Process Validation for Industries Concepts

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Benefits to you

- Improve your understanding of process validation
- Be confident your devices meet regulatory, quality and safety standards
- Be able to apply your knowledge to your business to ensure you produce compliance products
- Encourage professional development and knowledge sharing

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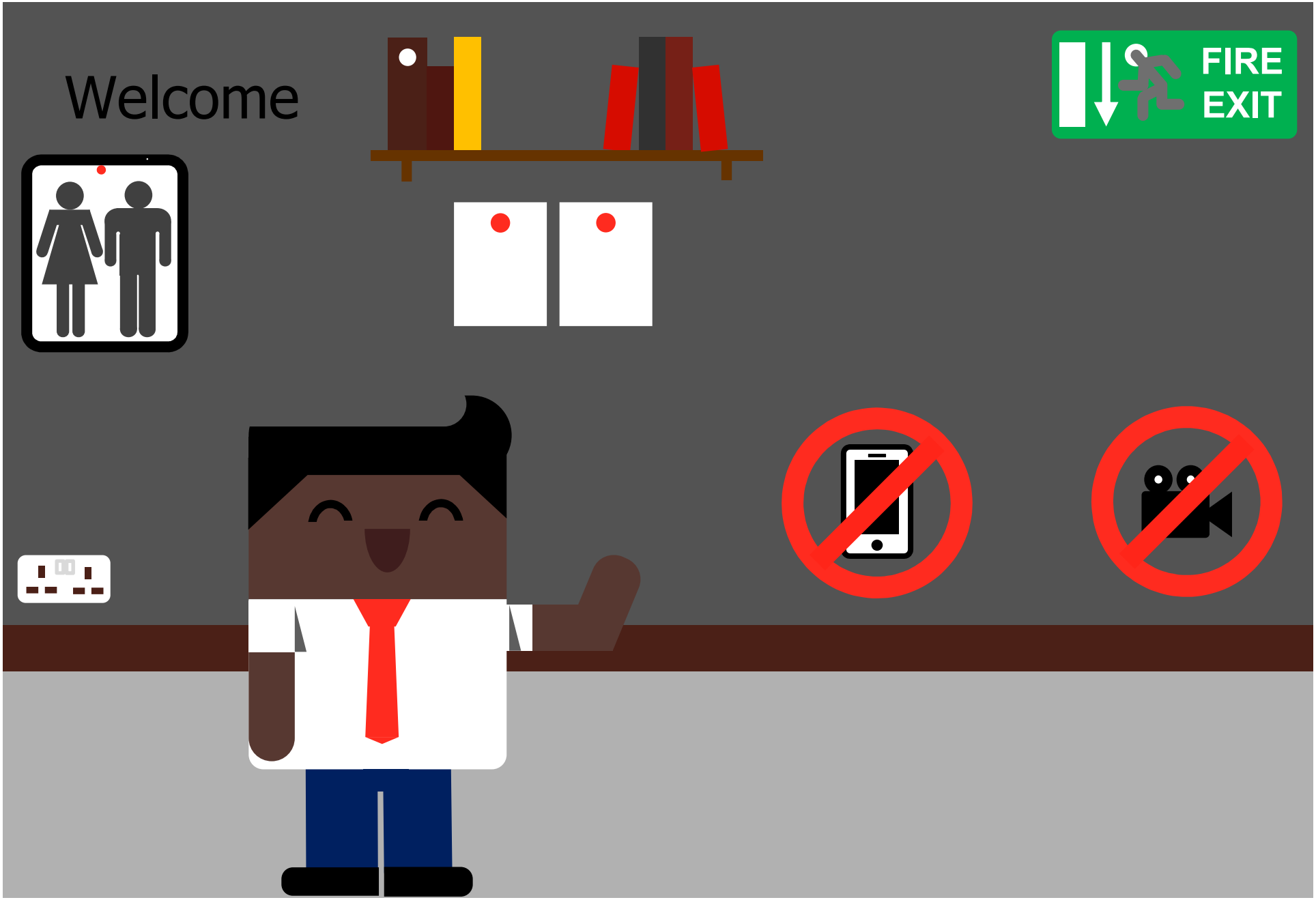
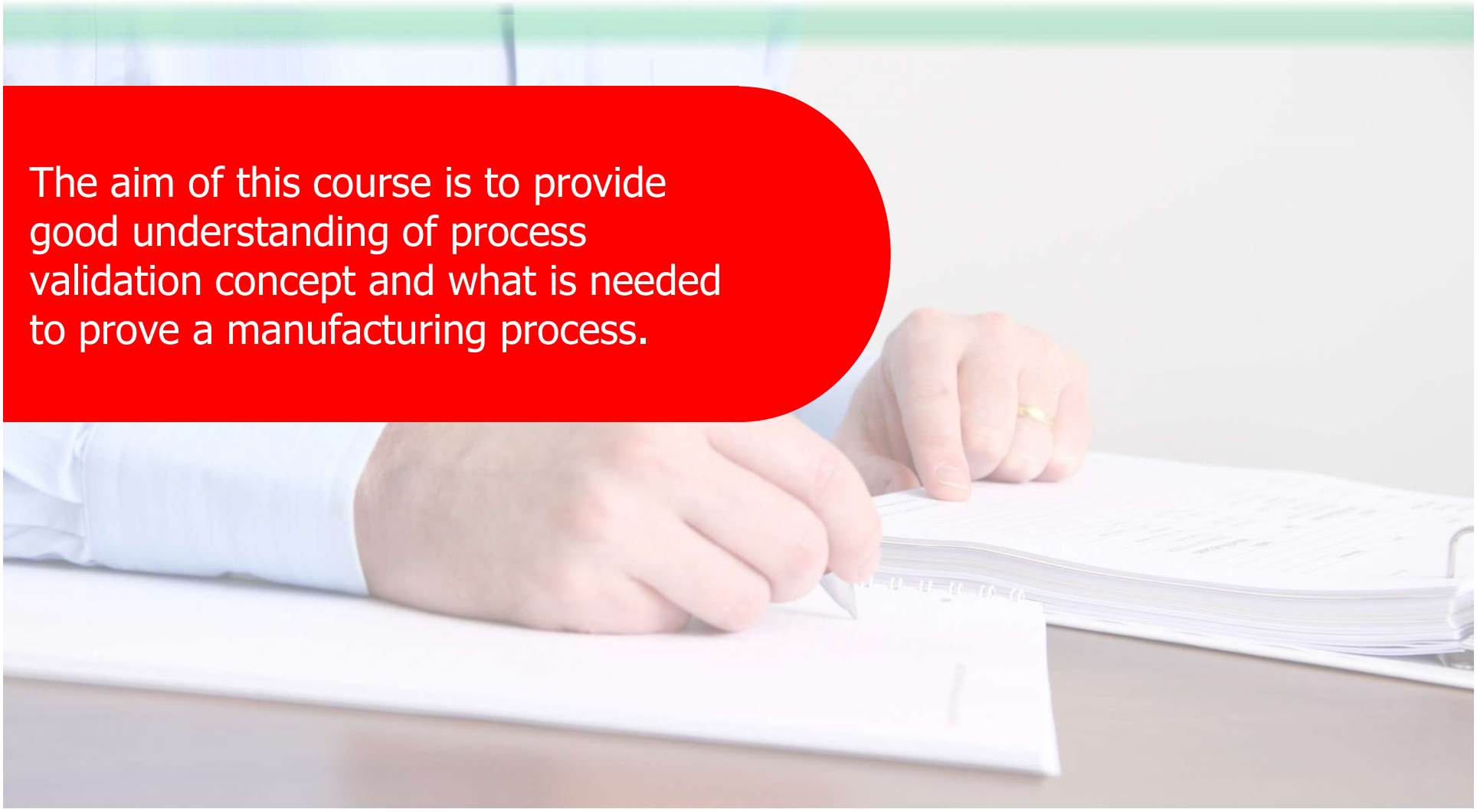


