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nibrt
National Institute for Bioprocessing Research and Training

# Biopharma Validation
# Lecture 1 – Introduction

# Introduction

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- Previous: Upstream Bioprocess Technician – Pfizer Biopharma
- MSc Bioprocess Engineering, BSc Genetics & Cell Biology
- MSc Commissioning, Qualification, and Validation for Biopharmaceutical Manufacturing
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# Module Breakdown

- Number of lectures
  - 9 lectures
  - All lectures will be live. Recording of lecture will be available soon after.
  - Lecture slides will be available on Moodle each week
  - No lecture on an assessment week
  - No lecture during Easter break
- Assessment details
  - Details/topic will be given next week
  - Dates shown on next slide
  - **Reminders will be sent to the email address registered with your IT Sligo account and on Moodle in advance of assessments. It is your responsibility to monitor these.**

# Schedule

| Week Number | Dates | Lecture Day & Time: Wednesdays 6 - 7pm |
|---|---|---|
| 1 | Jan 22nd | Lecture 1: Course Overview |
| 2 | Jan 29th | Lecture 2 |
| 3 | Feb 5th | Lecture 3 |
| 4 | Feb 12th | MCQ 1 10% |
| 5 | Feb 19th | Lecture 4 |
| 6 | Feb 26th | Lecture 5 |
| 7 | Mar 5th | Lecture 6 |
| 8 | Mar 12th | MCQ 2: 10% |
| 9 | Mar 19th | Lecture 7 |
| 10 | Mar 26th | Lecture 8 |
| 11 | Apr 2nd | Lecture 9 |
| 12 | W/C Apr 7th | Easter Break |
| 13 | Apr 16th | LAQ 30% |
| 14 | Friday Apr 25th | Project reports due (40%) |
| 15 | Monday Apr 28th | Project Presentations Due (10% |

- If you cannot do an MCQ/LAQ on the specified date, **you must give advance notice!!**
- **Failure to do so may result in a penalty!**

Understand the concepts of Commissioning, Qualification, & Validation in Biopharmaceutical production

Be aware of the different regulatory bodies and guidelines in Europe and USA associated with process validation

Compare traditional and modern Process Validation strategies

# Important to Note...

- There is no set process validation method. A process must be proven to be validated, but the pathway to that proof can differ.
- This can make the overall concept and process confusing and difficult to understand.
- There are some newer approaches and some older approaches, and some in-between.

# What is Process Validation?

- In simple terms…..
  - Proof that a process is capable of consistently performing its intended functions…

- In even simpler terms….
  - Proof that a process can do what it is supposed to do….

- It involves the systematic study of systems, facilities, and processes aimed at determining whether they perform their intended functions adequately and consistently as specified.

# Topics

- Introduction to Process Validation
- Introduction to Commissioning, Qualification, and Validation
- CQV – Traditional Approach
- CQV – Risk Assessment & Continuous Verification Approach

# Validation

*"It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process"* (EU GMP Annex 15)

- In the context of biopharma manufacturing, "validation" can refer to:
  - The drug manufacturing process as a whole (Process Validation)
  - A section of a process (e.g. Upstream, Downstream)
  - Utilities used within the main production process (e.g. Cleaning/Sterilization Validation)
  - Computerized systems (CSV)
  - Analytical methods (e.g. QC lab)
  - The entire facility

# Process Validation (EU vs USA)

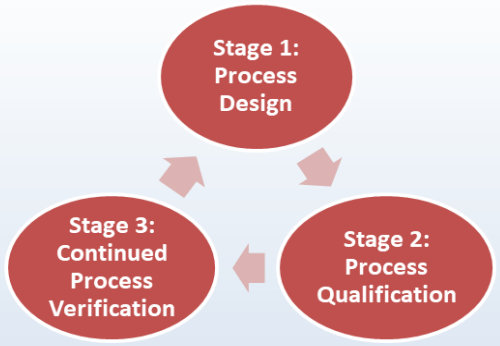

"Process validation is defined as the **collection and evaluation of data**, from the process design stage through commercial production, which establishes scientific evidence that a **process is capable of consistently delivering quality product**."


"Process validation is the **documented evidence** that the process, operated within established parameters, can **perform effectively and reproducibly** to produce an active substance or intermediate meeting its **predetermined specifications and quality attributes** (ICH Q7)."

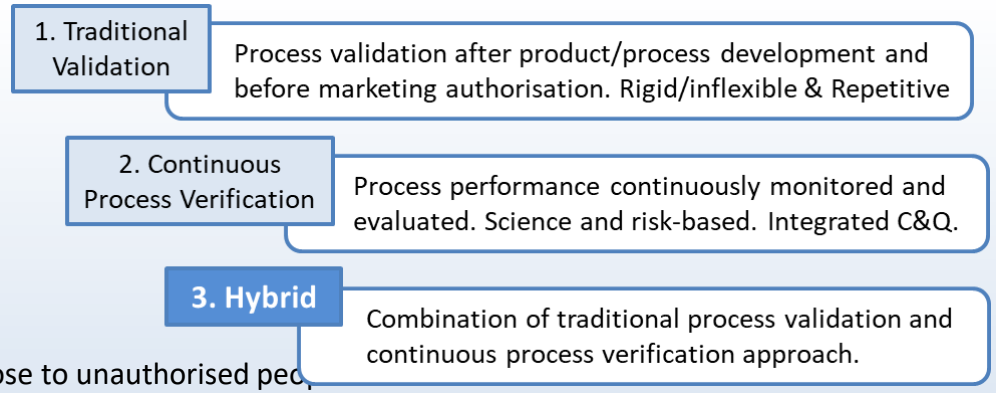
**Keywords:** Collection and evaluation of data / documented evidence, consistently / reproducibly, **Quality!**

