptable.
- List spare parts and change parts.

IQ Checks

- Include pressure test logs, motor checkout sheets, welders and welding qualification, piping pressure checks, cleaning & passivation records, instrument loop checks and any other document loop checks and any other document that demonstrates that equipment has been correctly supplied and properly installed.

IQ & Environment

- Is the equipment placed in the correct environment e.g. protection from vibration, placed to facilitate cleaning…

IQ continued

- Any discrepancy is resolved and documented in the IQ report
- IQ must be completed before initiating OQ
- Operator training is part of IQ

IQ Acceptance Criteria

- IQ requires a formal and systematic check of all installed equipment against the equipment supplier's specifications and additional criteria identified by the user as part of the purchase specifications.

In this Session we Learned

1. The Role of the IQ.
2. How to Perform an IQ.
3. Avoid Checklists during IQ.

Welcome to your
Process Validation Virtual Training Course

Operational Qualification - OQ

Module 8

Learn how to Preform the OQ.

In this Session you will Learn

1. The Role of the OQ.
2. How to Test Equipment Function.
3. Test Worst Case Conditions.

Definition – Operational Qualification

- Documented verification that equipment, system, or process performs as specified throughout representative or anticipated operating ranges.
- OQ frequently includes investigational work and statistical analysis for reduction of non-random variation and optimization.

Operational Qualification Studies

- The purpose of an equipment OQ protocol is to demonstrate that the equipment operates as expected under worst case conditions.
- Controls are adjusted during this phase of testing and performance trials are conducted to verify that the equipment operates in accordance with design specifications

FDA Worst Case Definition

- A set of conditions encompassing upper & lower processing limits & circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce process failure.

Operational Qualification Studies continued

- The OQ also serves as a final major component and systems operational audit prior to conducting Performance Qualification
- During the OQ, data is collected concerning critical operating parameters and quality attributes, which could affect production and this data is evaluated to determine the effectiveness and consistency of the operation.

OQ Protocol Format

- Validation Test Instrument and Calibration Complete a list of the instruments required to conduct the operational qualification testing. Verify that the instruments are within their calibration interval.
- Control Panel Checkout – List the manual controls and their relevant functions. Assemble the equipment components and operate the unit according to the applicable SOPs and test the operational functionality of the control panel.

OQ Protocol Format

- Alarms and Interlocks – Verify that all interlocks and alarms function as dictated by the design specifications by activating or simulating the alarm condition, documenting the procedure used to trigger/activate the devices and recording the expected and observed responses.

OQ Protocol Format

- Software Operational Checkout – where applicable carry out software functional testing, verify security access, check data entry by measuring expected results versus observed results, check back-up in the event of power failure

OQ Protocol Format

- Operational trials – Challenge operating variables by running the machine at extremes of the manufacturer's recommended tolerances. Examples of variables include speeds, temperatures, flow rates etc. Where possible specify run times for challenge tests. During these tests water or placebo product can be used

OQ Protocol Format

- Demonstrate process consistency e.g. filler yields consistent fill volumes, thermocouples indicate even heat distribution in a cold room or dry heat sterilisation.
- The relative importance of the specifications may be determined by addressing the quality requirements of the process or product which will be manufactured using the equipment.

OQ Acceptance Criteria

- The acceptance criteria for an OQ protocol must demonstrate that the equipment meets all operating specification and that product produced on the equipment also meets specification.
- The relative importance of the specifications may be determined by addressing the quality requirements of the process or product which will be manufactured using the equipment.

Acceptance Criteria & Specifications

- If any test or assessment fails, it is essential that Corrective Action is taken & appropriate retesting performed to confirm satisfactory resolution.
- If any inability to meet specification is shown, it is necessary to reassess the specification. For example filler does not show consistent performance at the upper speed specification. The equipment may not need to run at this speed. In this case the upper specification may be amended.

Oven OQ

- Place 21 thermocouples, 7 per shelf, in a X pattern including the top, middle & bottom shelves
- Run three empty cycles
- Run three minimum load cycles
- Run three maximum loads
- Acceptance criteria – Oven maintains a temperature of 130 deg C for 30 minutes +/- 5 when oven empty, and at min. & max. loads

In this Session we Learned

1. How to Identify Worst Cases.
2. How to Challenge Equipment.
3. Worst Case is not just USL and LSL.
4. How to Write OQ Tests.

Welcome to your Process Validation Virtual Training Course

Process Design

Module 9

Learn how to Optimise the Process

In this Session you will Learn

1. Process Stability and Capability.
2. How to Develop and Robust Process.
3. How to Calculate Process Capability.

What is the Enemy of Quality?

VaRiAtIOn

Process Design

- Define the process requirements and processing endpoints
- Establish how endpoint will be measured
- Propose a method or process which can achieve this end point
- Verify that this method works

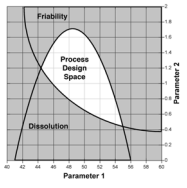
Quality by Design

- Define the Quality Target Product Profile (QTPP)
- Define the Critical Quality Attributes (CQAs)
- Select a suitable manufacturing process
- Define a control strategy

Systematic approach:

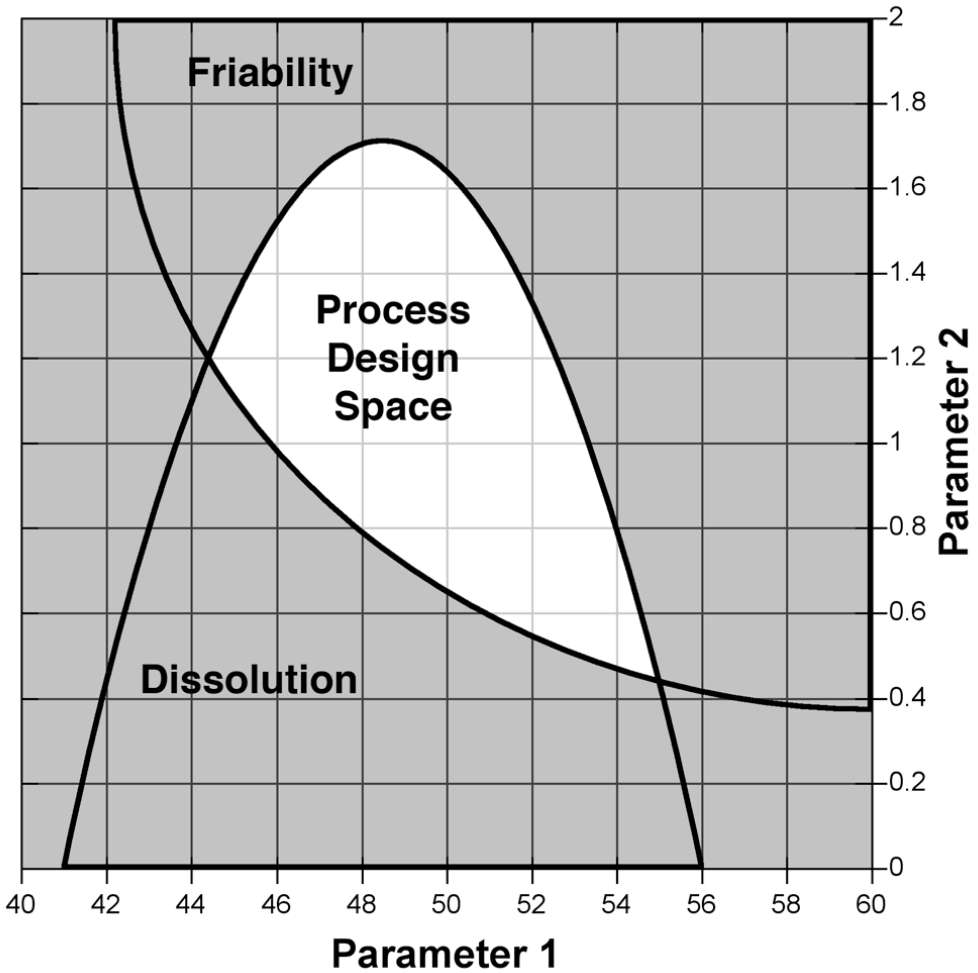
- Risk Assessment
- Experimentation
- Defining functional relationships

