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Lecture 3:
Process Validation Lifecycle

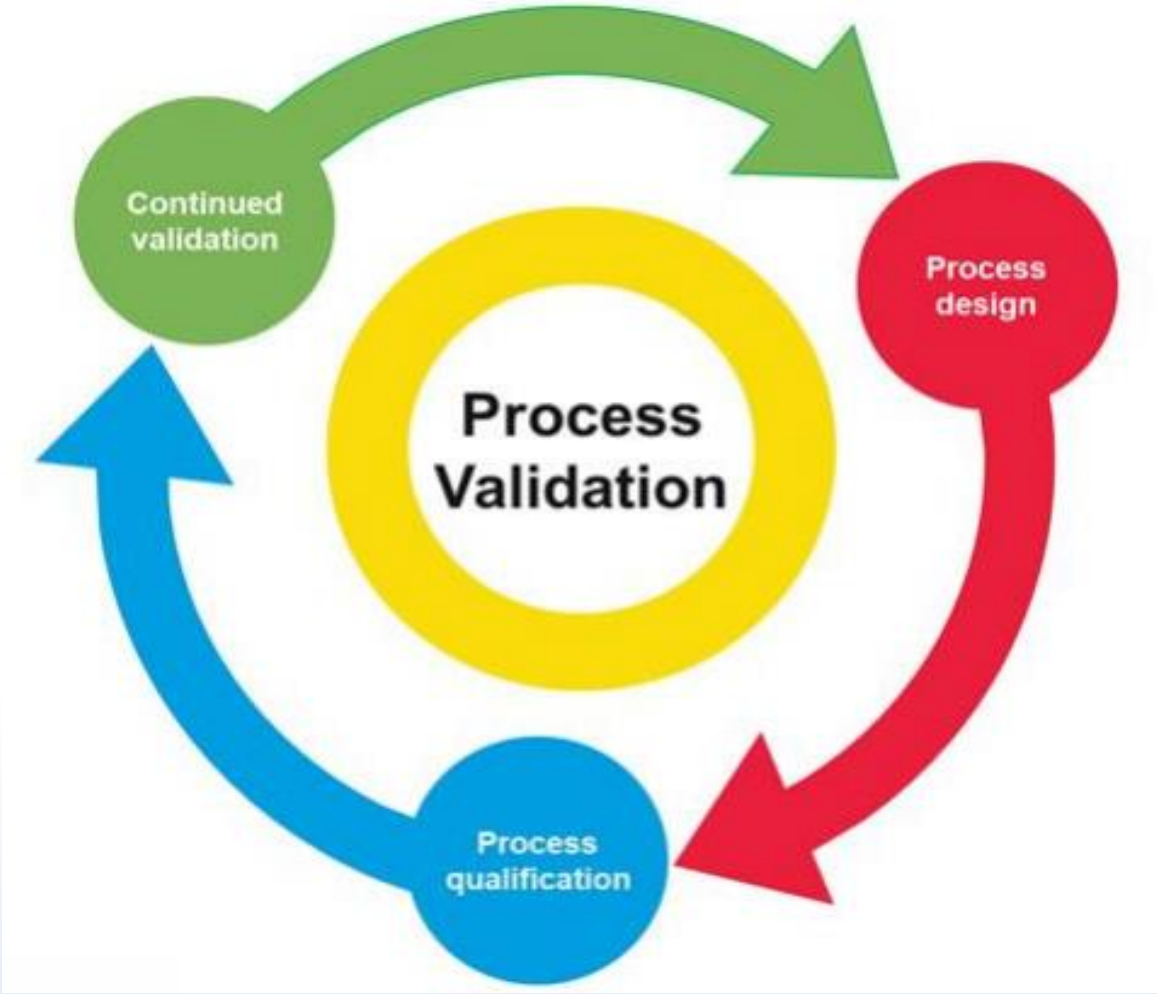
MCQ 1

- The first MCQ for your Biopharmaceutical Validation module will take place on **12th February 2025**.
- There will be **20 multiple choice questions** (one correct answer for each) and once you begin your attempt you will have **50 minutes to complete.**
- The questions will cover **lectures 1-3.** The MCQ is worth **10% of your overall grade.**
- You will have **one attempt** only and the 50 minutes will begin when you click "start attempt".
- The MCQ will be on moodle in the Week 4 section. **It will be open from 7.00am Wednesday 12th February to 7.00am Thursday 13th February 2025**
- IMPORTANT: attempts outside of this time frame will not be accepted except in certain extenuating circumstances. This is to ensure fairness to all students.