# Process Validation: FDA vs. EMA

| FDA |
| --- |
| FDA's 2011 Guidance on Process Validation: General Principles and Practices |
| Developed in conformance with ICH Q8, Q9 and Q10 |
| Defines Process Validation activities in 3 Stages:<br>1. Process Design, 2. Process Qualification, & 3. Continued Process Verification |
| Encourages Continued Process Verification |




| EMA |
| --- |
| 1. Guidelines for GMP Annex 15: Qualification and Validation<br>2. Guideline for Process Validation of Biotechnology-Derived Products<br>3. Guideline for Process Validation for Finished Products |
| Developed in conformance with ICH Q8, Q9 and Q10 |
| Some guidelines mention the 3 Stages of Process Validation.<br>Other guidelines mention 2 Stages: 1. Process Characterisation 2. Process Verification.<br>Annex 15 does not explicitly mention stages. |
| Mentions that a Hybrid Approach between Traditional Validation and Continuous Process Verification is acceptable |



# Process Validation

- The underlying requirements for process validation are the same for both the FDA and EMA:
  - Science and risk-based.
  - Identify Critical Quality Attributes (CQAs) of the product.
  - Identify the Critical Process Parameters (CPPs) which affect the CQAs.
  - Understand the impact of variability and set operating ranges for CPPs.
  - Establish a statistically-appropriate, real-time monitoring and control strategy.
  - Demonstrate a high-level of process understanding and justify all decisions.
  - Integrate protocols and systems for trend analysis.
  - Provide evidence of continuous adherence.

# Some Key Guidance Documents Over the Years

- **ISPE Baseline® Guide: Volume 5 (1st Edition) – Commissioning and Qualification (2001)**
  - ISPE's first guide to C&Q. Defined a better understanding of baseline cGMP requirements for a lifecycle approach to C&Q. Widely adopted and still referenced, but pre-dates ASTM's risk-based guide of 2007.

- **ASTM E2500-07 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Systems & Equipment" (2007)**
  - This document was the first time a science- and risk-based approach to CQV was formally introduced. The guide focused on Quality by Design based on risks to product quality and patient safety, as well as integrated C&Q (where applicable) termed "Verification".

- **ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems and Equipment (ISPE FSE Guide) (2011)** ***and*** **ISPE Good Practice Guide: Applied Risk Management in Commissioning and Qualification (2011)**
  - These two guides were released by ISPE following the release of the ASTM guide in 2007 to provide some additional guidance which references the modern risk-based thinking.

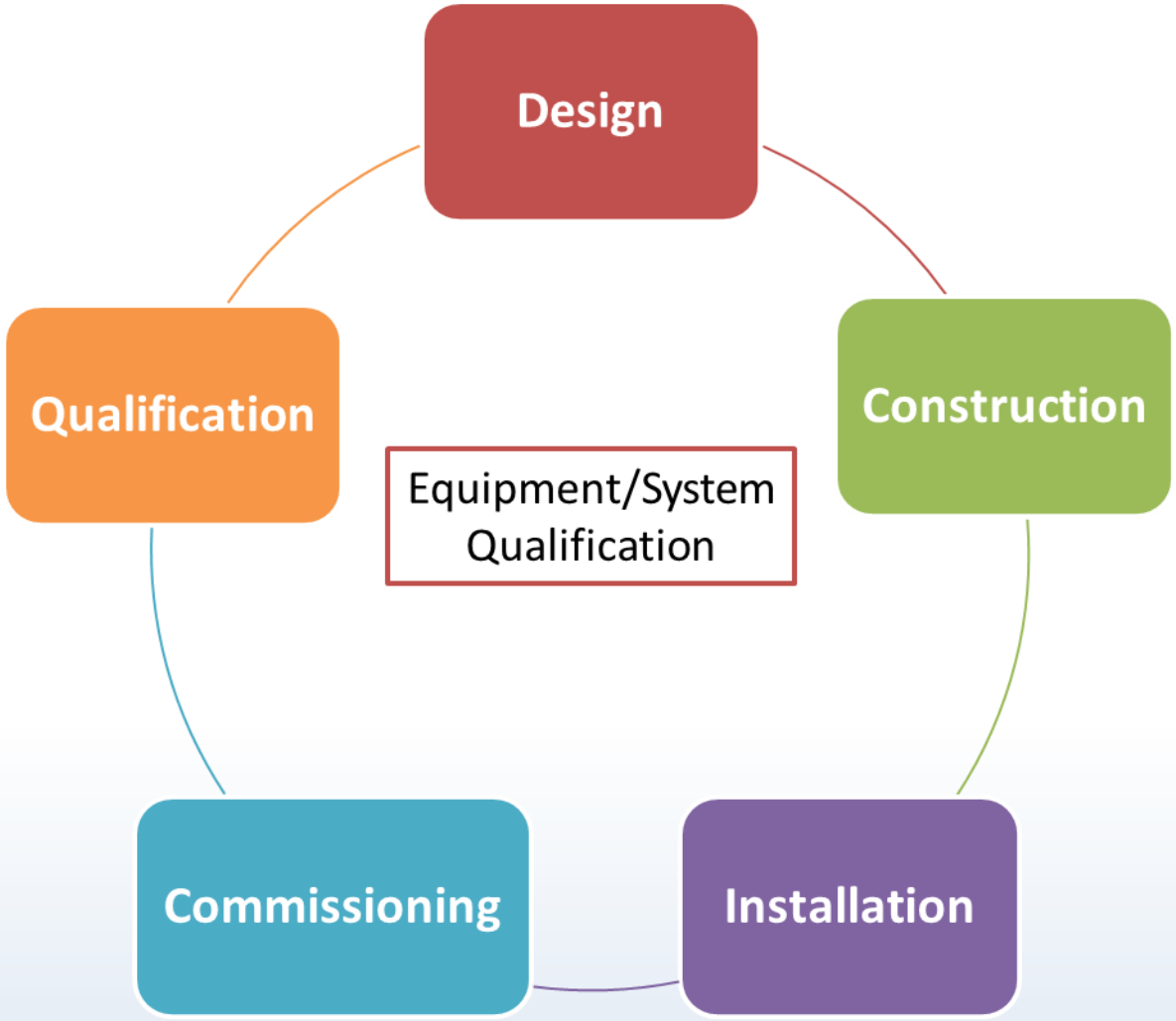
- **ISPE Baseline® Guide: Volume 5 (2nd Edition) – Commissioning and Qualification (2019)**
  - A simplified, risk-based C&Q guide that meets present-day standards and provides focus for compliant, efficient, and cost-effective C&Q. This guide supersedes the 1st edition ISPE Baseline 5 guide and the two 2011 ISPE guides outlined above.