Process Characterisation



- Define;
  - The Process Steps and Manufacturing Methods
  - The Process Equipment, Accessories and Utilities
  - The Critical Process Parameters – with Limits and Rationale
  - The Raw Materials and Consumables – Part Numbers
  - The Products to be Produced – Codes and Families
  - Critical Quality Attributes of those Products
  - Test Methods

Define the Design Space



Obtaining a consistent process…

- Process validation requires that a process is established that can consistently conform to requirements and then studies are conducted demonstrating that this is the case.
- Nonconformities often occur because of errors made and because of excessive variation.

- This requires a balanced approach using variation reduction tools and mistake proofing methods.

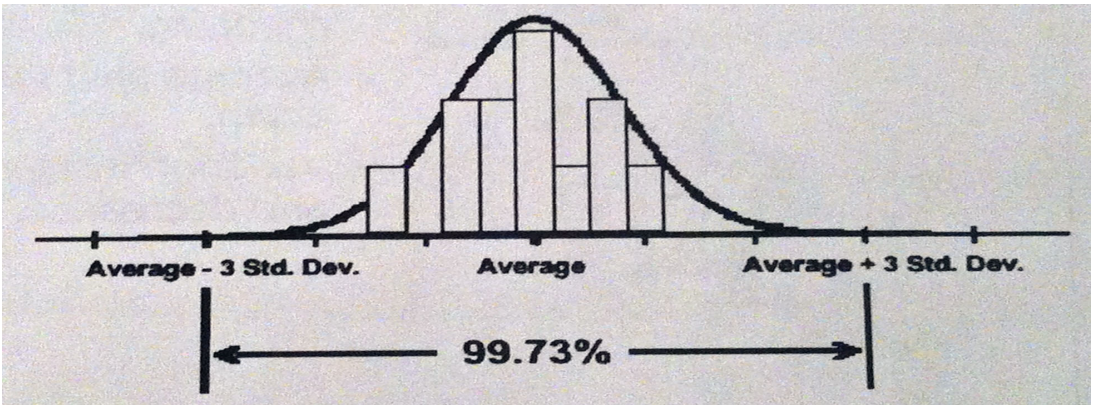
Mistake Proofing Methods

- This method attempts to make it impossible for the error to occur or if it does, to make it impossible to go undetected!
- Japanese refer to this method as Poka-Yoke
- For example in designing an assembly process ensure that parts fit together in one way only or possibly design a gauge which will reject parts which are too large.

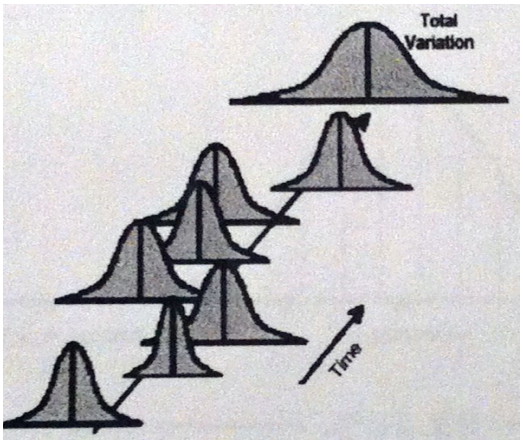
Reducing Variation

- Reducing variation and proper targeting of a process requires identifying the key input variables and establishing controls on these inputs to ensure that outputs conform to requirements.
- One key tool here is a capability study.

Normal Curve

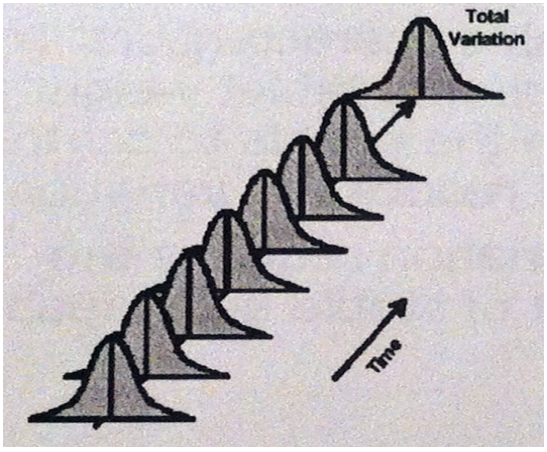


Unstable process



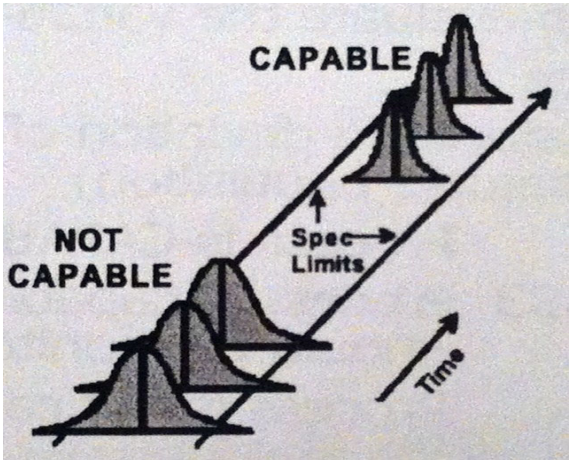
- Process constantly changing.
- Average shifts up & down.
- Variation increases and decreases.

Stable process



- Consistent level of performance.
- Total variation is reduced.
- Process more predictable.

Capable Process



- Once a consistent performance is achieved, the remaining variation must be made to safely fit within the upper and lower specification limits.