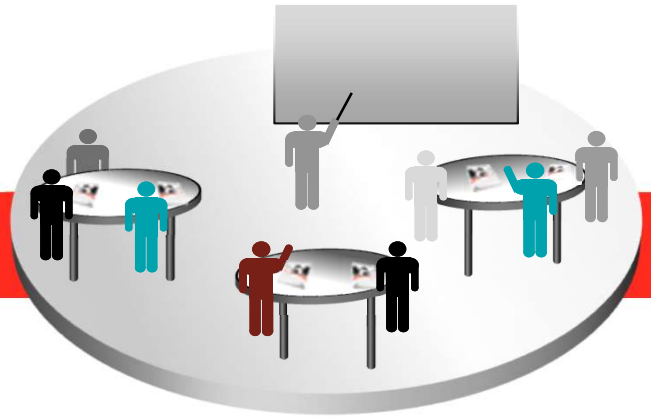
Course aim



The aim of this course is to provide good understanding of process validation concept and what is needed to prove a manufacturing process.

Objectives

Knowledge



Upon completion of this course, delegates will be able to:

- Appreciate concepts and rationale of process validation
- Gain awareness of IMDRF guidance
- Recognize the importance of process validation
- Recognize situations where a process requires validation
- Complete installation, operational and performance qualification
- Maintain a state of validation

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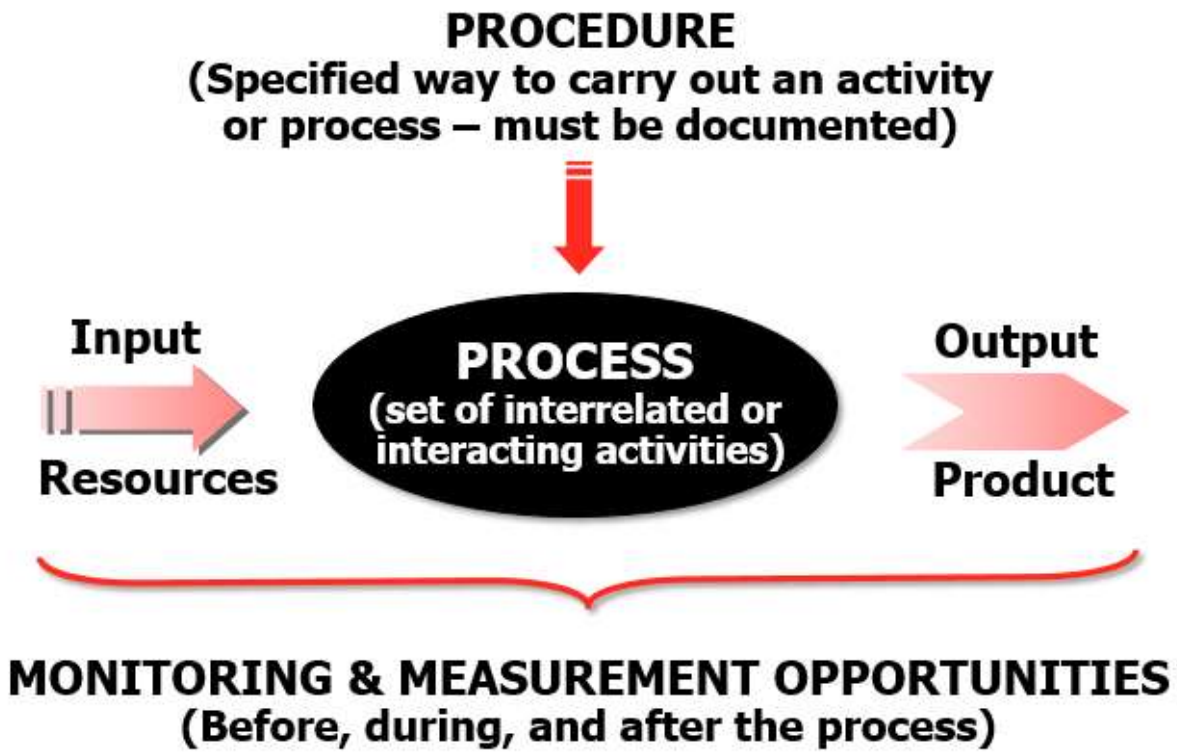
Process Validation

Overview and definitions

What is a Process?

A process is one or more activities, subject to controls, which use resources to transform inputs to outputs



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What is Validation?

Systematic method to demonstrate that a process produces consistent output over time

Plan ✓

At the process ✓

This is not <u>just</u> paperwork for a quality system

What is Process Validation?

- Term used in the medical device industry to indicate that a process has been subject to such scrutiny that the result of the process can be practically guaranteed

- Validation of a process entails demonstrating that, when a process is operated within specified limits, it will consistently produce product complying with predetermined design and development requirements

GHTF/SG3/N99-10:2004 – Edition 2, available on IMDRF website

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Why Validate?

- Regulatory / legal requirement
- Enhance quality
- Eliminate scrap
- Reduce cost
- Increase customer satisfaction
- Process control
- Consistency of product
- Improve overall quality

Process Validation Terminology

- Installation Qualification (IQ):
  - *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 recommendations of the supplier of the equipment are suitably considered.*
- Operational Qualification (OQ):
  - *establishing by objective evidence process control limits and action levels which result in product that meets all predetermined requirements.*
- Performance Qualification (PQ):
  - *establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.*