# Topics

- Introduction to Process Validation
- Introduction to Commissioning, Qualification, and Validation
- CQV – Traditional Approach
- CQV – Risk Assessment & Continuous Verification Approach

# Qualification vs. Validation

- Before a drug manufacturing process can be considered “validated” all individual equipment, systems, facilities, and utilities must be Commissioned and Qualified, as appropriate.
- Commissioning ensures that equipment is suitable, safe, and functional.
- Qualification ensures that equipment/systems can do their job in the process.



# 1. Commissioning

**Commissioning:** *"a well planned, documented, and managed engineering approach to the* ***start-up and turnover of facilities, systems, and equipment to the end-user*** *that results in a safe and functional environment that meets established design requirements and stakeholder expectations"*
(ISPE)

Effective commissioning:

- Verifies correct construction, installation, and safe function of equipment.
- Ensures user requirements are met prior to moving to qualification.
- Supports engineering and qualification success.
- Leads to a focused and "first-time-success" validation effort.

Commissioning focuses on Good Engineering Practices (GEP)

# 2. Qualification

**Qualification:** *"the demonstration of **suitability for intended use** which has been formally documented and approved"* (ISPE)

1. Design Qualification (DQ): *"The documented **verification** that the **proposed design** of the facilities, systems and equipment **is suitable for the intended purpose**"* (EMA).

2. Installation Qualification (IQ): *"The documented **verification** that the facilities, systems and equipment, **as installed or modified**, comply with the **approved design and the manufacturer's recommendations**".* (EMA).

3. Operational Qualification (OQ): *"The documented **verification** that the facilities, systems and equipment … **perform as intended throughout the anticipated operating ranges**."* (EMA).

4. Performance Qualification (PQ): *"The documented **verification** that the equipment and ancillary systems can **perform effectively and reproducibly** based on the approved process method and product specification"* (EMA).

# System Classification

All systems require Commissioning to establish that they are safe and functional. However, not all systems require Qualification.

Using System Impact Assessments (SIA), systems are classified as
(ISPE Baseline Guide 5, 2nd edition):

1. **Direct Impact:** has “a direct impact on product quality” and is therefore Commissioned **AND** Qualified (e.g. bioreactor, WFI).

2. **Not Direct Impact:** does not have “a direct impact on product quality” and is Commissioned only (e.g. plant steam, Instrument Air)

# Integrated Commissioning & Qualification

Many commissioning activities support qualification:

- Inspection activities support and are similar to IQ.
- Basic functionality tests are similar to OQ testing.
- Factory Acceptance Tests (FATs) and Site Acceptance Tests (SATs) support the overall qualification effort.

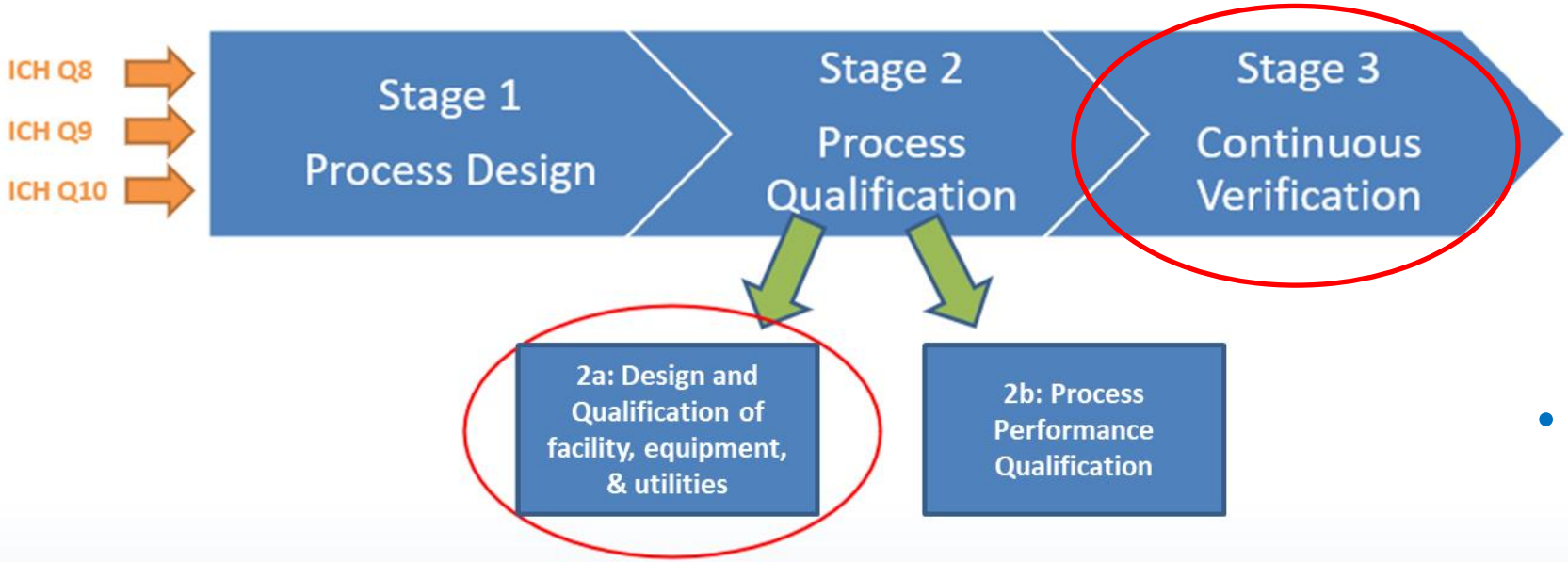
Recent guidance's emphasise that Commissioning and Qualification should therefore be integrated/leveraged where appropriate – don't do things twice!