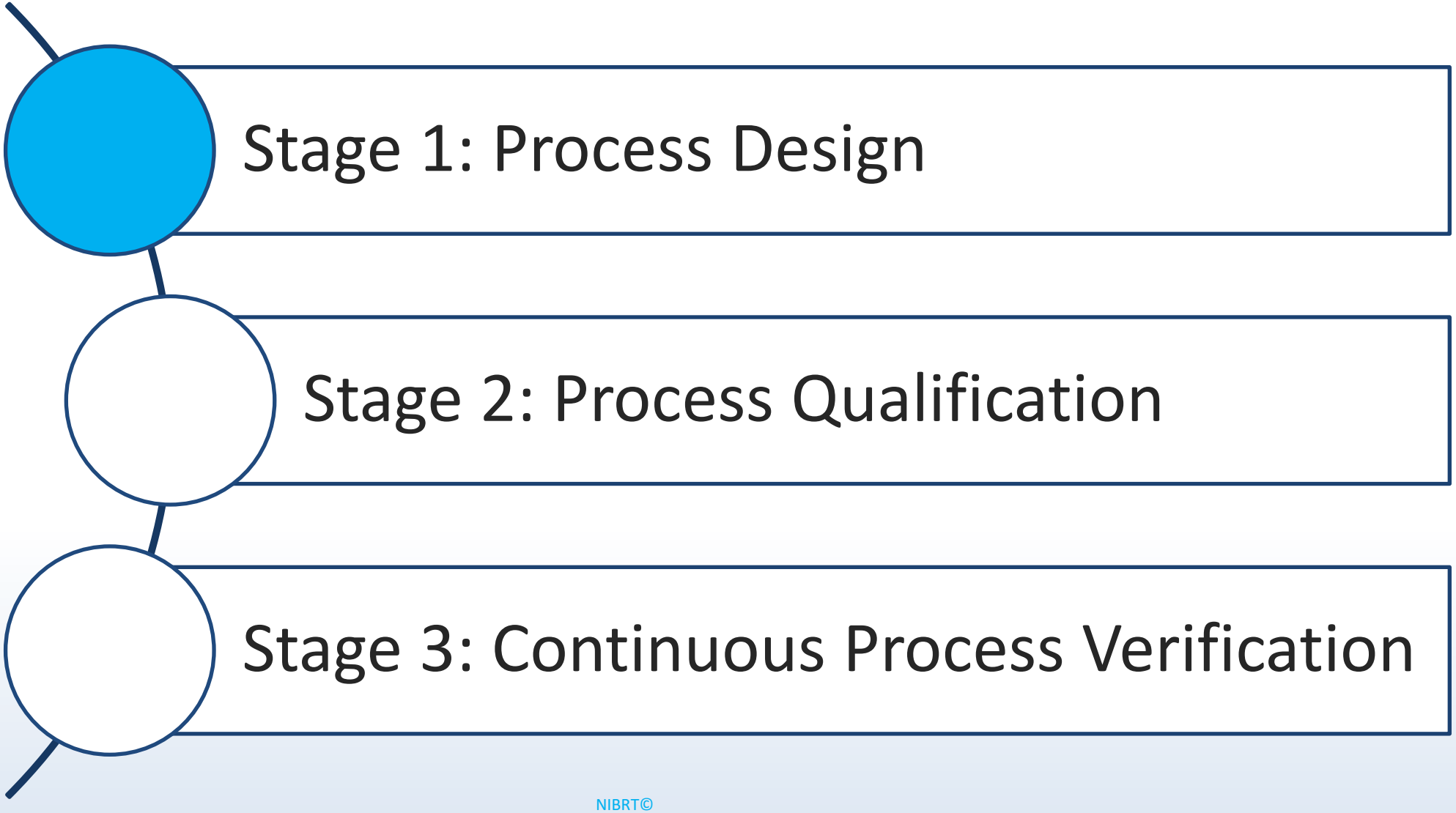
Process Validation Lifecycle

Process Validation is not an event or task that can be completed.

Rather, it is a lifecycle of control across the entire product and process lifecycle.



Topics



Stage 1 – Process Design

- The foundation of CQV is laid during design:
  - Consider what the equipment ***needs*** to look like to be able to produce the product.
- The manufacturing process should be designed based on **risk** to the product and patient.
- During the Process Design stage, product and process knowledge are accumulated and used to establish a control strategy.
- The control strategy requirements will guide the initial design of the process/equipment.
- The effectiveness of the Process Design will be tested in Stage 2 – Process Qualification.

Quality by Design (QbD)

Quality by Design (QbD): *"A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management".* (ICH Q8)

A QbD approach to process validation is the best way to ensure regulatory conformance

Quality must be designed into the process. It can not be adequately ensured by inspection, sampling, and testing alone.

https://www.genengnews.com/magazine/achieve-qbd-by-managing-impurity-data/

FDA & EMA Reference to QbD

FDA:

- Direct reference made to ICH Q8, Q9 & Q10
- PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.
- 21 CFR Part 210/211 – reference to quality

EMA:

- Direct reference also made to ICH Q8, Q9, Q10 & Q11
- Eurdralex Vol 4: Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

2013: *"EMA-FDA pilot program for parallel assessment of Quality-by-Design applications: lessons learnt and Q&A resulting from the first parallel assessment"*

Process Design: Understand Your Product & Process

First, identify the criteria and specifications that must be met to deem your product safe, effective, and of acceptable quality