IMDRF Definitions, *GHTF/SG3/N99-10:2004 (Edition 2)*

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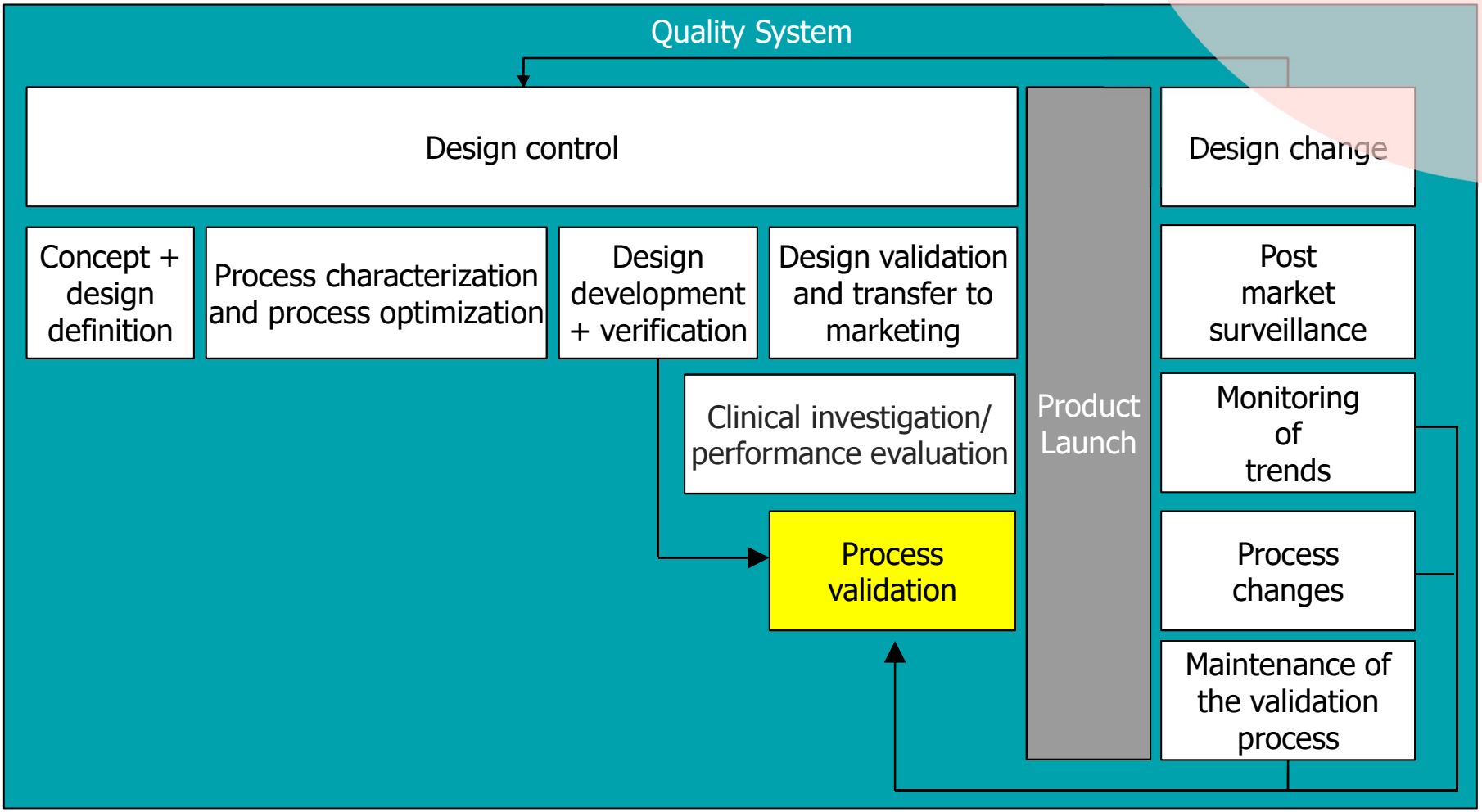
Process Validation

Regulations, Standards and Guidance

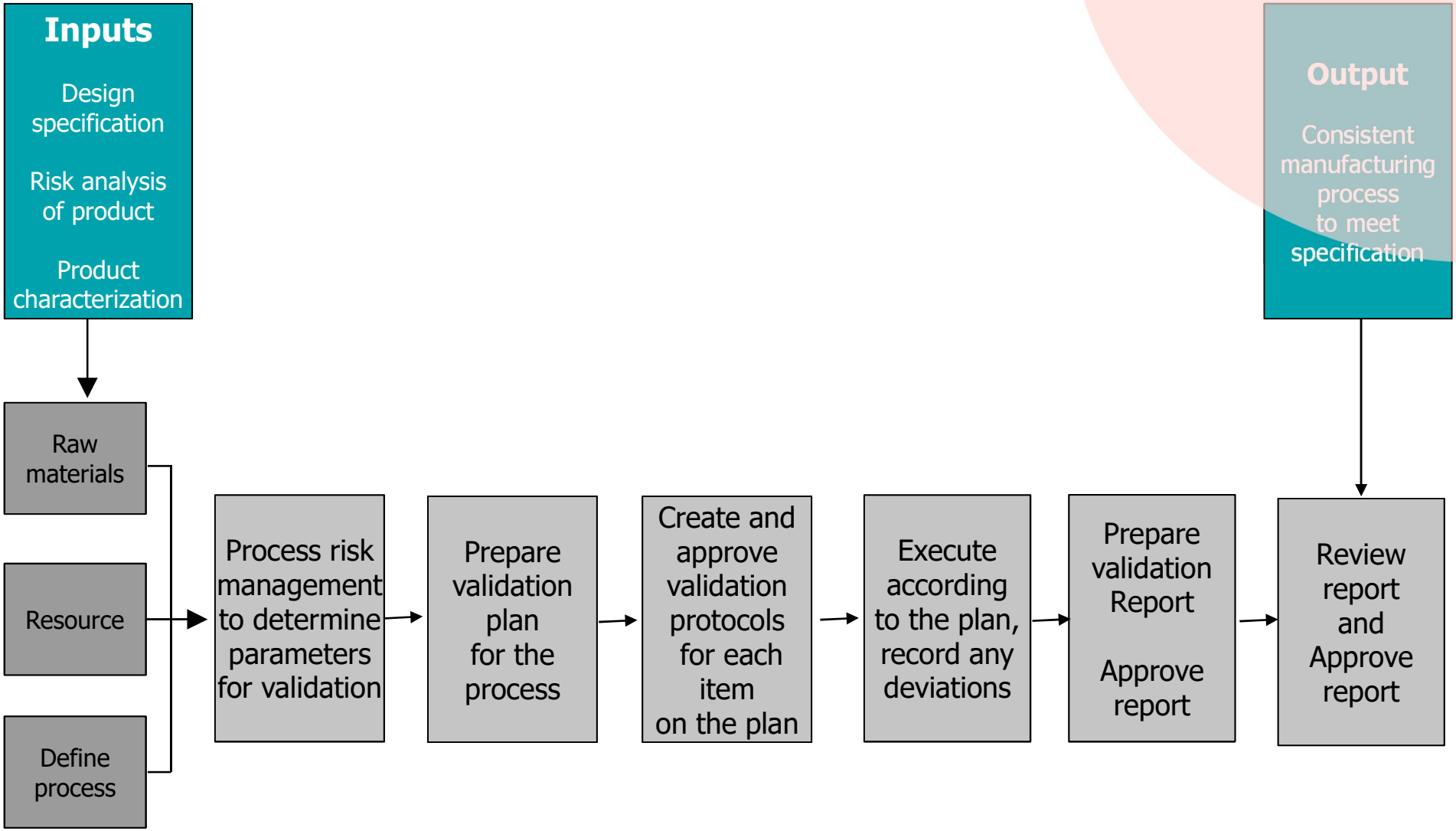
Process Validation and the Quality Management System

Process validation is part of the integrated requirements of a quality management system.

Process Validation and the Quality Management System



Process Validation



Approach to Process Validation

- ✓Form a multi-functional team to plan and oversee the validation activities
- ✓Plan approach and define requirements
- ✓Identify and describe processes
- ✓Specify process parameters and desired output
- ✓Decide on verification and or/validation
    - Create a Validation master plan
    - Select tools and methods for the validation
    - Create validation protocols
    - Perform IQ, OQ and PQ and document results
    - Determine continuous process controls

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When is Validation Required?

Validation vs. Verification

Validation versus Verification

Verification

- Confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled

Process validation

- Establishing by objective evidence that a process consistently produces a result or product meeting its pre-determined requirements

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Validation versus Verification

- Verification often destroys the product
- For a process to be fully verified this may mean that all the product is destroyed as 100% testing would be required
- Some manufacturers validate many processes in order to maintain high quality without endless testing- fully validated/verified

When do you Validate?