**Commissioning and Qualification (C&Q):** *"the process for establishing that facilities, systems, utilities, and equipment are suitable for their intended purpose"*

- (ISPE Baseline Guide Volume 5, 2nd Edition)

# Where does C&Q fit in?

- Commissioning and Qualification typically fall under Stage 2 of the FDA Process Validation Lifecycle
  - After equipment is designed, and before product goes to market.




- When C&Q are integrated as per modern guidelines, the term “Verification” is often used to describe any of the testing carried out i.e. verifying that equipment is fit for purpose.
- However, this is not the same as “Continuous Verification”, which means verifying that the process remains in a validated state after marketing approval.

# 3. Validation

**Process Validation:** *"collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that* ***a process is capable of consistently delivering quality products****"* (FDA Guidance on Process Validation, 2011)

- Process Validation is usually demonstrated by producing several consecutive "**Process Performance Qualification (PPQ)" or "Validation"** batches on the fully qualified equipment and services.
- PPQ batches prove that the entire process, when operated under actual/simulated manufacturing conditions, can produce safe, acceptable, and repeatable outputs.
- Once this is proven, product can be sold on the market.
- The validated state of the process should then be Continuously Verified.

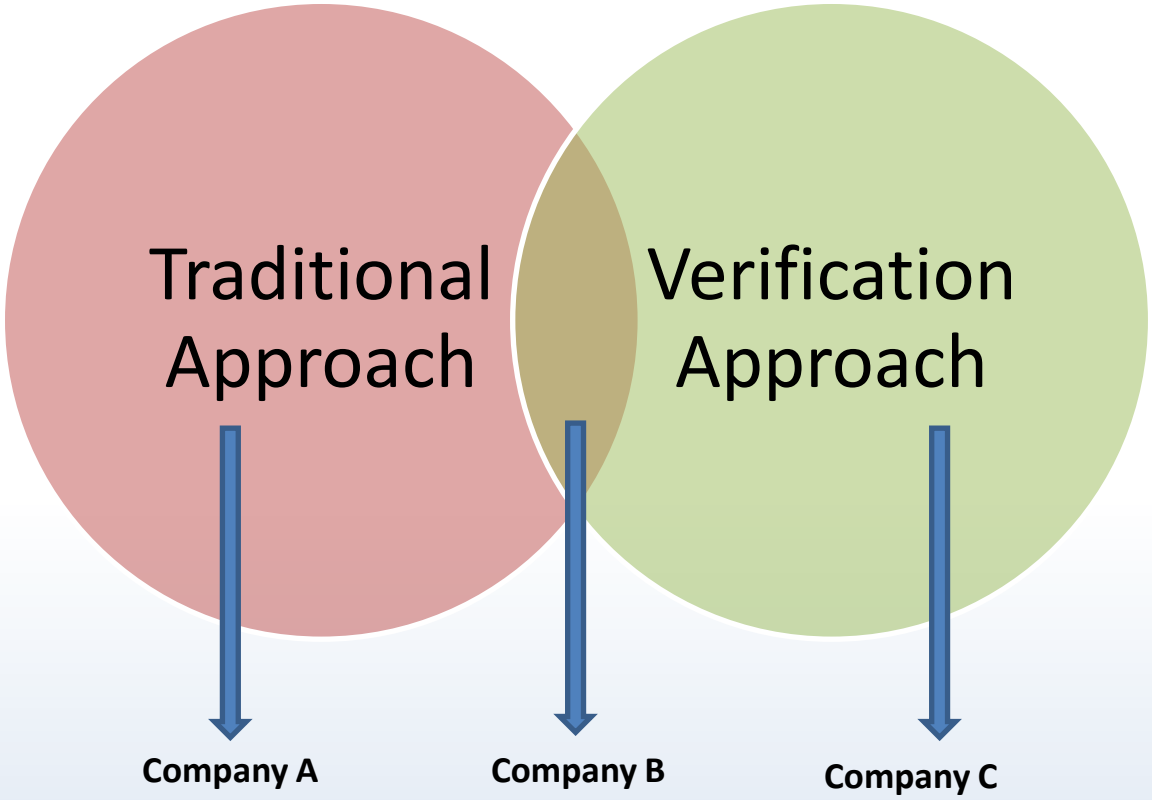
# Process Scale-up

- Some validation tests for the production scale process *may* be conducted on/leveraged from pilot scale batches.
  - The pilot batch size should correspond to at least 10% of the production scale (ICH), and the equipment must be justifiably similar.
  - Any decision to do this must be justified in advance and you must use science to explain why the test results will still be relevant at production scale.


https://www.repligen.com/technologies/opus

# CQV – Traditional vs. Continuous Verification

- Current guidelines emphasize a **Continuous** validation approach throughout the **lifecycle** of a drug.