Process Capability - C_p

C_p is used to evaluate the Variation versus the Specification.

$$C_p = \frac{USL - LSL}{6\sigma}$$

Where;

USL = Upper Specification Limit

LSL = Lower Specification Limit

σ = the standard deviation

C_p > 1.33 Process is CAPABLE
C_p = 1.0 – 1.33 Process is capable but should be monitored.
C_p < 1.0 Process is not capable

Process Capability - C_{pk}

C_{pk} is used to evaluate the centering of the process.

$$C_{pk} = \frac{USL - \bar{x}}{3\sigma} \quad \text{or} \quad \frac{\bar{x} - LSL}{3\sigma} \quad \text{(whichever is the smaller).}$$

LSL = lower specification limit
USL = upper specification limit
$\bar{x}$ bar = mean
σ = standard deviation

C_{pk} > 1.33 Process is CAPABLE
C_{pk} = 1.0 – 1.33 Process is capable but should be monitored.
C_{pk} < 1.0 Process is not capable

C_{pk} has a negative value: This shows mean is outside of the specification limits.

C_{pk} = 0: This shows that the mean falls on one of the specification limits.

C_{pk} > 1.0 This means that 'all the data' (6σ) falls within the specification limits.

The terms Cp and Cpk are used for Short Term Capability e.g. During an OQ Study (Sample Size 30 to 100.

The terms Pp and Ppk are used for Long Term Capability e.g. During a PQ or in Production. Large Sample Size

Determine the KPVs

- What are the Key Process Variables?
- How do these affect the CQAs?
- DOEs
- Select Optimum Values
- Establish Stability
- Establish Process Capability
- Generate Control Charts

CQA: Critical Quality Attribute
DOE: Design of Experiments (also; a DEO = A Designed Experiment)
KPV: Key Process Variable

Examples

- For a device, a specification for the electrical resistance of a pacemaker lead is established so that the lead would be acceptable only if the resistance is within a specified range.
- For an ophthalmic solution, the solution is acceptable only is it is shown to have a pH within the narrow established range.
- The ranges set at this point should chosen to allow for increased variation during scale up.

Design of Experiments (DOE)

- This technique can be used to determine key process parameters.
- Traditionally a designed experiment involves purposely changing one or more inputs and measuring resulting effect on one or more outputs.

DOE Example

- Consider a sealing process which has three critical parameters pressure, time & temperature
- By keeping temperature constant, runs using high, medium & low pressure and time can be undertaken.
- To check all possible combinations is not practical and is expensive in time, money and resources

Design of Experiments (DOE)

- Statistical methods are used to reduce the number of runs
- Small experiments are conducted
- Information is gathered & analysed
- Parameter variations are defined

Types of DOEs

- Classical Full Factorial
- Fractional Factorial
- Taguchi
- Response surface study
- Analysis of variance (ANOVA)
- Screening experiments

Sampling Plans

- AQL sampling plans are used to accept or reject lots of product.

- LTPD sampling plans, allow a confidence statement to be made such as:
  'with 95% confidence, the defect rate is below 1%'

  C = 0 LTPD sampling plan formula
  n = ln(*1-confidence* level) / ln(*reliability*)
  n = ln(1- 0.95)/ ln(0.99) = 299 samples

AQL: Acceptable Quality Level

LTPD: Lot Tolerance Percent Defective

ln = natural log

Sampling Plans & Worst Case

- Design sampling plans to investigate worst case e.g. clean room particulate counts with maximum number of personnel, hot spots during cleaning, blend uniformity…

Process Validation General Principles & Practices FDA Jan 2011

A successful validation programme depends upon information & knowledge from product & process development. Manufacturers should:

- Understand the sources of variation
- Detect the presence & degree of variation
- Understand the impact of variation on the process & ultimately then on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process & product

In this Module we Learned

1. What a Robust Process is.
2. Don’t Validate a Process that is not both Stable and Capable.
3. How to Calculate Cp and Cpk

LSL: Lower Specification Limit
USL: Upper Specification Limit

Welcome to your Process Validation Virtual Training Course

PQ & Validation Maintenance

Modules 10 & 11

Learn how to
Capture Variation in the PQ
and
Maintain the Validated State

In this Session you will Learn

1. Build previously unassessed sources of variation into the PQ.
2. Apply Continuous Process Verification
3. Maintain the Validated State

Performance Qualification
3 Types

Equipment PQ
Process PQ
Product PQ

Definition- Performance Qualification

- Establishing confidence that process equipment is capable of consistently producing product which meets its quality attributes and specifications.
- If qualifying equipment independently of the process 3 batches (minimum) may be sufficient at this stage.

Equipment Performance Qualification Studies

- PQ studies must confirm that when the equipment is operated under specified conditions, it continues to operate as expected and the resulting process or product meets specification.

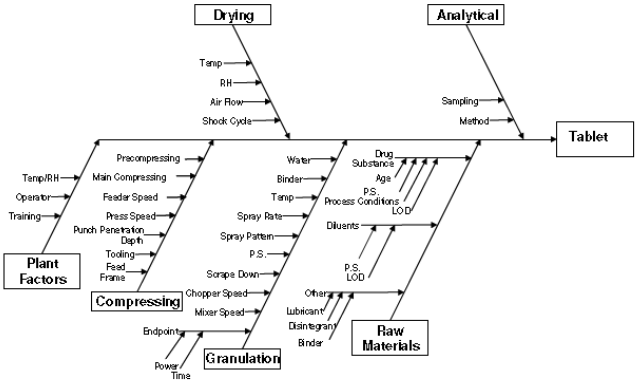
PQ Acceptance Criteria

- Plant or equipment are considered fully qualified when manufactured product or processes conducted using them are shown to meet all specifications.
- Often separate equipment PQ is not carried out as this data is captured during the individual product validation study.

Process Performance Qualification

- This means establishing confidence that the process is effective & reproducible
- A process is rigorously tested to determine whether it is capable of consistently producing an output or in-process product or finished product which meets specification.

Sources of Variation



Product Performance Qualification

- This means establishing confidence through appropriate testing that the finished product produced by a specified process meets all release requirements for functionality and safely.
- Product PQ shows that the PROCESS has not adversely affected the finished product
- Product PQ and device Design Validation are closely related.

Product Performance Qualification

- Companies conduct design validation using finished products made during process validation and this approach satisfies the requirement for product PQ.
- Design validation shall ensure that devices conform to defined user needs & intended users & shall include testing production units under actual or simulated use conditions

Steps to be completed before Process and/or Product Validation

- Process specifications are established and proven acceptable ranges have been demonstrated through laboratory or other trial methods (development).
- The facility and process equipment have been qualified
- The process is defined with sufficient specificity so that employees understand what is required.

Factors include…

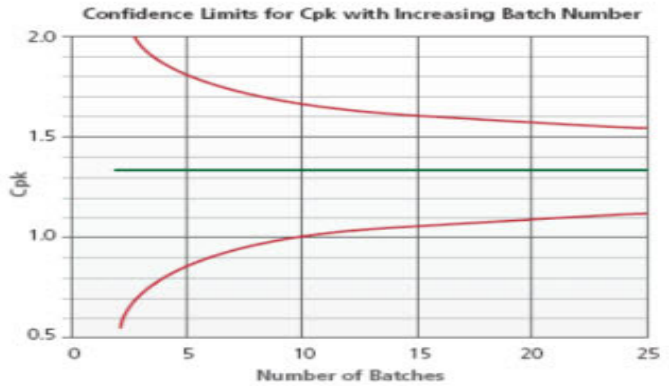
- Component specifications
- Air & water handling systems
- Environmental controls
- Equipment functions
- Equipment wear & tear
- Human factors (training, ergonomics, stress)
- Process Control operations

Validation Life Cycle for a New Process – PQ

- Conduct **Process & Product Validation Studies.**
- Assemble and document evidence of **process robustness** and reproducibility

PPQ ≠ 3

- How many lots?