- Process output cannot be verified by 100% inspection and test
- Process output can only be verified by destructive testing
- Process improvement and reduce cost
- Special or critical process:
  - Sterilization
  - Heat treating
  - Injection molding
  - Electro-Plating or polishing
  - Gluing, bonding or welding assemblies

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Types of Validation

Prospective, Retrospective and Concurrent

Types of Validation

- **Prospective**
  - Performed after the product is fully developed and prior to manufacturing the device
- **Concurrent**
  - Concurrent validation is a subset of prospective validation and is conducted with the intent of distributing product that has been manufactured in the validation
- **Retrospective**
  - Performed on existing processes where sufficient data is available to demonstrate that the process is in control

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Validation Plans

Preliminary Considerations

- Validation must be undertaken within the overall scope of the Quality System, and with attention to specific aspects appropriate to the technology under study
- Detailed protocols for performing the validations are essential, to ensure a comprehensive study with meaningful and valid results
- Detailed Reports
- A cross functional team should be used for plans and protocols.

Preliminary Considerations

- Verify the validity of acceptance specifications:
  - Through testing and challenges

- Once demonstrated as acceptable, any changes to specification must be made using control procedures:
  - For example ECN – Engineering change notice system

- Check the process used at the development stage can meet the requirements for mass production.
    - Cost effective
    - Able to be validated
    - Meets output requirements
    - Meets quality requirements

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Process Validation Sequence

Validation Master Plans

- **Site MVP**
  - Used to overview site validation activities
  - May have list of planned activities.

- **Product MVP**
  - Combines the approach to validation of a product that may require validation of several processes, or processes for several components.

  - May control a variable which increases the risk to the product as multiple processing is performed. i.e. glove manufacturing process
    - Compounding process
    - Dipping process
    - Chlorination process

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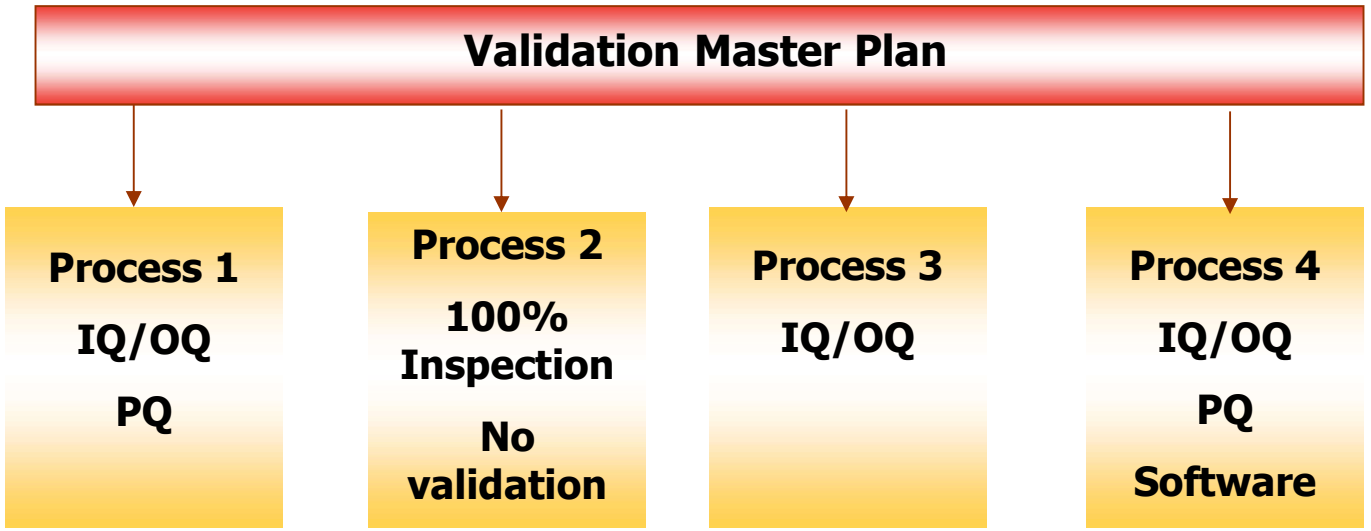
Validation Master Plans

Validation Master Plan (MVP)

- For complex or large systems a plan is established to define what process require validation and what validations will be performed (IO, OQ, PQ, Software)
- Define if a process is to be validated or verified
- Used to define the approach to validation for a site or product range as well as individual processes



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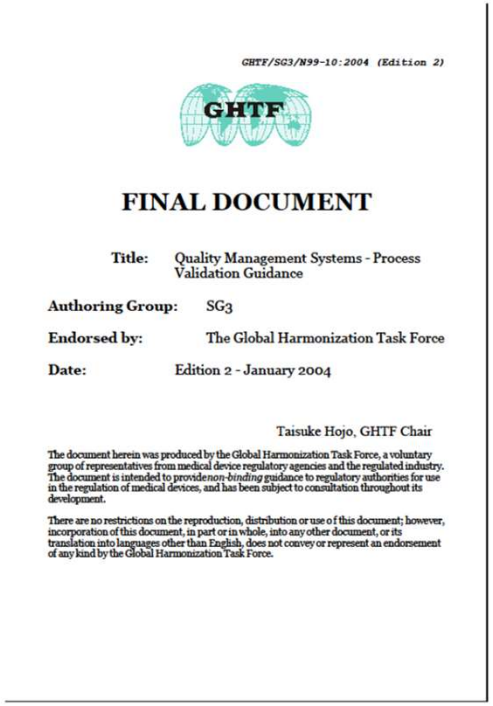
Statistics and Process Validation

IMDRF (was GHTF) Annex A

Process Capability: An introduction

- Process Capability is a method of *proving* a manufacturing process is capable of making a device and *practically guarantees* performance and safety
- It is a technique often used in process validation studies
- It is mentioned in IMDRF (GHTF) guidance



GHTF/SG3/N99-10:2004 (Edition 2)