- Verification approach (modern): focuses on risk and continuously verifying the validated state of the process.
- Traditional approach: focuses less on risk and verification, and more on failure impact and initial validation.
- The two approaches are very similar. The Continuous Verification model is a streamlined version of the Traditional model.

# Topics

- Introduction to Process Validation
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- CQV – Traditional Approach
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# 1. Traditional CQV

- Normally performed when process development is complete, after scale-up to production, and prior to marketing the finished product.
- Validation data should be provided in the marketing application on several consecutive batches at production scale (typically 3).
- Less focus on Quality by Design, Continuous Verification, and Risk Assessment than modern approaches.
- More focused on process functionality at a point in time and the impact of failure.
- The overall process is very repetitive and time-consuming.

# Traditional CQV – Impact Assessments

Impact Assessment: What *impact* does a system/component have on the product, or what would be the *impact* if it failed.

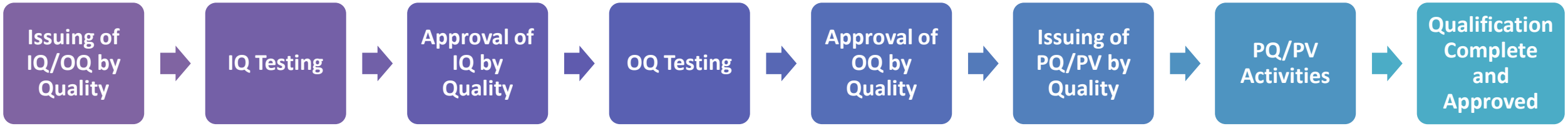
- In Traditional CQV, Impact Assessments alone dictate the scope of validation activities.
- The issue with Impact Assessments is that they do not (typically) consider probability of occurrence (i.e. risk) – some issues have high-product impact but are unlikely to occur.
- Large amounts of time can be spent focusing on problems that are highly unlikely to occur.

# Traditional CQV – Commissioning

- Commissioning: considered solely as an engineering activity that required no involvement from the quality/process team but *did* require QA sign-off before progressing through stages.
- Tests were carried out by engineers and results stored in Commissioning databases. Many tests were then repeated during Qualification.
- Commissioning was completed and systems were turned over to a separate Qualification team.
- A lack of overlap/integration between C&Q leads to slow progress, unnecessary repetition, and additional cost.

# Traditional CQV - Qualification

- A sequence of rigid stages, where one stage must be fully completed and signed-off by QA before the next stage begins.

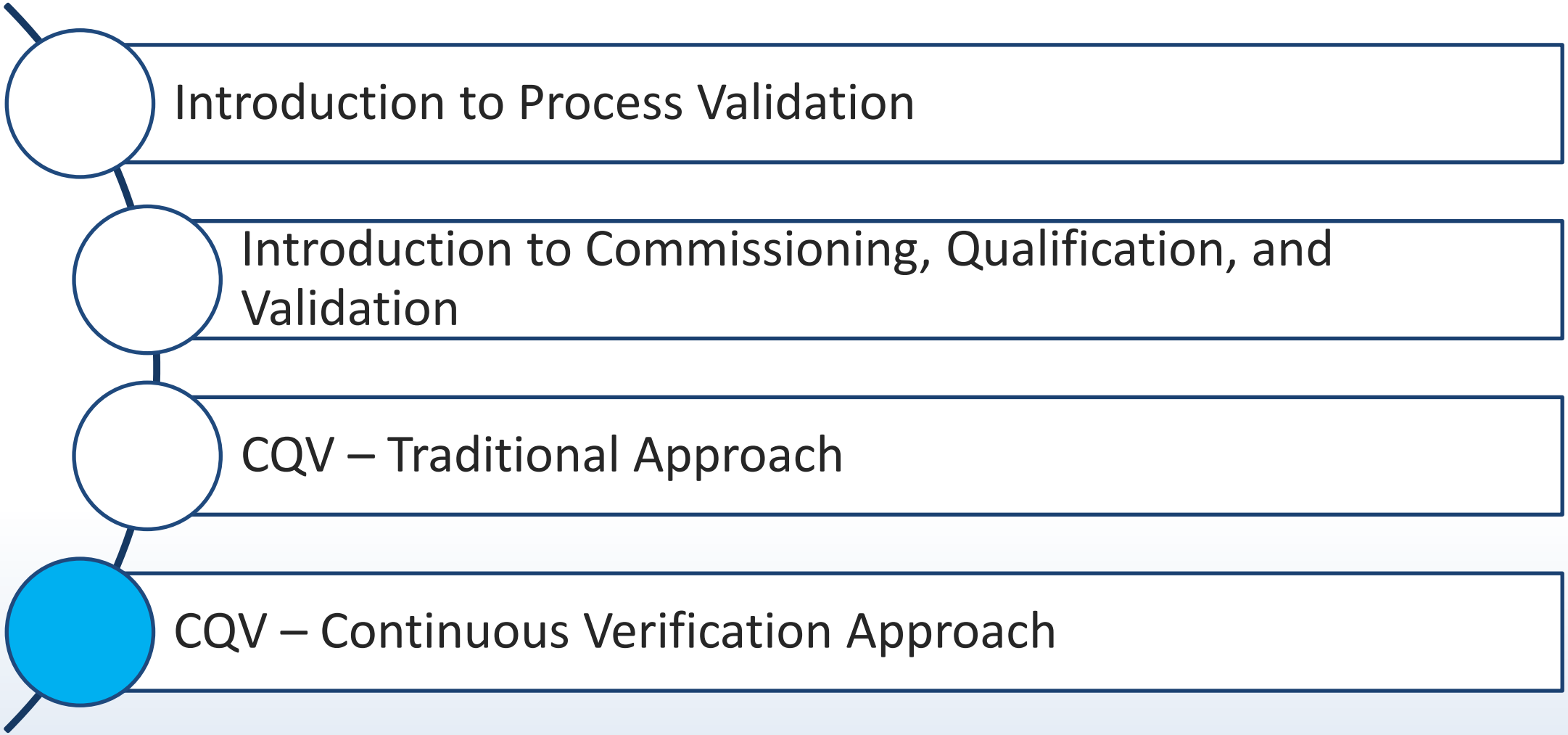



- No testing leveraged from Commissioning.
- Automated systems and control equipment qualified separately.
- Deviations from low-risk items diluted Quality team's attention.
- No activities from different qualification stages completed in tandem – time wasted.