Process Performance Qualification

Success at this stage signals an important milestone in the product lifecycle. A manufacturer must successfully complete PPQ before commencing commercial distribution of the drug product.[16] The decision to begin commercial distribution should be supported by data from commercial-scale batches. Data from laboratory and pilot studies can provide additional assurance that the commercial manufacturing process performs as expected.

The approach to PPQ should be based on sound science and the manufacturer's overall level of product and process understanding and demonstrable control. The cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches) should be used to establish the manufacturing conditions in the PPQ. To understand the commercial process sufficiently, the manufacturer will need to consider the effects of scale. However, it is

PPQ Sampling

The sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production.

Source: FDA Guidance for Industry: Process Validation General Principles and Practice 2011

Continued Process Verification and Maintaining a State of Validation

Continuous Monitoring & Maintenance

- One of the key outputs of development studies and process & product validation is the development of attributes for continuous monitoring & maintenance.
- Process & product data should be analysed to identify any variation due to controllable causes

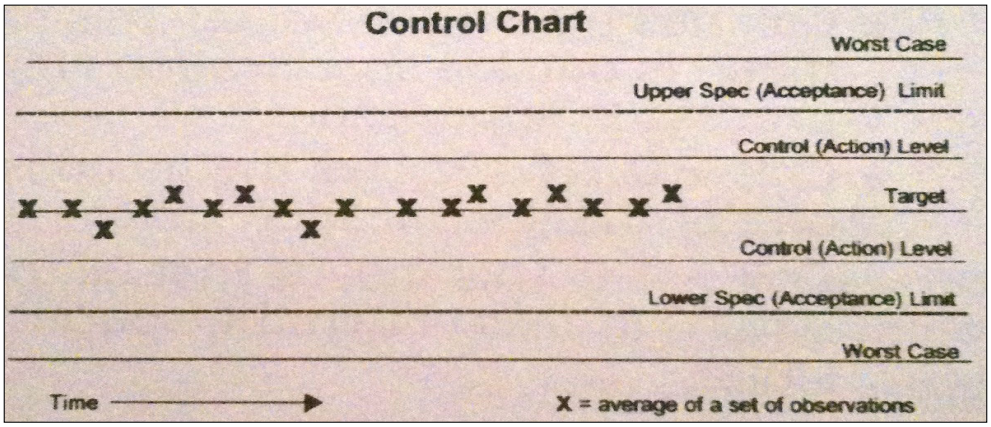
Are we in Control?

- Control Charts
  - X bar R
  - Key Process Variables
- Repeat Capability
- Investigate if out of control or reduced capability
- Revalidate if necessary

Control Chart

- 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
- Control charting may be used to continuously monitor the process and assure a state of validated control.
- Action levels can be determined to adjust the process and maintain it within the control limits.

Sample Control Chart



Control Chart Explanation

- A sample (e.g. 5 consecutive units) is selected periodically
- The average & range is calculated & plotted. The plot of averages shows if the process average changes. The plot ranges shows if process variation changes.
- Control limits are calculated & added to the plots. These represent the maximum amount that the average or range should vary if the process does not change.

Control Chart Explanation

- A point outside the control limits indicates that the process has changed.
- When a change is identified by the control chart, an investigation should be made as to the cause of the change.
- Control charts help to identify key input variables causing the process to shift.

Controllable causes of variation include

- Temperature
- Humidity
- Variations in electrical supply
- Environmental contamination
- Process water purity
- Operator training
- Operator shift patterns
- Component variation
- Tooling wear & tear
- Equipment maintenance

Eliminate Controllable Variation

- Establish measures to eliminate controllable variation
- Examples include HVAC systems, UPS systems…
- Eliminating controllable variation results in processes which are more stable & predictable

Monitor & Control Process Trends

- Monitor trends to ensure that the process remains within the established parameters
- When trend data shows a shift in the property monitored, investigate the root cause, identify corrective action and consider revalidation.

Process Trend Data & Revalidation

- Where the quality indicators for monitored, validated processes show negative trends, such processes must be revalidated
- Examples – High number of process deviations observed, low product yields, failing batches, product in specification but great variation noted

Changes in Process & or Product

- Change is inevitable!
- Comprehensive change management is essential

Two types of change:

- Planned changes
- Unexpected changes, deviations

Purpose of Change Management Programmes

- Detection of unexpected deviations from validated processes & root change to the validated product or process.
- Impact assessment of proposed change to the validated product or process

Change Control Measures Apply to…

- Equipment
- SOPs
- Manufacturing Instructions
- Environmental conditions
- Any aspect of the process which affects its state of control

Internal Change Monitoring Programmes

- Specification testing for incoming components, in-process products and finished products
- Stability programmes
- OOS reporting systems
- Internal audit programme & APRs
- PM & calibration programme
- Training programmes
- Cleaning monitoring programmes

External Change Monitoring Programmes

- Complaint monitoring
- Review service reports
- Supplier audit programmes
- Post Market Surveillance
- Product distribution data

Planned Proposed Change

- When change is proposed for validated products, processes or methods, an evaluation must be conducted to assess the potential effects of the change BEFORE the change is implemented.
- The need for revalidation forms part of this assessment!

Change & Regulatory Approval

- FDA & other body regulatory approval for a change prior to implementation may be required
- Examples – PMA supplement is required for a device safety or effectiveness, new indication for use, change in manufacturing facility, change in expiry dating…

Regulatory Guidance on Change

- FDA – 1997, Deciding When to Submit a 510 (k) for a Change to an Existing Device
- FDA SUPAC convention (Scale-up & Post Approval Change)

Changes Requiring Revalidation

Scale-up of Manufacturing Processes may result in:

- New equipment or new equipment surfaces
- Changes in processing times increasing environmental exposure times
- Change in manufacturing site
- Change in intermediate product holding times

Changes Requiring Revalidation

Changes in Packaging Material may result in:

- Change in sterilisation effectiveness e.g. EtOH new residues could be generated when combined with new packaging components.
- Label adhesive material could have altered properties over the product's shelf life.

Changes Requiring Revalidation

Personnel Changes may result in:

- Altered performance where a new supplier is used
- A change in product quality due to changed training levels

Changes Requiring Revalidation

Subtle Changes Over Time

- Many companies decide to validate after a period of time to confirm that a series of minor has negative impact on validation status.