GHTF

FINAL DOCUMENT

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Taisuke Hojo, GHTF Chair

The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide *non-binding* guidance to regulatory authorities for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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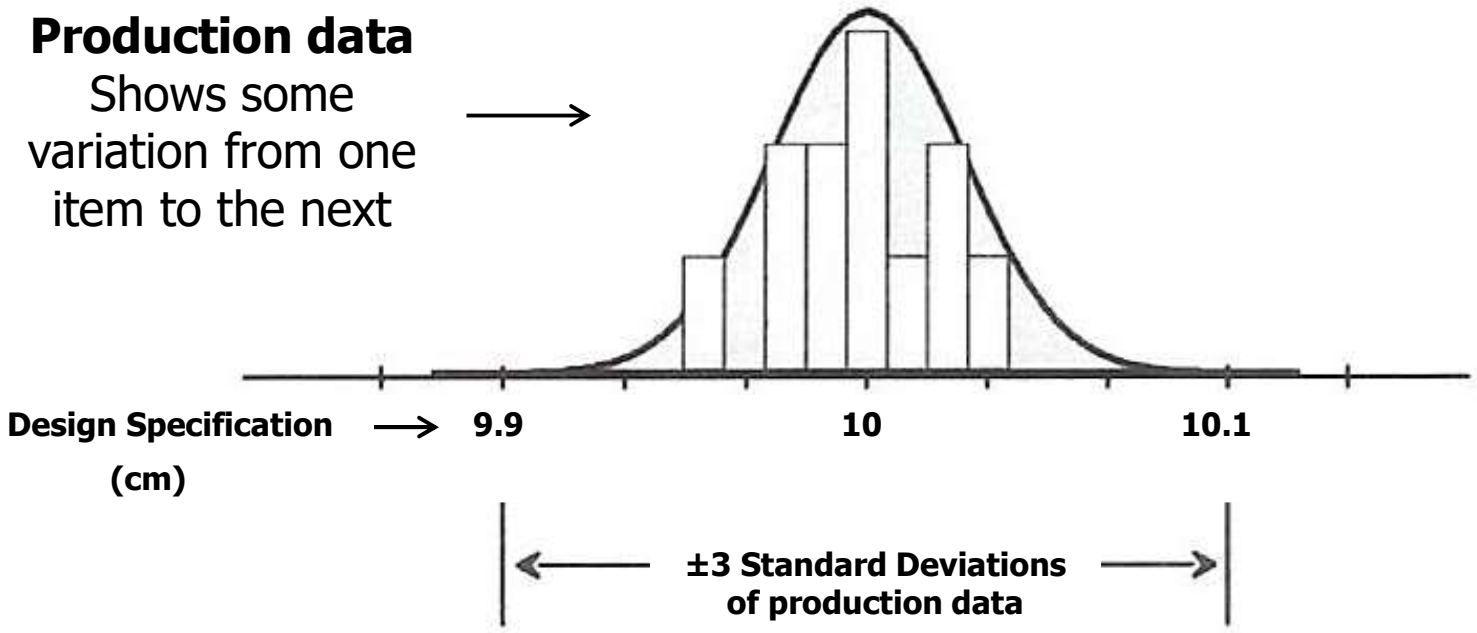
Process Capability: An introduction

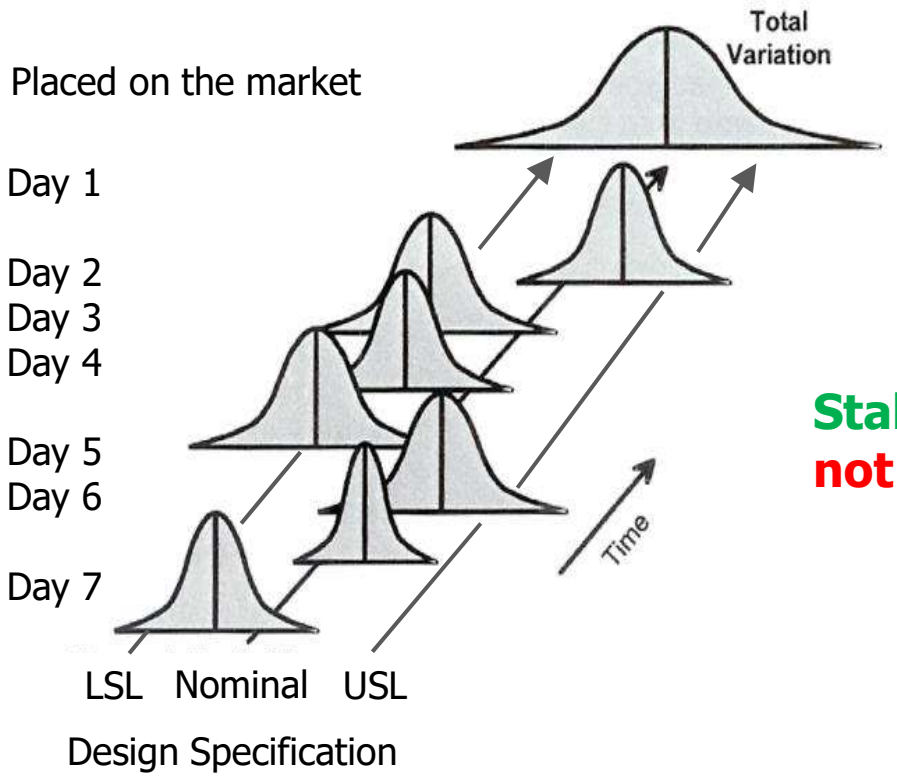
If production follows the normal distribution curve then 99.73% of what is made falls within ±3 Standard Deviations.



Process Capability

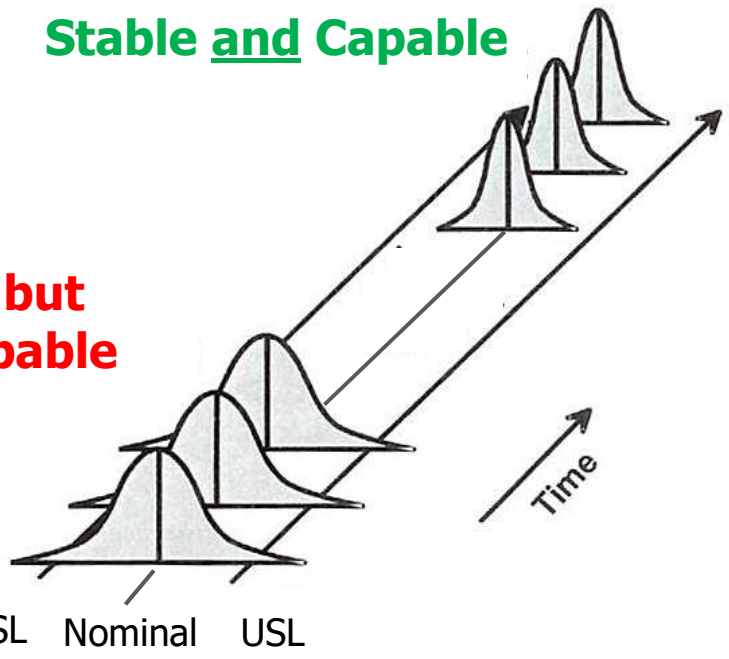
To achieve a capable and stable manufacturing process, variation needs to be reduced to well within design limits, and be central

Unstable Process



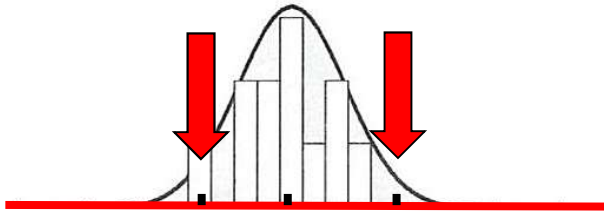
Stable and Capable

Stable but not capable



Evaluating Process Capability

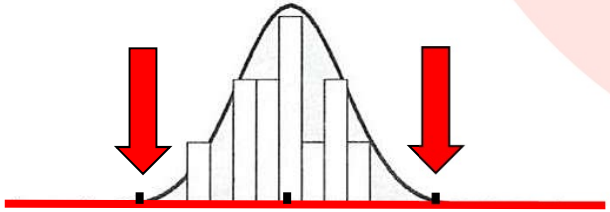
- Cpk compared to the engineering specification.



9.9 10 10.1

LSL Nom USL

Cpk <1



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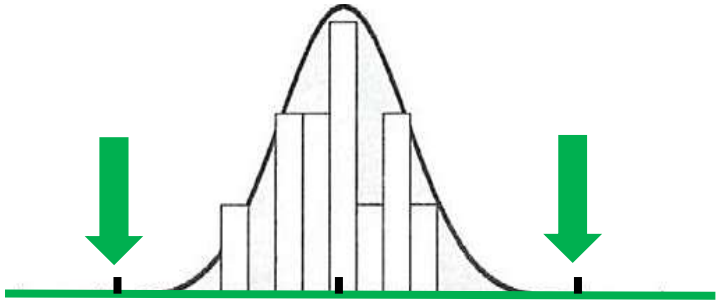
LSL Nom USL

Cpk = 1



9.9 10 10.1

LSL Nom USL

Cpk >1

Common starting point Cpk=1.33

Sampling

Sampling has its risks, that need to be understood whenever a sample is taken:

Ensure the sample is:

- **Representative of all the 6 Ms**: man, machine, material, measurements, methods, Mother Nature (environment)
- From a process in statistic control (stable and variation generally random)

If all samples taken are within limits but spread over the whole tolerance range, then Cpk is probably <1.