# Traditional Process Validation

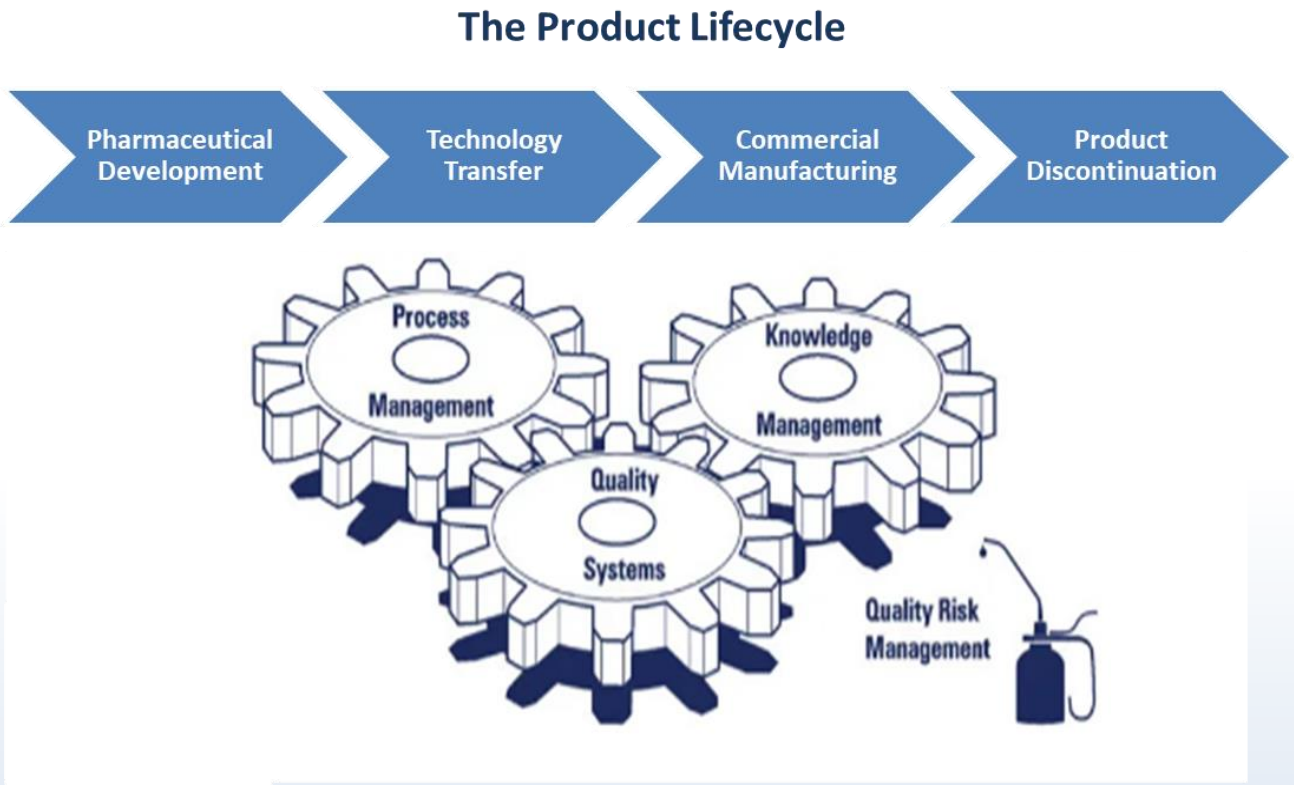
- Relied primarily on end-product analysis and the collection of large quantities of data from “validation batches”:
  - Lack of analysis of process/product changes over time i.e. Continuous Verification.
  - Lack of process understanding or incentive for improvement.
  - “End-point” product analysis and sub-optimum quality assurance.
- As regulations regarding the production and distribution of medicinal products evolved over time, traditional approaches to process validation became out-dated.

# Topics



# Lifecycle Process Validation

In the 21st Century, new guidelines emphasising a **Continuous Validation** approach throughout the **lifetime** of a drug were developed.




The focus of Validation strategies shifted to:

- Product Knowledge
- Process Knowledge
- Control Strategy
- Continuous Analysis/Verification
- Continuous Improvement

PDA TR 60 Process Validation: a Lifecycle Approach

# 2. Continuous Verification Approach

- Formally introduced in 2007 by ASTM E2500 - *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment.*
- Sometimes referred to as the “Enhanced approach”, “Risk Assessment & Verification approach”, “Modern approach”.
- “Risk-based” - Risk management evaluates the product, the process design, and the process operation.
- “Science-based” – Decisions are based on product and process knowledge/scientific studies.
- Aim is to have the product’s quality requirements satisfied by the design of the process and continuous verification that the process remains in the validated state.

# Impact AND Risk Assessment

A **risk-based approach** to process validation provides a rational framework for developing an appropriate **scope for validation activities**, **focusing on processes/elements that have the greatest potential risk** to product quality – "critical aspects" (ASTM-E2500-07).