Changes Requiring Revalidation

- Change in product intended use
- New reprocessing methods

Unplanned:

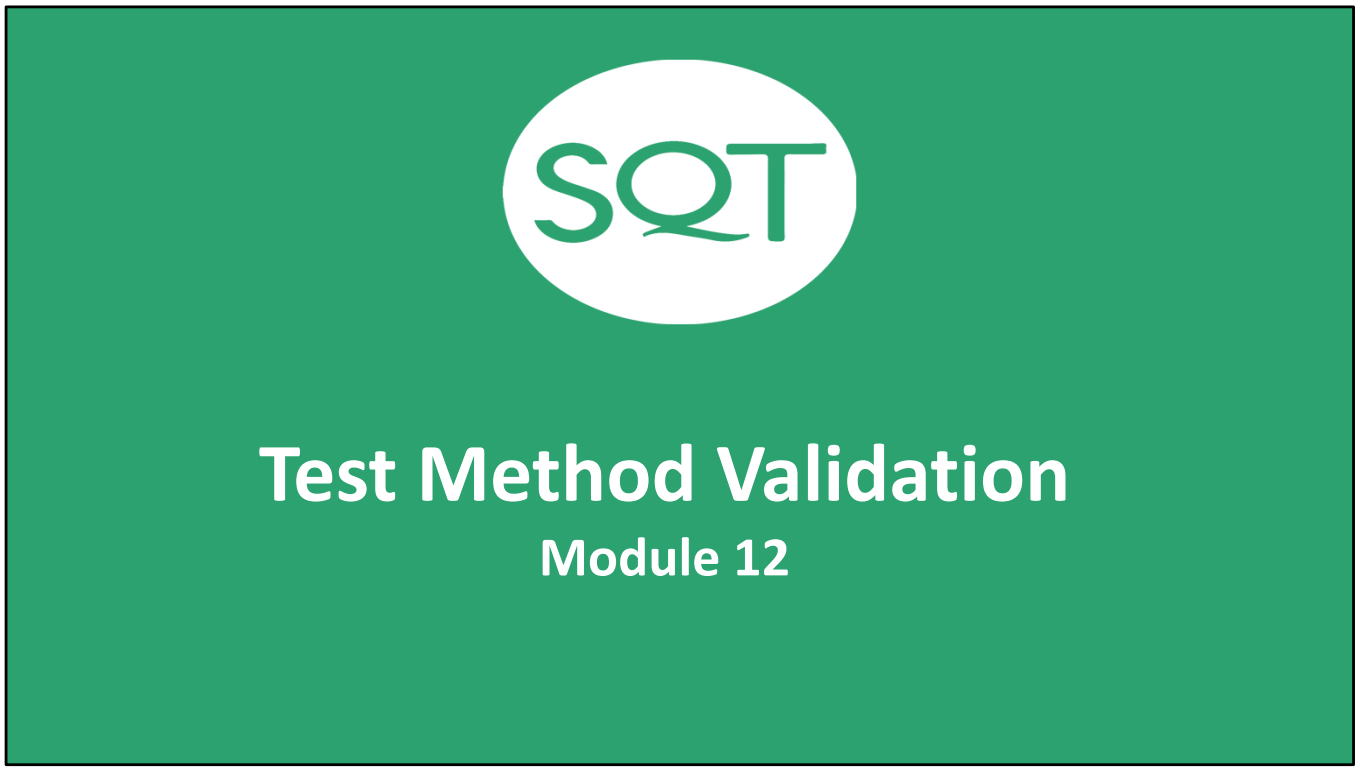
- Changes as a result of breakdowns.
- Changes as a result of failures.
- Out of Control
- Reduced Capability

Extent of Revalidation

- Revalidation studies are not always as intensive as the initial validation. For example a new packaging material is used for forming blister strips – revalidate the packaging process but the original equipment qualification still holds true!
- But change the sealing machine PLC, here you would carry out a full revalidation on both the equipment and the sealing process.

In this Module we Learned

1. It is going to Happen it Will, Capture it in your PQ.
2. Change is Inevitable, Control it.
3. Periodic Reassessment of the Validated State is a Regulatory Requirement.



CSV: Computerised Systems Validation
TMV: Test Method Validation

Learn Requirements for Validation of Test Methods

In this Session you will Learn

1. How to Validate Test Methods for Attributes and Variables.
2. How to Analyse Gauge R&R
3. Alternatives to Gauge R&R

Who watches the watcher?

- How can you trust the tests results that your validation is based on?
- How can you trust the people who inspect your product?

Definition: Analytical TMV

- **Analytical Test Method Validation:** Validation of test method to confirm that the results it produces are specific, precise, accurate, repeatable and reproducible over a given range.
- Two validation approaches
  - USP or ICH

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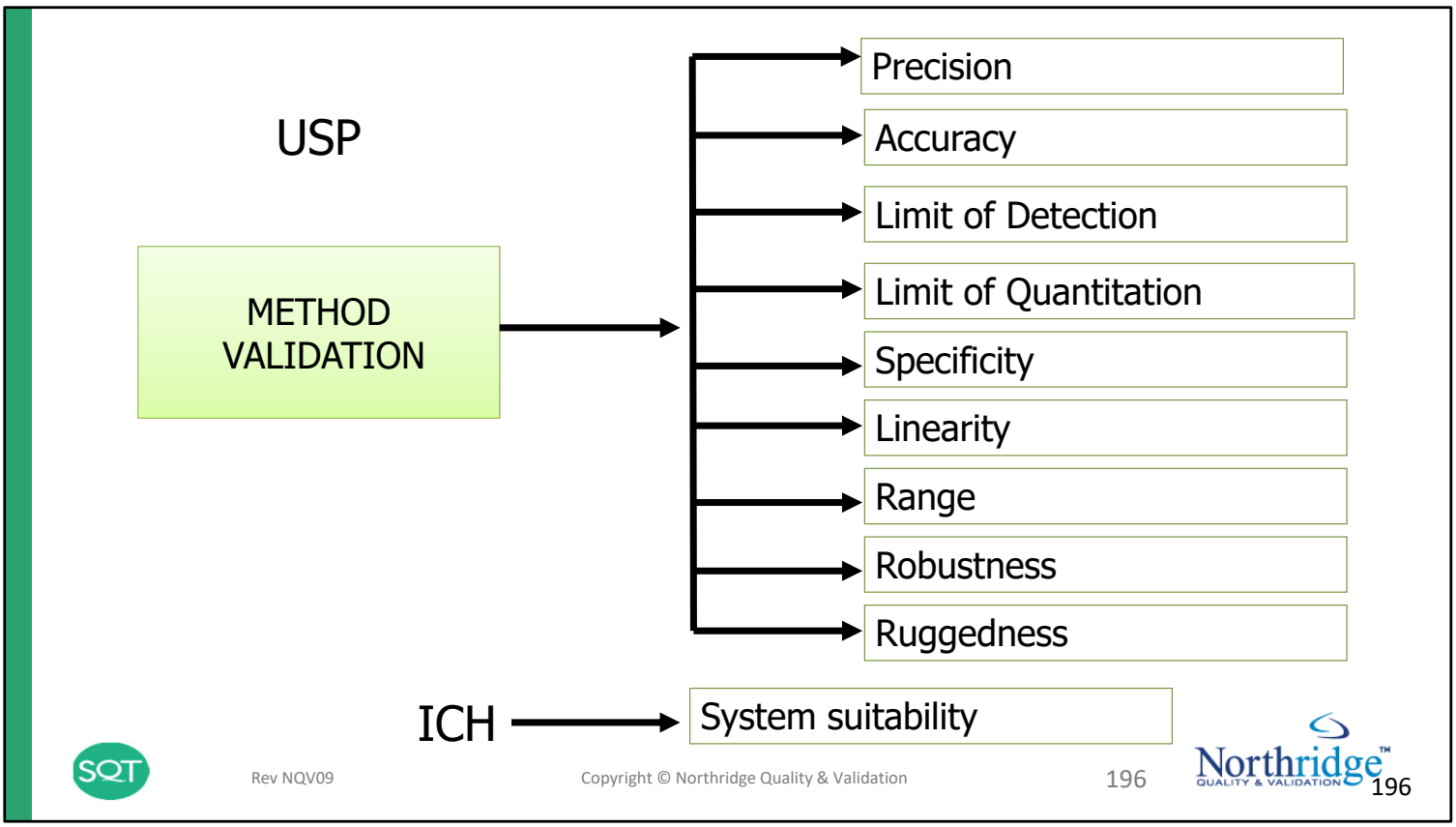