Risk based Process Validation

- Designers should identify all the key characteristics of the device that affect performance and safety
- All key characteristics to be defined in terms of nominal value and tolerance
- Using a cross functional team of the designers and manufacturing process experts, identify those parts of the manufacturing process that create the key characteristics
- Use risk analysis to identify all the process variables (time, temperature, pressure etc.) that cause those parts of the manufacturing process to change
- During OQ:
  - evaluate the sensitivity of the device key characteristics with respect to the process variables

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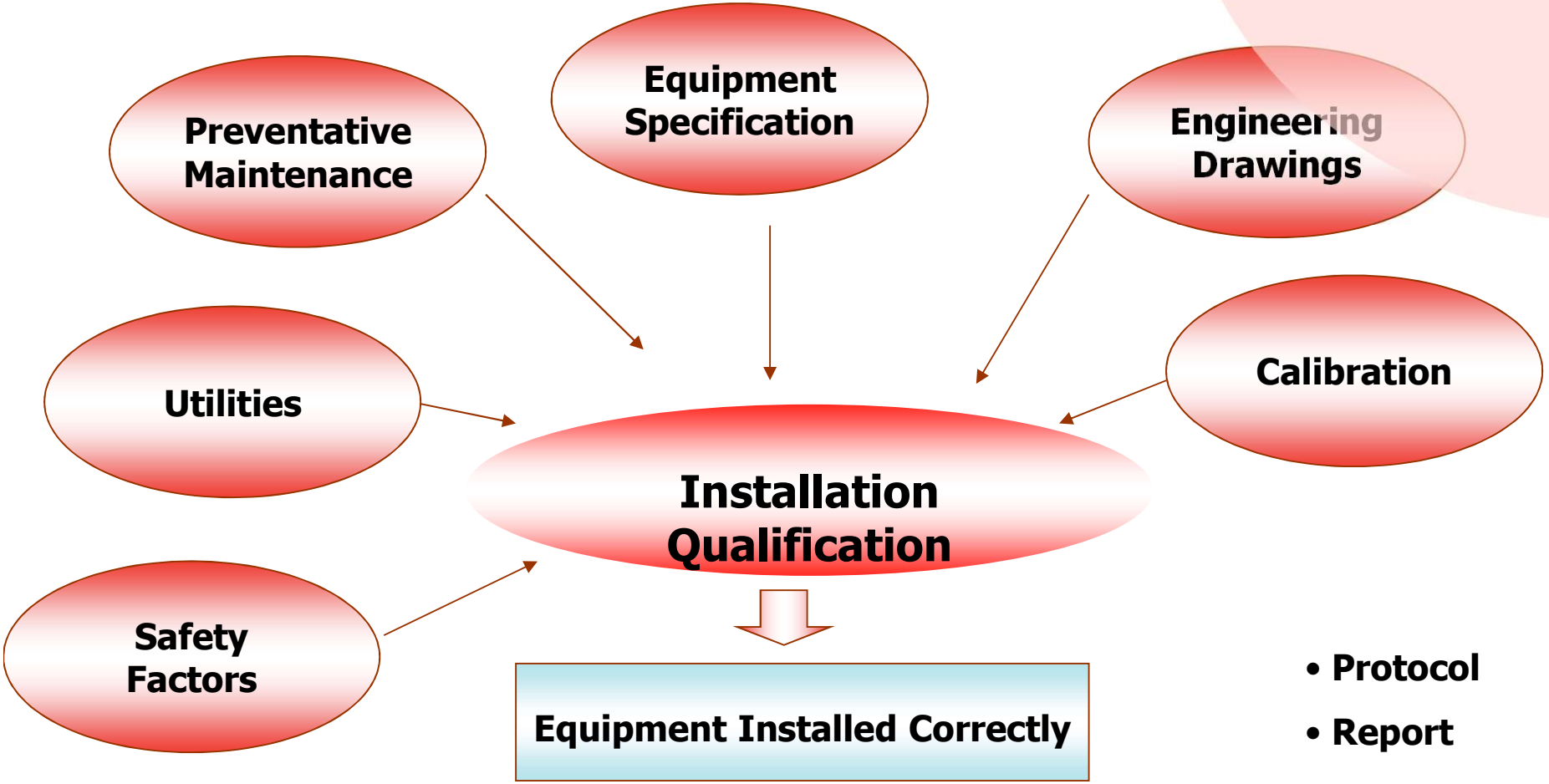
Protocol and Report Development

IQ,OQ,PQ

Installation Qualification



Installation Qualification

- Simply put, "IQ" means "It is installed correctly?"
- Installation qualification studies establish confidence that the process equipment and ancillary systems are capable of consistently operating to needed tolerances and established limits
- IQ usually takes the form of a checklist to establish is the equipment installed correctly and is a self contained protocol/report

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Installation Qualification

The IQ phase will address aspects such as:

- Equipment design features (materials, clean-ability, ergonomics)
- Supplier documentation (manuals, drawings)
- Installation conditions (power, compressed air, etc.)
- Maintenance requirements (PM, spare parts)
- Adjustment and/or calibration requirements
- Safety features (guards, operability)
- Critical features that affect process/product
- Spare parts list

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Installation Qualification

Some examples of equipment characteristics:

- Temperatures,
- Pressures, and
- Cycle times of injection molding machines
- Speed/rpm of mixers
- Temperature, dwell and cycle for ultrasonic weld
- Temperature, dwell and pressure for heat seal
- Temperature, pressure and cycle of sterilization chambers
- Temperature, vacuum and cycle for lyophilization unit

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Installation Qualification

- Utilize this information from the initial IQ evaluation to establish written procedures:
  - Equipment maintenance program
  - Set-up and/or adjustment instructions
  - Gauge and instruments calibration method
  - Operating parameter guidelines / control plans
  - Cleaning schedules

Installation Qualification

Finally, consider the implications of situations that change the original conditions, e.g.

- Relocating the equipment
- New utility services to existing equipment
- Emergency repairs and planned refurbishment
- Replacement of failed auxiliary equipment
- Replacement of tooling, molds, dyes
- Instrumentation adjustments / recalibrations.

Is revalidation required ?