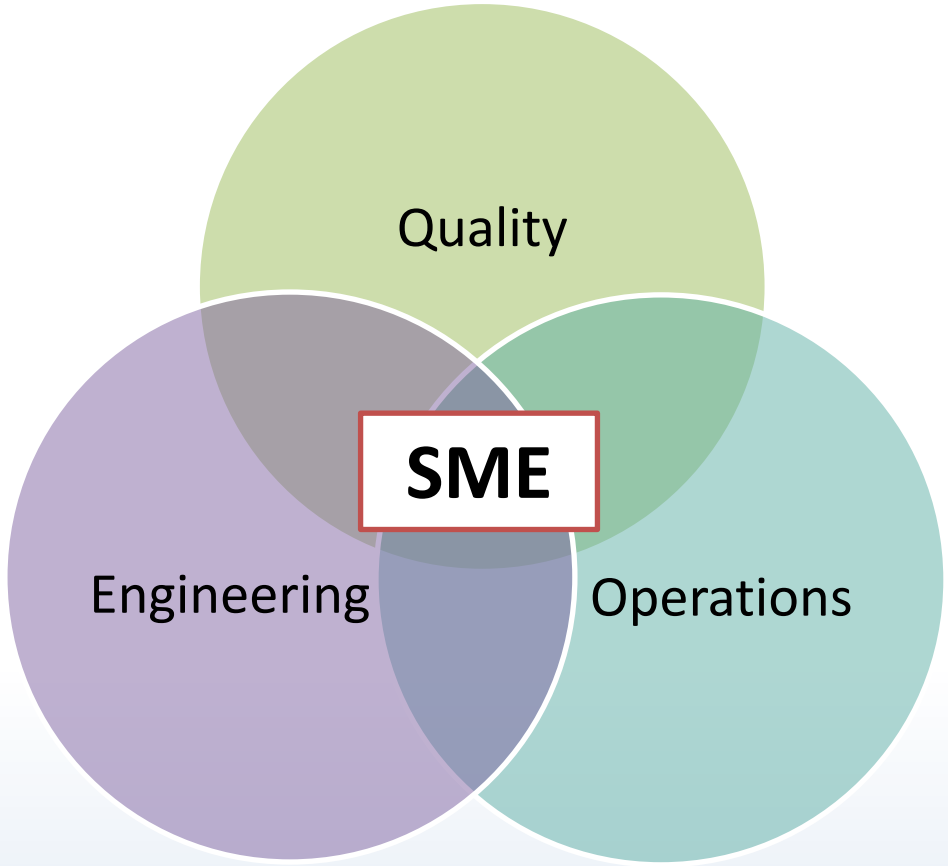
- Risk assessment tools can be used to evaluate potential failures, their impact/severity, and their likelihood of occurrence.

- The validation effort in each case should be commensurate with (match) the risk – saves time and effort!

# Subject Matter Experts (SMEs)

The Continuous Verification approach emphasizes the inclusion of Subject Matter Experts and their development and approval of all design and verification documentation.

SME's define acceptance criteria, review and approve the design, develop and approve test plans, specifications, and are responsible for ensuring that all documentation and verification is completed.



# Commissioning & Qualification

- Some Commissioning and Qualification activities can/should be integrated.
- Results from certain Commissioning tests can be leveraged and used to satisfy Qualification requirements.
- C&Q often combined into a single phase (often called Verification).
- The level of testing & documentation detail should be proportionate to the identified risks to product & patient.
- This leads to a shorter and streamlined C&Q experience **but** risk assessments and streamlining must be appropriate, considered, and justified.

# Validation

- Similar to Traditional CQV, a number of successive PPQ batches are used to validate the process.
- PPQ batches involve running the process from start to finish under normal/simulated manufacturing conditions. The aim is to prove the product can be repeatedly produced within the required safety and quality standards.
- The number of PPQ batches required is usually three. However risk assessment is used to determine the optimum number needed.
- If it is justified, a company may do more or less than 3 PPQ batches.

# Post-Validation - Continuous Process Verification

"Continuous process verification is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated" (ICH Q8).

- A science and risk-based, real-time approach to verify that a process, operating within predefined parameters, consistently produces material which meets its CQAs.
- It involves extensive in-line, on-line, or at-line controls and monitoring of process performance and product quality.
- This is achieved using Process Analytical Technology (PAT), intelligent control systems, and data collection.

# Validation is Complex!

# CQV Approaches- Summary

1. Traditional Approach – rigid/inflexible procedures
   - Performed after process development and prior to marketing.
   - Impact assessments (without appropriate risk/probability consideration) used during validation meaning that large amounts of time spent on trivial potential issues.
   - Commissioning & Qualification considered separately – repetition.
   - Cannot progress to next stage until QA sign-off on previous stage.
   - Effective but time-consuming and repetitive.

2. Continuous Process Verification Approach – science and risk based
   - Risk assessments performed to manage/identify risk and necessary effort.
   - Typically, still performed on consecutive batches pre-marketing **BUT** manufacturing process performance is continuously monitored and evaluated post-marketing (continuous verification).
   - Verification of some data from vendor/commissioning - reduction in time.
   - Some elements can be carried out in tandem.
   - Typically used by newer sites.

# Topics

- Introduction to Process Validation
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- CQV – Traditional Approach
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# Glossary

- **Amendment:** a controlled change, prior to execution, to an approved protocol
- **Calibration (Metrology):** a process/program that demonstrates that a measuring device produces results within specified limits of those produced by a reference standard device over an appropriate range of measurements
- **Certification:** documented testimony by qualified authorities that a system qualification, calibration, validation, or revalidation has been performed appropriately and that the results are acceptable; personnel certification is proof that a person has achieved a certain level of qualification.
- **Change Control:** a formal process that follows a predetermined procedure set out in a Quality Assurance document or Master Validation Plan for making changes to equipment, systems, or procedures that may change the parameters or affect expected outcomes
- **Current Good Manufacturing Practices (cGMP):** guidelines defining acceptable manufacturing methods and facility standards that ensure safety, purity, and potency of a biologic, as applicable to APIs, per 21 CFR, subparts 210 and 211 and ICH Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
- **Commissioning:** a well-planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user or validation; this results in a safe and functional environment that meets established design requirements and stakeholder expectations.