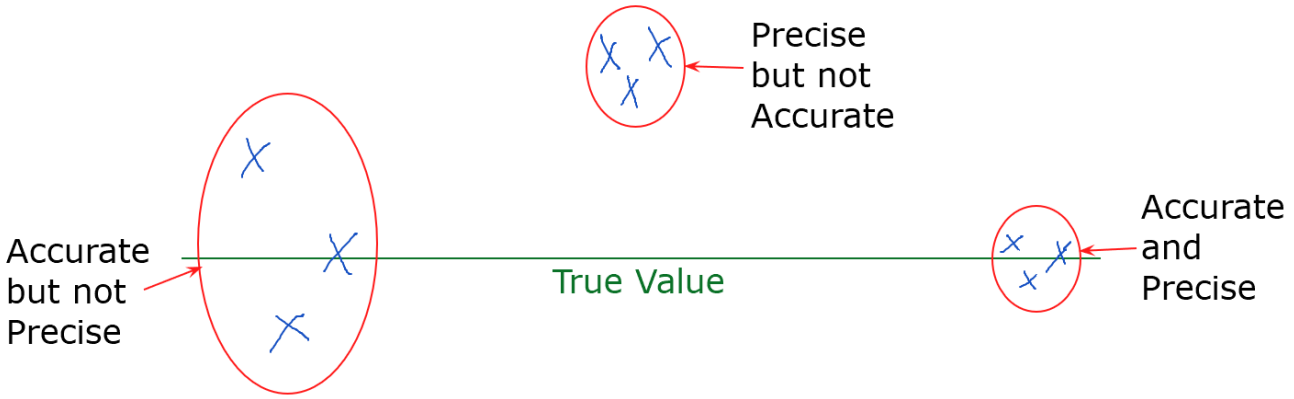
The steps are known as ***analytical performance parameters*** or ***analytical figures of merit.***

Due to differing interpretations across laboratories the ICH developed the guideline ***" Validation of Analytical methods - definitions and terminology"***

No major difference except ICH treats system suitability as part of method validation while the USP guidelines separate it from the method validation.

USP has harmonised to the extent possible with the ICH.

Accuracy and Precision



Accuracy: Closeness to the True Value.
Precision: The degree to which repeated measurements under unchanged conditions show the same results.

Precision, Repeatability and Reproducibility are degrees for the same thing.
Precision is repeatability in highly controlled setting e.g. a calibration laboratory.
Repeatability is the term used in normal conditions with no variation contribution from operator to operator variation.
Reproducibility is the term used for operator to operator repeatability.

Reproducibility may also refer to gauge to gauge repeatability or lab to lab repeatability depending on how the study is set up.

Attributes and Variables

Attributes: Only Two Values

- Pass/Fail, On/Off, Red/Green, Black/White.

Variables:

- **Discrete Variables;** Multiple Distinct Values
  - Forward/Reverse/Neutral, Red/Orange/Yellow…, RAL 1002/RAL 1003/RAL 1004.., Mon/Tue/Wed…
- **Continuous Variables;** Infinite Number of Values
  - 10.123492 kg, 20.25 Pa, 33.012 mm, 9.7%
    - Will normally be accompanied by a unit of measure.
    - Should be reported to a specified number of decimal places.

RAL is an European colour matching system which defines colours for paint, coatings and plastics etc.

Definition: (Variable) Test Method Validation (TMV)

- **Test Method Validation:** Validation of test method to confirm that the results it produces are accurate, precise, repeatable and reproducible.
- The 1st two are achieved by calibration
- The last two are by gauge R&R

TMV: Test Method Validation
R&R: Repeatability and Reproducibility

Definition: ATMV

- **Attribute Test Method Validation:** Establishing confidence through blind testing that a person or machine can determine the difference between an acceptable and an unacceptable sample.

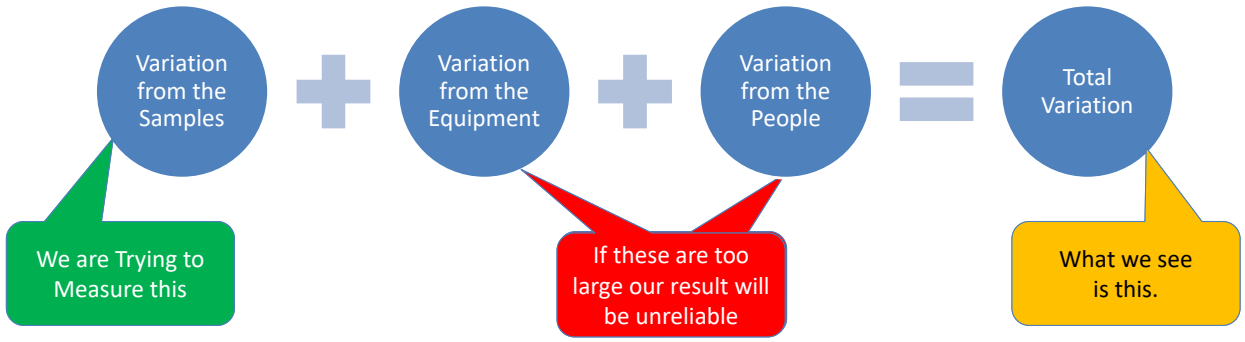
ATMV: Attribute Test Method Validation

TMV

- Four Methods
  - Gauge R&R
  - Precision to Tolerance
  - Process to Tolerance
  - Conforms to a standard

TMV aka MSA

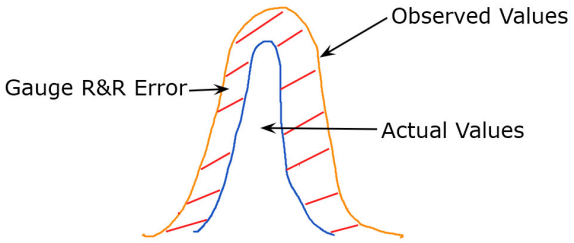
Measurement System Analysis



MSA: Measurement System Analysis
TMV: Test Method Validation

Gauge R&R

- How much variation comes from
  - A. The samples
  - B. The Gauge (Repeatability)
  - C. Operator to Operator (Reproduci