- This determines your product's **Quality Target Product Profile (QTPP):** labelling info that relates to quality, safety, efficacy, dosage form, route of administration, etc.
- An important component of QTPP are **Critical Quality Attributes (CQAs):** specific to the product and its important attributes for the patient
- **Risk Assessments** determine which aspects of the process could impact the CQAs of the product. These are known as **Critical Process Parameters (CPPs).**

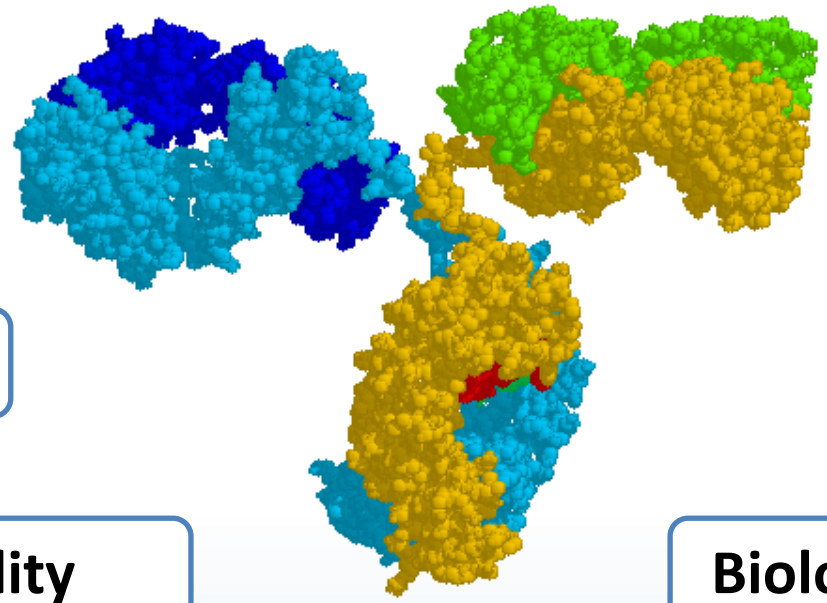
CQAs – Some Examples

Size and Shape (3D Structure)

Aggregation

Charge & Isoelectric Point

Glycosylation



Efficacy

Purity

Sterility

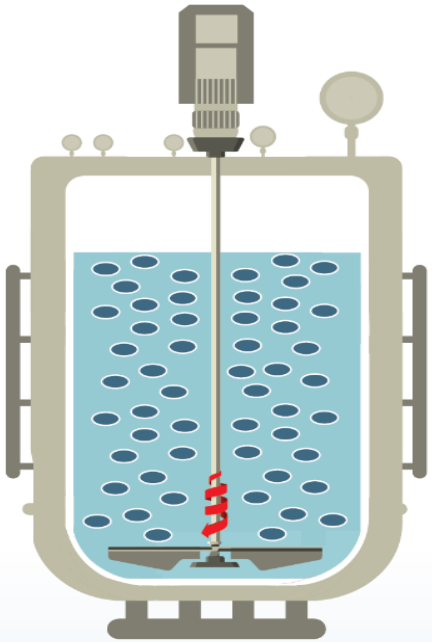
Biological Activity

Which **parameters** throughout the process could impact these critical quality attributes?

CPPs – Upstream Processing Examples

Agitation Rate

Medium Osmolality



Temperature

Pressure

pH

Acceptable operating ranges for each of these CPPs must be determined to ensure that CQAs are not negatively impacted!

Process Characterisation and Design Space

We now know:

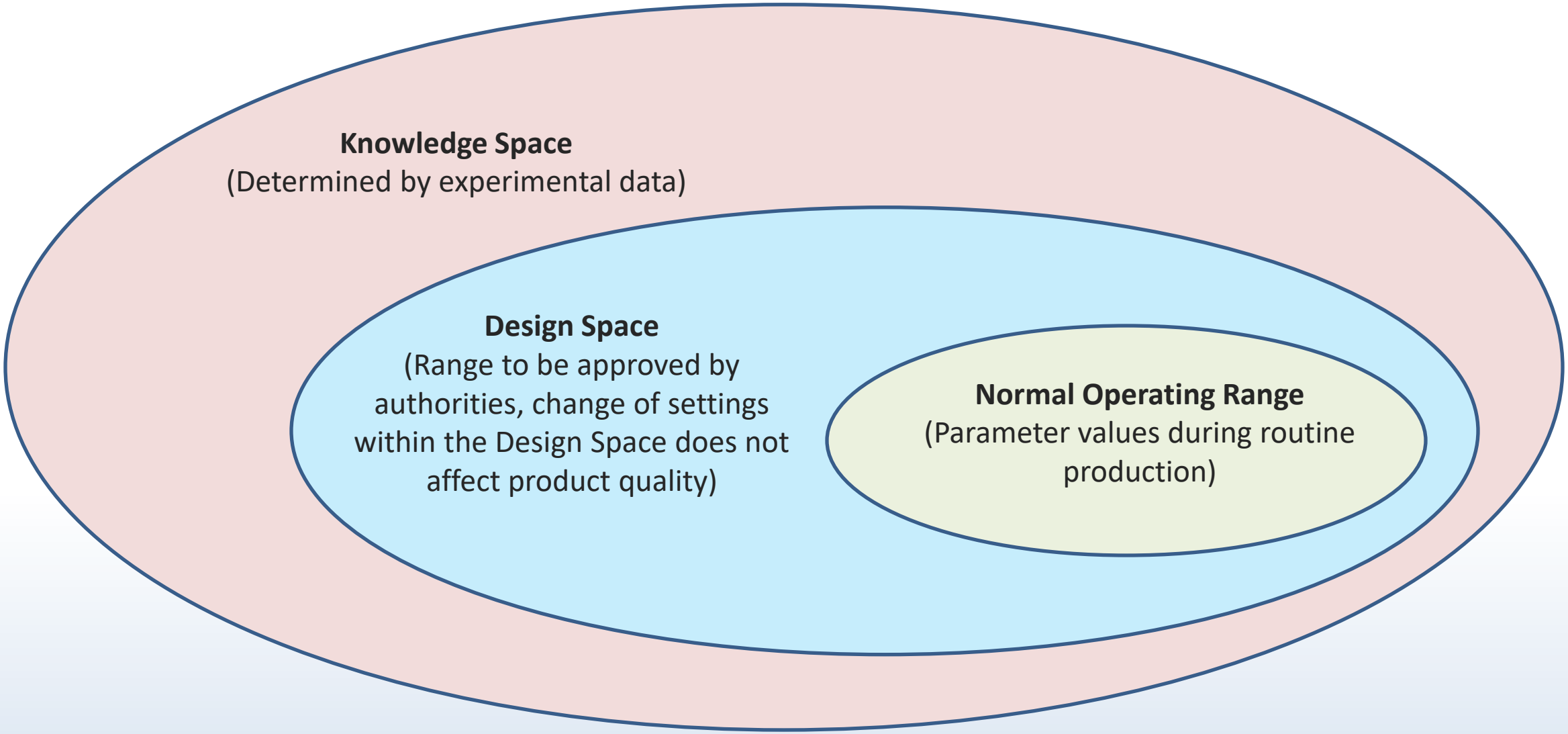
1. Product requirements (CQAs)
2. Affecting parameters (CPPs)

- Process Characterisation: Max/min **operating specifications for all CPPs** are then determined based on: Experimentation, statistical analysis, and simulations.

- The concluding data is known as the **Design Space:**
  - Manufacturing boundaries for end-product quality assurance – must be approved by the Regulators.
  - The Design Space helps to design your process control strategy and equipment.

A Design Space allows for a degree of flexibility during operation without compromising quality or requiring change control procedures.

Design Space



Development of a Control Strategy

- Exists to manage the influence of **CPPs** on **CQAs.**

- Should allow for control of:
  - Raw materials
  - Process parameters
  - Process intermediates
  - Final product

- Risk assessments, process characterization studies, and the Design Space allow a Control Strategy to be established. Its effectiveness will be verified during **PPQ**.

- Process Descriptions are tools used to assist in the execution of risk assessments, development of the control strategy, and design of the equipment. The process is described as a series of high-level unit operations (e.g. Block Diagrams, Process Flow Diagrams).