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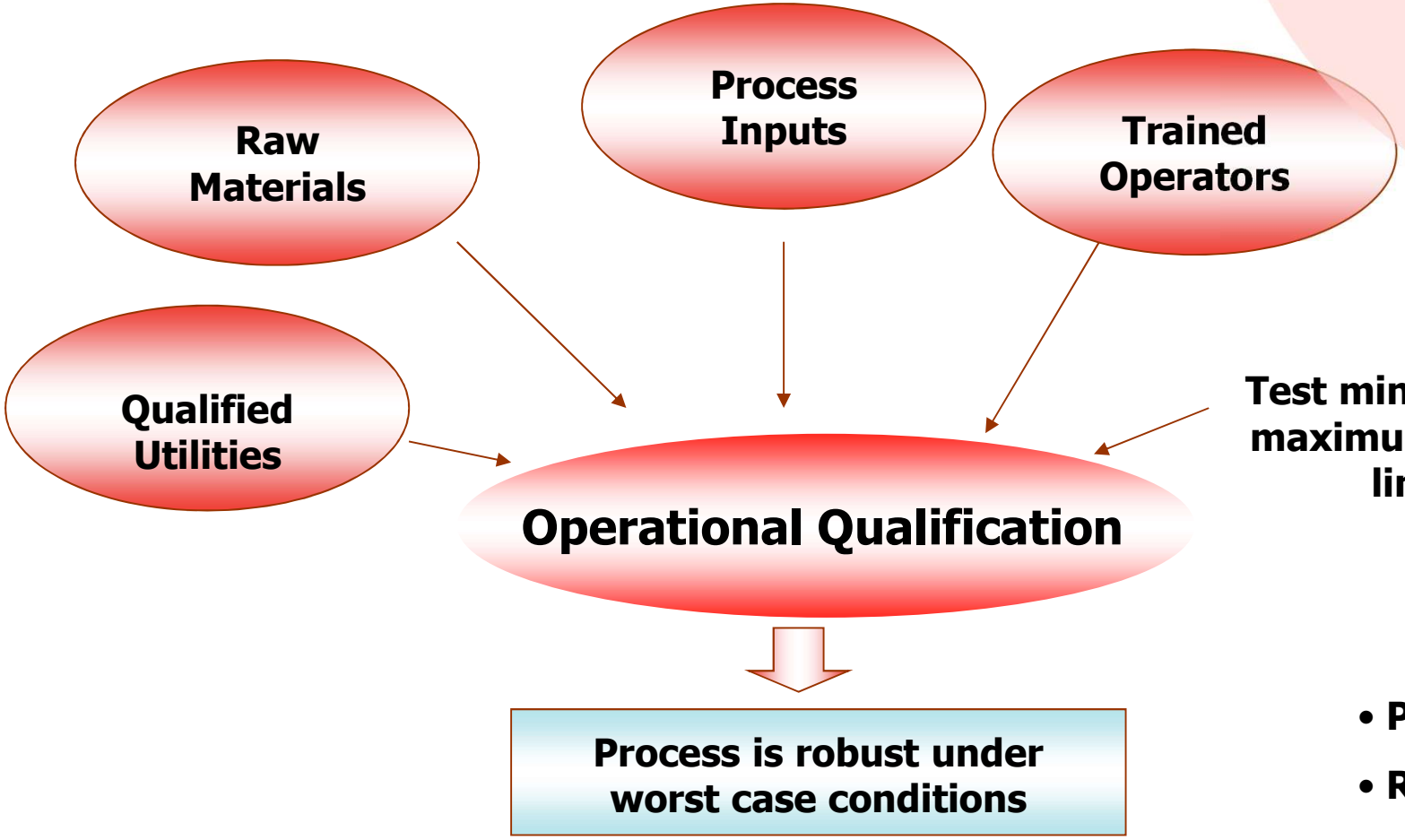
Operational Qualification



- Protocol
- Report

Operational Qualification

- An Operational Qualification challenges the process parameters to ensure that under "worst case conditions" and normal operating conditions that the equipment is capable of producing product that meets the predefined specifications

- Considerations:
  - Process inputs (temperature, time, pressure, line speed, set up)
  - Raw material specifications
  - Operating procedures
  - Training
  - Process stability and Control
  - Potential failure modes.

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Operational Qualification

- Establish process parameters and windows:
  - Temperature range [low, mid, high]
  - Pressure range [low, mid, high]
  - Cycle or dwell times [short, nominal, long]
  - Conveyor belt speed [slow, nominal, fast].

Operational Qualification

- **Plastic injection:**
  - Injection speed
  - Injection pressure
  - Cycle time
  - Clamp force

- **Production of disinfections by aseptic filling—aspects to challenge:**
  - Sterilization and removal of pyrogens (substance which produces fever) of containers/closures
  - Sterilization of solutions
  - Sterilization of filling equipment, product contact surfaces
  - Filling and closing of containers