# Glossary

- **Control Chart:** a statistical trending tool that graphically represents whether a process is either in- or out-of-control by depicting a variable compared to calculated upper and lower control limits over time
- **Design Qualification:** a process to ensure that equipment and systems are suitable for their intended use; an example of design qualification parameters would be checking that the water system has sufficient capacity to serve the needs of the facility (including production, testing, steam generation, and autoclave operations)
- **Development Studies:** studies that are performed prior to validation to determine the extent and scope of required validation testing; examples of development studies may include temperature mapping of autoclaves to identify cold regions as well as cleaning studies in dishwashers to identify hard to clean items
- **Deviation:** any event occurring during validation of a system that is a departure or variation from a written procedure or acceptance criteria
- **Direct Impact System:** a system that is expected to have a direct impact on product quality; these systems are designed and commissioned in line with Good Engineering Practice and
are subject to Qualification Practices that incorporate the enhanced review, control, and testing against specifications or other requirements necessary for cGMP compliance

# Glossary

- **Indirect Impact System:** a system that is not expected to have a direct impact on product quality but will typically support a Direct Impact System; these systems are designed and commissioned following Good Engineering Practice only

- **Installation Qualification (IQ):** documented verification that the equipment or systems, as installed or modified, comply With approved design, manufacturer's recommendations, and/or user requirements

- **Installation Verification (IV):** the verification or checkout that all equipment and/or systems are installed as designed and specified; the IV is performed during commissioning and as equipment and/or systems are installed over the life of the Installation (construction) phase; all installation is verified and documented to reflect as-built conditions; IV is executed by making a complete field verification of all trade contractors' work and vendors' deliverables by performing line-by-line checks using purchase orders, design documents, P&ID5, specifications, electrical drawings, instrument & control drawings, testing procedures, SOPs, and all other available tools

- **Issued For Construction (IFC):** the stage of design for specifications, drawings, and/or other design documents when the design document is deemed acceptable to use for construction

# Glossary

- **Limit of Detection (LOD):** the lowest amount of analyte that can be detected in a sample but not necessarily quantified
- **Limit of Quantification (LOQ):** the lowest amount of analyte in a sample that can be quantified with suitable precision and accuracy
- **Master Validation Plan (or Validation Master Plan):** a document that pertains to the entire facility and describes which equipment, processes, systems, and methods will be validated and under what conditions; the Master Validation Plan should include a format for the 10. OQ, and PQ protocols and include the types of information to be found in each document
- **Out of Specification Results (OOS):** results of any measurement that differ from predetermined specifications
- **Operational Qualification (OQ):** the documented verification that the system or subsystem operates as expected according to the manufacturer's specification and/or the user functional requirements
- **Operator Interface Terminal (OIT):** a graphic display panel serving as the interface between an operator and a control system
- **Overkill Approach:** a cycle that provides a minimum 12-logarithm reduction of a resistant biological indicator with a known D-value of not less than one minute; this approach assures a reduction of the bioburden that is substantially greater than a 12-log reduction; therefore only minimal information on the bioburden is required

# Glossary

- **Performance Qualification (PQ):** documented verification that the system or subsystem performs as intended, meeting predetermined acceptance criteria under actual production conditions; establishes confidence through appropriate testing that the process is effective and reproducible

- **Precision:** describes the closeness of agreement or degree of scatter between a series of analytical measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions

- **Process Validation:** the scientific study of a process conducted in order to: prove that the process works as intended (process is under control); determine the process-critical variables and their acceptable limits; and set up appropriate in-process controls

- **Programmable Logic Controller (PLC):** a specialized industrial computer used to program and automatically control production and process operations by interfacing software control strategies to input/output devices

- **Relative Standard Deviation (RSD):** Deviation x is the absolute value of the Coefficient of Variation

# Glossary

- **Re-Qualification (RQ):** documented verification that the system or subsystem remains in a validated state; this can apply to a specific function or the entire operation of a system and/or equipment
- **Retrospective Validation:** validation of a process or piece of equipment for a product already in distribution based upon accumulated and statistical reviews of production, testing, and control data; these reviews are primarily accomplished by graphic representation of the data in chronological order; the review is limited to quantitative results that are indicative of product quality
- **Second-order Kinetics:** chemical reactions that proceed at rates that are proportional to the square of the concentration of one of the reaction ingredients; reactions that proceed by second order kinetics decrease faster than reactions that proceed through first order kinetics
- **Stakeholders:** departments with a vested interest in facility, system, and/or equipment validation

# Glossary

- **Steam In Place (SIP):** the introduction of steam to sanitize or sterilize a piece of equipment without disassembling the equipment
- **Sterilization:** an act or process, either physical or chemical that destroys or eliminates micro organisms
- **Terminal Sterilization:** a process whereby a product is sterilized in its final container, permitting the measurement and evaluation of quantifiable microbial lethality
- **Turn Over Package (TOP):** data package(s) consisting of critical data and documentation to support system validation; documentation of the design basis, fabrication, assembly, installation, and testing of equipment and facilities, which provides the basis for validation, operation, and maintenance; the documentation package that is provided with each qualified system is typically supplied by the facility or equipment provider/installer
- **Validation Protocol:** a written plan describing the process to be validated, including production equipment and how validation will be conducted; this includes the kind and number of samples and replicates, the tests to be used, and acceptance criteria for the test results; the validation protocol addresses objective test parameters, product and process characteristics, predetermined specifications, and factors which will determine acceptable results.

# Thank You