Process Descriptions

1. Block Flow Diagram

Gives detail of type and size of equipment and how they are connected

15L Bioreactor
10L Working Volume

Inoculum 4.0L

30L Bioreactor
20L Working Volume

Media 14.0L
Nutrients 2.0L

Inoculum 18.0L

150L Bioreactor
100L Working Volume

Media 60.0L
Nutrients 20.0L

Harvest 98.0L

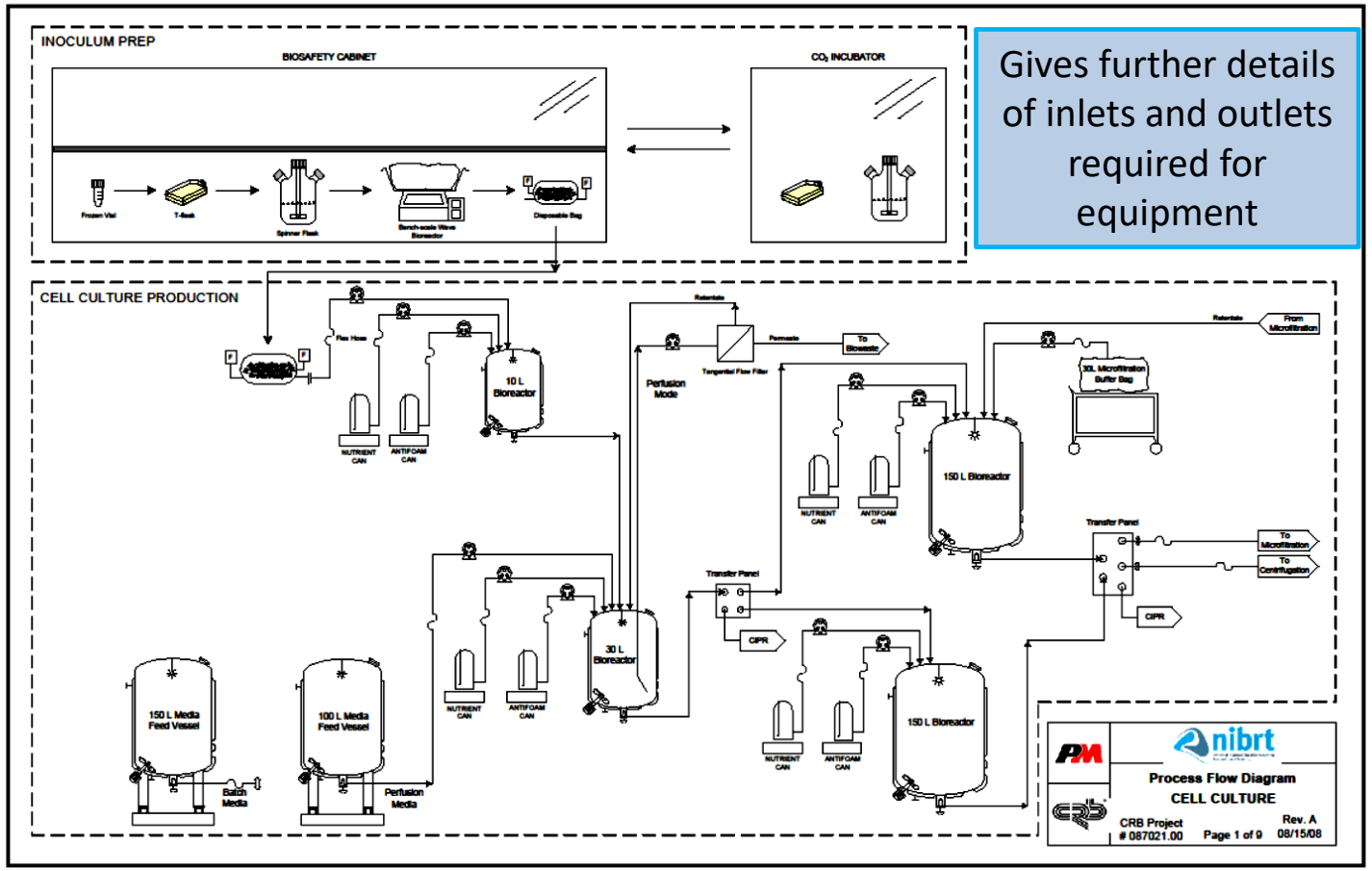
Centrifugation

Flush Buffer 18.0L

Centrate 98.0L

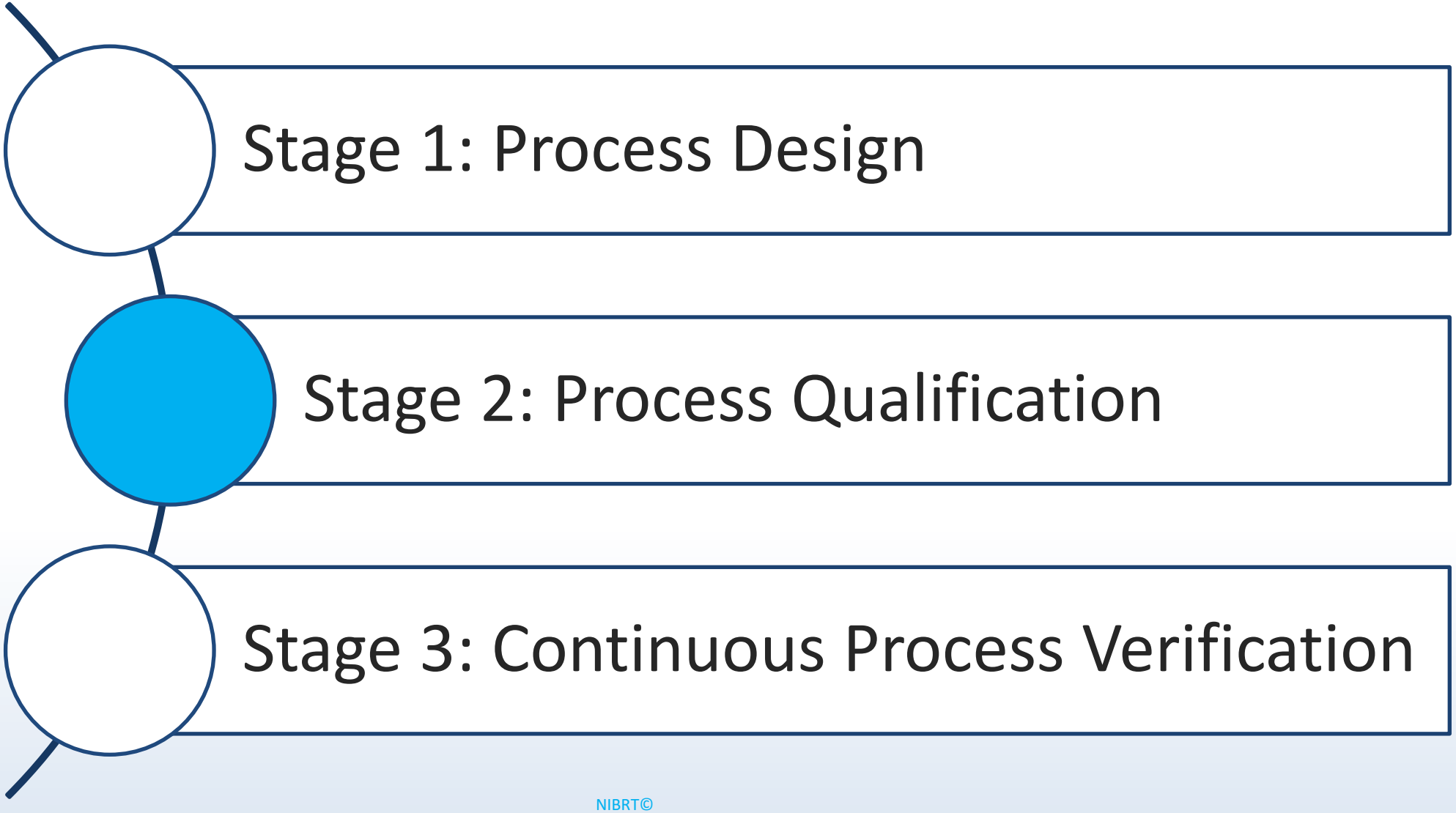
Depth Filtration

2. Process Flow Diagram

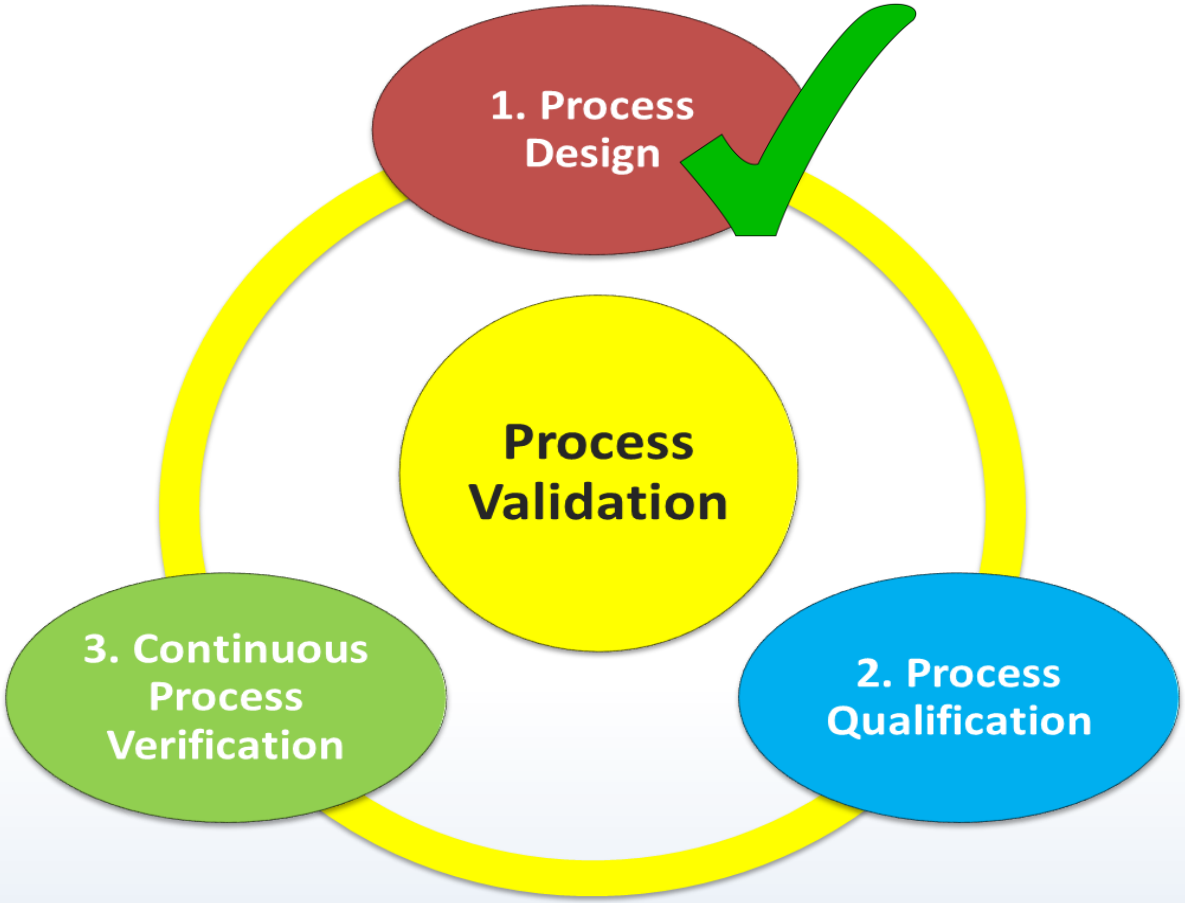


Gives further details of inlets and outlets required for equipment

Topics



Stage 2 – Process Qualification