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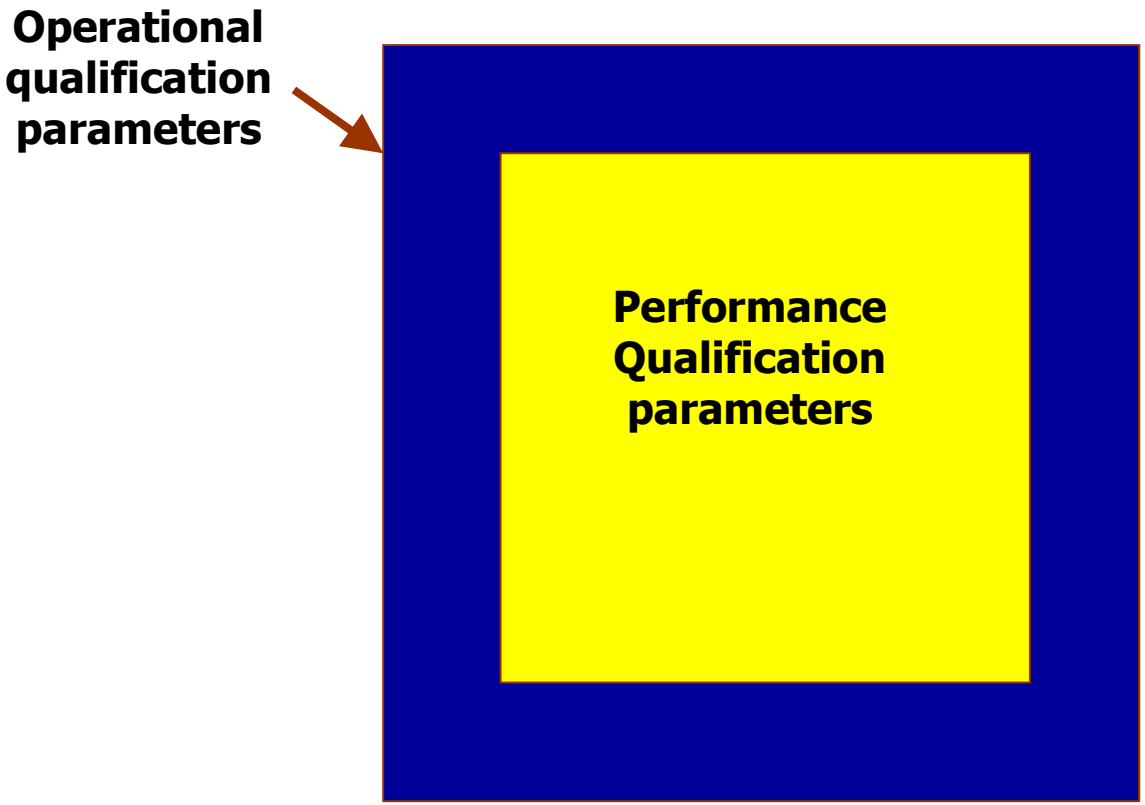
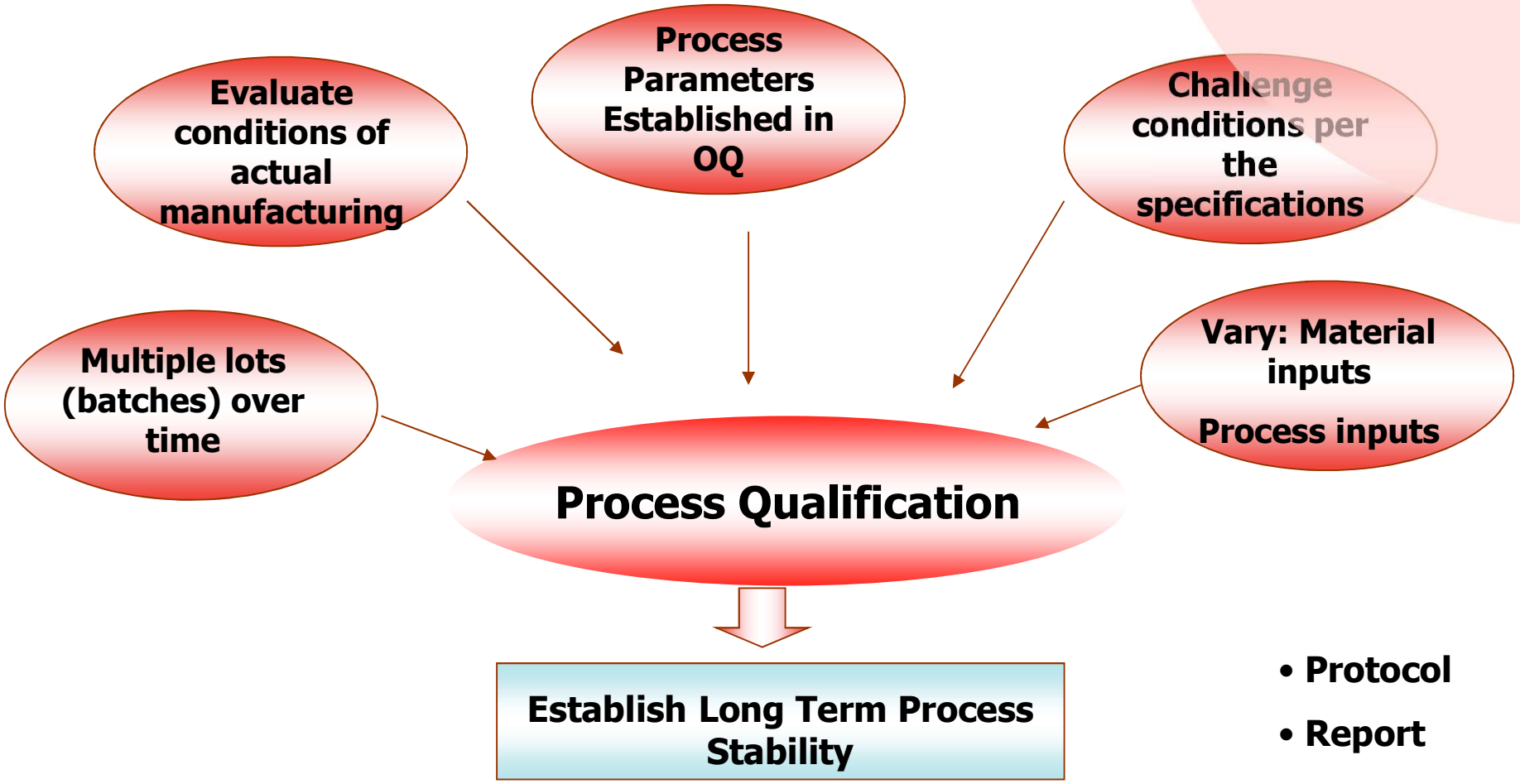
Relationship of OQ to PQ



Performance Qualification



- Protocol
- Report

Performance Qualification

- At this point, the IQ and the OQ will have been completed and deemed acceptable.
- GOAL of the PQ: long-term performance qualification
- Over the long-term, a process will see a wider range of variation (common cause), such as:
  - Material lot changes
  - Utilities fluctuations
  - Environmental temperature/humidity swings
  - Different shifts / different operators
  - Routine cleaning, housekeeping

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Performance Qualification

The PQ should demonstrate that:

- The process will consistently produce acceptable product
- The process does not adversely affect finished device production
- Statistical methods should be used to prove product meets specifications and all quality requirements

Performance Qualification

The PQ should demonstrate that:

- PQ should be conducted under conditions that simulate actual production:
  - Identical equipment as used in production
  - Same methods and procedures
  - Same personnel normally operating the machines

Performance Qualification

A formal technical review should be conducted as final step of the PQ stage:

- After actual production units have passed the PQ
- Comparison of the agreed product specifications to the actual product qualified
- Review the validity of test methods used to determine conformance to specifications
- Ensure the adequacy of the specification change control program

The Validation Protocol

For all three phases—IQ, OQ and PQ, the Validation Protocol should include a determination of:

- WHAT to verify, measure, monitor
- HOW to verify, measure, monitor
- HOW MANY to verify, measure, monitor (for statistical significance)
- WHEN to verify, measure, monitor
- Acceptance criteria, and rejection criteria
- Required documentation

The Validation Protocol

Detailed protocols for performing the validations are essential, to ensure a comprehensive study with sound and valid results

Process validation protocols should include:

- Identification of the processes to be validated
- Identification of the device (or family of devices) to be manufactured using this process
- Objective and measurable criteria for successful validation
- Length and duration of the validation study
- Equipment, shifts, operators to be used in the study
- Identification of utilities needed for the equipment
- Identification of operators and operator qualifications

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The Validation Protocol

Process validation protocols should include:

- Complete description of the process
- Relevant specifications that relate to product, materials and components
- Special controls or conditions placed on the process
- Process parameters to be monitored
- Methods for controlling and monitoring parameters
- Product characteristics to be measured
- Method for measurement of product characteristics
- Any subjective criteria used to evaluate product
- Definition of “acceptance” and non-conforming

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The Validation Protocol

- Process validation protocols should include:
  - Statistical methods to be used for data analysis
  - Maintenance aspects
  - Criteria for re-validation

How to Report Results

- Outline of (OQ/PQ):
  - Objective
  - Equipment
  - Reference Documents
  - Procedure
  - Acceptance Criteria
  - Results
  - Analysis and Discussion
  - Conclusion

Validation Non Conformance

When the requirements of the plan/protocol are not met

- Investigation to determine the cause of the failure
  - Have all the OQ's or PQ's been defined?
- Corrective action which may lead to the repeat of the characterisation of the process and repeat of the validation
- This would be detailed in the validation report

Maintaining a State of Validation and Revalidation

Maintaining a State of Validation

- Monitoring of the trends of the process to ensure that the process is within the established parameters
- Consideration of validation if a change is made to the process

Revalidation

Instances and reasons for revalidation:

- Significant changes in the process that will likely affect quality
- Changes that affect the validation status
- Negative trend in quality indicators
- Significant changes in product design that affect the process
- Transfer of process/equipment from the facility
- Relocation of equipment within a facility
- Change of the application of the process
  - Revalidation may not be as extensive as original validation activities
  - Link to Risk Management

Review and Reflect

Consider what can go wrong with process validation:

- Protocol not approved before use
- Test method validation not completed before Process Qualification
- Training of personnel
- Final manufacturing process and equipment not used
- Process not characterized
- Process Validation not completed in the manufacturing environment
- PQ larger than OQ.

Reflective quiz

...making excellence a habit.™