If B+C ≤ 10%: Good

≤ 30%: May be possible to accept

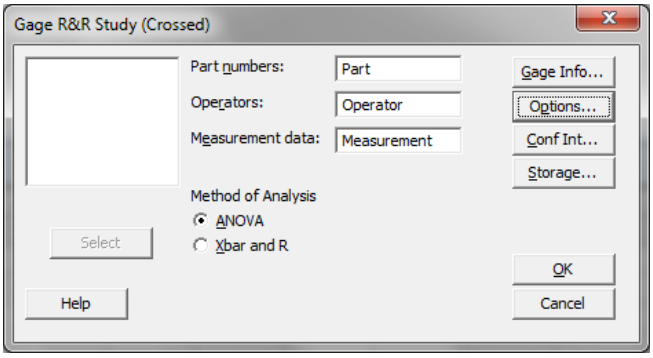
> 30% Reject

B+C known at the Total Gauge R&R

The above example shows the setup for multiple operators using the same gauge.
If there are multiple operators each their own gauge, you will not be able to distinguish between the variation coming from the operators from that coming from the gauges

How to Gauge R&R

- Ten samples
- Measured each twice
- By three inspectors
- Plan and Analyse using a statistical package such as Minitab.



Recommended to have a least 30 readings.

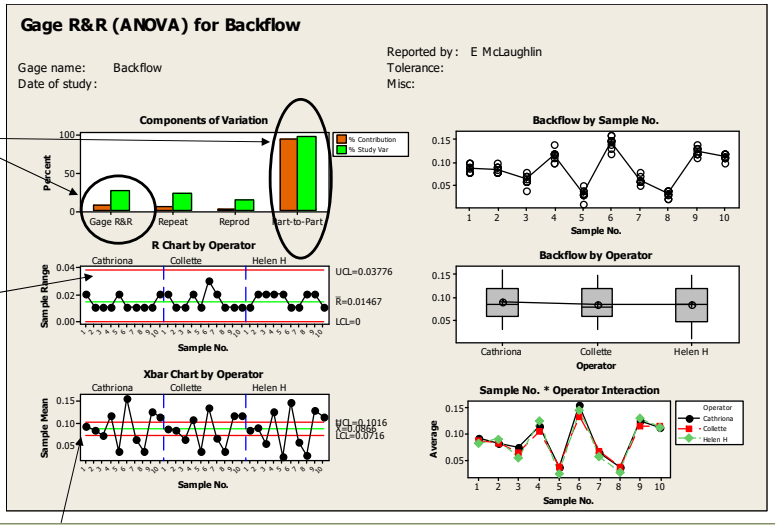
Use a 'Crossed' Gauge R&R study where the same samples may be measured multiple times.

Select 'Nested' Gauge R&R study where the same samples cannot be measured multiple times e.g. Where testing is destructive.

Gauge R&R Graphical Output

Gage R&R should be small compared to the Part-to-Part

The R Chart should be in control.
Out of control may indicate a measurement issue.



The Xbar chart **should be out of control,** if not then either there is not enough variation in the samples or not enough randomness in the study.

Gauge R&R ANVOA Table

Two-Way ANOVA Table With Interaction

Source	DF	SS	MS	F	P
Sample No.	9	0.121677	0.0135196	88.3850	0.000
Operator	2	0.000536	0.0002678	1.7506	0.202
Sample No. * Operator	18	0.002753	0.0001530	1.9667	0.027
Repeatability	60	0.004667	0.0000778		
Total	89	0.129632			

Alpha to remove interaction term = 0.25

The ANVOA Table can be used to exclude non-significant (α ≥ 0.25) interactions.
In this case the interaction sample-to-operator is significant and can not be excluded from the analysis.
If there are non-significant interactions then the ANOVA table will be re-run without them.

Gauge R&R Variance and Standard Deviation Tables

Source	VarComp	%Contribution (of VarComp)
Total Gage R&R	0.0001067	6.70
Repeatability	0.0000778	4.89
Reproducibility	0.0000289	1.81
Operator	0.0000038	0.24
Operator*Sample No.	0.0000251	1.57
Part-To-Part	0.0014852	93.30
Total Variation	0.0015919	100.00

Gage R&R Variance Table. The Variance is used to calculate the % contribution of each of the components. The percentages here should add to 100.

Source	StdDev (SD)	Study Var (6 * SD)	%Study Var (%SV)
Total Gage R&R	0.0103280	0.061968	25.89
Repeatability	0.0088192	0.052915	22.10
Reproducibility	0.0053748	0.032249	13.47
Operator	0.0019563	0.011738	4.90
Operator*Sample No.	0.0050062	0.030037	12.55
Part-To-Part	0.0385381	0.231229	96.59
Total Variation	0.0398980	0.239388	100.00

Gage R&R Standard Deviation Table. **This is the table that tells us the study results.** In this case the GR&R is 25.89% which is acceptable only for low risk or screening tests. Values in this table will not add to 100.

Number of Distinct Categories = 5

This indicates the number of groups within data that the measurement system can discriminate. The number should be >4 if the study has been successful.

How these Results are Calculated:

% Contribution = Percent that each factors contributes to the Total Variation. For example, Repeatability = 100 * repeatability variation/Total Variation

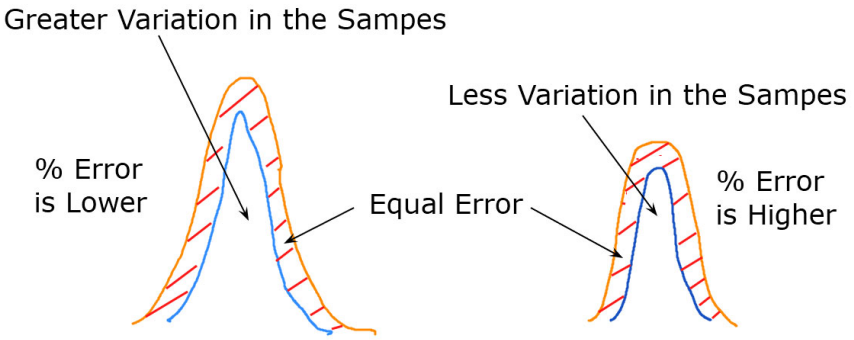
% Contribution:
Total Gauge R&R = Repeatability + Reproducibility
Reproducibility = Operator + Operator-Sample-Interaction

% Study Variation = Percent of the Total Standard Deviation that each component accounts for. Example, Repeatability = 100 * Repeatability standard deviation / Total Standard Deviation

Number of Distinct Categories = 1.41 times Part Standard Deviation divided by the R&R standard deviation.

A Potential Problem with Gauge R&R

The lower the variation in the samples the worse the Gauge R&R will appear.



To avoid this;

- Ensure that the variation used in the study is between 80% and 120% of the product specification or
- Use the Process-to-Tolerance Method

This can occur where the Process Capability is high and it is not possible to manufacture samples specifically for the Gauge R&R study.