URS – User Requirements Specification

- Process descriptions and control strategy data can be used in the design of the pilot-scale and production-scale equipment.
- A **User Requirements Specification (URS)** is developed for each piece of equipment specifying all of its functional and design requirements.
- Created by the end-user and given to the vendor.
- The approved URS supports design, commissioning and qualification, operation, and maintenance.

System Classification: Direct vs Not Direct Impact

- Using System Impact Assessments (SIA), systems should be classified based on their impact on product quality:
  1. **Not Direct Impact** Systems will be subject to **Commissioning only.**
  2. **Direct Impact** Systems will be subject to **Commissioning AND Qualification.**

- Direct Impact Systems will be further subject to System Risk Assessments (SRAs)
  - identifies which parts of Direct Impact equipment pose the greatest risk to the product i.e. the Critical Aspects (CAs).

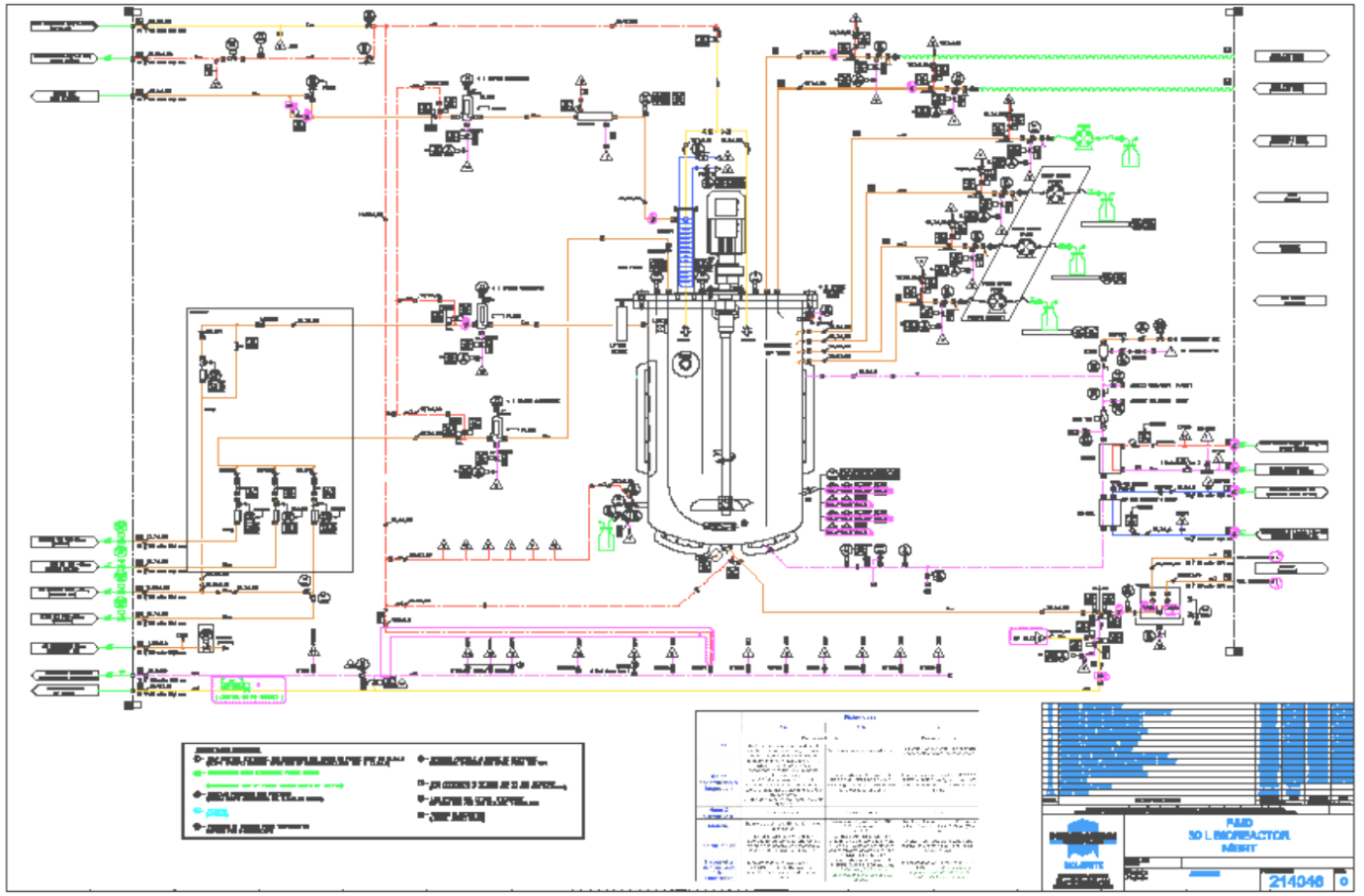
- The results of the System Risk Assessment help to:
  - ensure that the identified Critical Aspects are appropriately considered in the system design (i.e. translated into Critical Design Elements (CDEs)).
  - focus the validation effort of the constructed equipment on the highest-risk components.