Precision to Tolerance Method (P/T)

P/T compares the measurement error to the specification

P/T = 6 x Gauge R&R Standard Deviation/Tolerance Width

P/T = $6\sigma_e$ /(USL-LSL)

If P/T ≤ 0.1 - Good
≤ 0.3 - May be possible to accept
> 0.3 - Reject

For 1-Sided Spec may use the Mean and 3 Sigma

Looking at the above example again;
P/T = $6\sigma_e$ /(USL-LSL)
Total Gauge R&R Std. Dev = σ_e = 0.0103280, $6\sigma_e$ = 0.061968
If the specification is 2.55 +/0.15 then
P/T = 0.062/(2.7-2.4)
P/T = 0.21 – may be possible to accept.

Source	VarComp	%Contribution (of VarComp)
Total Gage R&R	0.0001067	6.70
Repeatability	0.0000778	4.89
Reproducibility	0.0000289	1.81
Operator	0.0000038	0.24
Operator*Sample No.	0.0000251	1.57
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Total Variation	0.0015919	100.00

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Operator*Sample No.	0.0050062	0.030037	12.55
Part-To-Part	0.0385381	0.231229	96.59
Total Variation	0.0398980	0.239388	100.00

Number of Distinct Categories = 5

Gauge Capability Cg

$Cg = K/100 * (USL-LSL) / L\sigma_e$

$Cg = 0.2 (USL-LSL)/6\sigma_e$

$Cg \geq 1.33$ is desired.

For 1-Sided Spec use 0.1 (SL +/- the Mean) over 3 Sigma

Where:

K percentage of the tolerance (20 is the default)

s standard deviation of measurements

L = number of standard deviations that represent the entire process spread (6 is the default)

Looking at the example;

Cg = $0.2(USL-LSL)/ 6\sigma_e$

If the specification is 2.55 +/0.15 then

Cg = 0.2x(2.7-2.4)/0.061968

Cg= 0.97 – not capable.

Source	VarComp	%Contribution (of VarComp)
Total Gage R&R	0.0001067	6.70
Repeatability	0.0000778	4.89
Reproducibility	0.0000289	1.81
Operator	0.0000038	0.24
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Number of Distinct Categories = 5

Process to Tolerance Method

- Perform a capability study.

If the total variation is < 30% of the specification i.e. Cp ≥ 3.34

then

The variation from repeatability and reproducibility must be < 30%.

This meets the second acceptance criteria for Gauge R&R

If the Process to Tolerance Acceptance Criteria of; Total Variation < 30% of the product specification has been met then the test method can be declared suitable for use.

If the Cp value is < 3.33 then the Process to Tolerance Criteria has not been met and another means of demonstrating that the test method is suitable must be used.

Conformance to a Standard

- If the method conforms to a Standard e.g. ISO, ASTM, ANSI, AAMI, ISTA or DIN document this.
- Protocol
  - Audit of Test Procedure vs The Standard
  - Audit of the Test Practice vs the Test Procedure x 3
- Report

ATMV

- Want to establish with 95% confidence that an operator will not accept a rejectable sample.
- Need suitable sampling plans.

Example:

- 15 good/15 bad blind test
- Must reject all bad
- Must not reject more than one good
- 95% confidence achieved

Protocols and Reports

- As for all validation studies a validation protocol and reports are required with clearly identified acceptance criteria.
- Should have an SOP.

In this Session we Learned

1. Gauge R&R is used for Variables.
2. Systematic challenge is used for Attributes.
3. Alternatives to Gauge R&R are Precision to Tolerance, Gauge Capability and Process to Tolerance.

Welcome to your Process Validation Virtual Training Course

Computerised System Validation

Module 13

CSV: Computerised Systems Validation

Learn Requirements for Validation Computerised Systems and Software

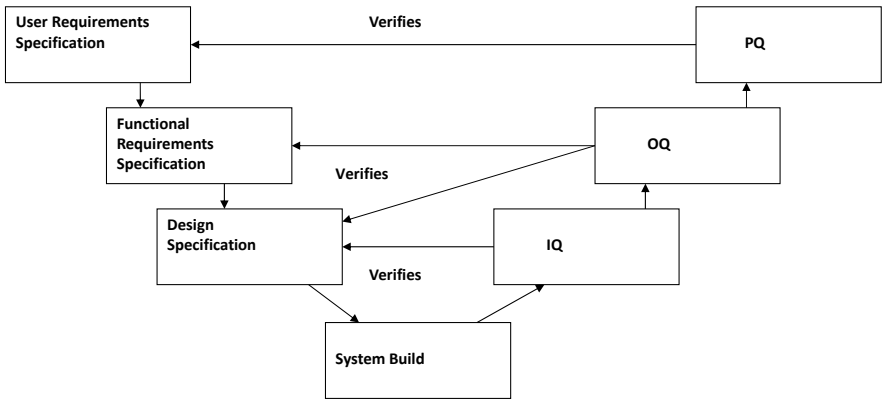
In this Session you will Learn

1. The V Model Approach to CSV.
2. GAMP Classification
3. Software IQ, OQ and PQ at a High Level

Computerised Equipment

- Equipment qualification studies should demonstrate that the equipment performs consistently when directed by the software.
- Examples include controllers on freeze driers, weight check devices on tablet presses, controllers on blenders…

V Model



GAMP 5 Classification

Gamp Class	Category	Validation
1	Infrastructure Software	Record Version
2	Obsolete	N/A
3	Non- Configurable Packages	Review supplier & validate functionality and any bespoke code.
4	Configurable Systems	Audit supplier, validate system functionality and review code in accordance with full life cycle requirements.
5	Systems Specifically written for Owner.	Audit supplier, validate all code Full life-cycle requirements.

Control System

- Commercial Off-The-Shelf (COTS)- Intended Use validation.
- Is customised software is used – full software validation is required.
- Reference – Good Automated Manufacturing Practices for Validation of Automated Systems GAMP 5 Guide

Software IQ

- Record the version provided with the equipment
- Verify that the installation requirements and specifications for the software and equipment system are met (hardware configuration, wiring and cabling etc.)

Software OQ

- Demonstrate input/output integrity i.e. did you get the anticipated result?
- What happens in a power outage situation?
- Challenge security features.
- Check data archiving.

Software PQ

- Studies demonstrate in the user environment in the hands of the user.
- May be carried out during process validation study

The PQ should incorporate potential sources of variation that the software may experience during use that had not been challenged in the OQ.

In this Session we Learned

1. The RHS of the V Model produces good Software.
2. The LHS confirms this.
3. A Test the Software Rejects tell us Much More than one that it Accepts.

LHS: Left hand side.
RHS: Right hand side.

Course Assessment Form – We Value Your Feedback

Please open the email you received with a link to a Course Assessment Form which we kindly ask you to complete.

We will use your feedback to *Guide & Inform* us so we can;

- *Rate our Learner's satisfaction*
- *Maintain & improve the quality of our training*
- *Better understand our Learner's training needs*
- *Provide added-value to our Learners*

Thank you for taking the time to complete the Course Assessment Form.

DEVELOP REAL CAPABILITY