FDS – Functional Design Specification

- Functional Design Specification (FDS) or Functional Specification (FS)
  - Specification in which the requirements of the end-user (URS) are translated into a technical solution (from the Manufacturer‘s point of view)
- FDS is a more detailed document which is generated by the vendor and based off the URS.
- FDS should detail all design features, functions, operator interactions, controls, and sequencing associated with the system, thus allowing the user to confirm, before the system is developed, that the proposed system fully meets its requirements.
- Once formally agreed upon, the FDS becomes part of the contractual agreement.

Piping & Instrumentation Diagrams (P&IDs)

- P&IDs are generated by the vendor and form an integral part of the Design Qualification, as well as later-stage validation activities.
- P&IDs are controlled GMP drawings and should be kept up-to-date at all times.
- What are P&IDs used for?
  - Design and construction of the equipment and automation.
  - Validation of the equipment
  - Identifying flow paths or isolation points for troubleshooting and maintenance.



Design Qualification (DQ)

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

- Once the Functional Design Specification (FDS) and equipment drawings (P&IDs) have been established, they are analysed by experts as part of the Design Qualification (DQ).
- Aim is to establish whether they meet the criteria set out in the URS, as well as GMP standards.
- Equipment designs are finalised and signed-off by the responsible parties i.e. Qualified.

Equipment Construction

Following successful Design Qualification, equipment and systems are constructed by the vendor.

- Once constructed, they must be Commissioned and Qualified (as appropriate) to ensure that they:
  - Meet the design specifications and user requirements.
  - Are safe to use.
  - Are fit for their intended use.
  - Can perform to acceptable standards on a repeated basis.

FAT - Factory Acceptance Test & SAT – Site Acceptance Test

- **FAT:** Testing of equipment and relevant documentation **at the vendor‘s site** against the requirements of an approved URS/FDS.
  - not a general requirement, i.e., not required for small, standard equipment (off-the-shelf).

- **SAT:** Testing of equipment and relevant documentation **at the site of use** against the requirements of an approved URS/FDS.
  - If activity/testing will be completed during Commissioning and/or IQ/OQ, SAT can be skipped.

- Some FAT/SAT test results can be leveraged during IQ/OQ *“if it can be shown that the functionality is not affected by the transport and installation”* (Annex 15).

- Any instances of leveraging test results must be justified in the **Validation Master Plan.**

Commissioning

Commissioning ensures appropriate construction, install, operation, and safe function of the system.

- It focuses more on the functionality of the system, rather than whether the product/output is acceptable.
- Commissioning ensures all fundamental user requirements are met prior to moving to qualification.
- Safety, inspection, and functional testing occur, and draft Standard Operating Procedures (SOPs) are often developed which define how to use the system in a safe manner.

Commissioning:
Inspection and Functional Testing

- **Pre-commissioning:** preliminary planning/system development, URS/FDS reviews, defining test requirements, field inspection, etc. (pre-mechanical work)
- **Functional Commissioning:** follows pre-commissioning. The actual inspections and testing of functionality.
- **Commissioning** will test the functional requirements and the design in the plant environment. It does not necessarily assess system performance in terms of product/output requirements.
- Mainly a series of Engineering activities which ensure that a system is ready/safe to go live/handover. Activities associated with **Good Engineering Practice (GEP).**
- A broad topic covering the final system inspection, installation check, connections/welds, system start-up sequence, functional verification, etc.

Installation Qualification (IQ)

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).

- Ensures equipment is installed as per design drawings and specifications, and in accordance with cGMP requirements by performing walkdowns.
- IQ should also include: Collation of vendor operating instructions and maintenance requirements, confirmation of instrument calibrations, and verification of the materials of construction.
- Should start before completion of Commissioning activities – some test results can be leveraged from FAT, SAT, Commissioning.

System Walkdown

- P&IDs are often used during Installation Qualification (IQ) as part of equipment “walkdown” activities.
- Personnel will walk the physical system and compare it to the P&ID, which was designed based on the URS/FDS and approved prior to the system construction.
- This will establish whether :
  - The system has been installed correctly.
  - All items are tagged correctly and present as per P&ID.
  - All utilities are connected appropriately and at the correct locations.
- Similar activities may have been carried out/required during FAT/SAT - leverage.

Operational Qualification (OQ)

Can the system “do what it’s supposed to do”?

OQ: *“The documented verification that the **facilities, systems, equipment** … **perform as intended throughout the anticipated operating ranges**”* (EMA).

Examples of OQ tests:

- System components (e.g. pumps, agitators, probes) function within min. and max. operating ranges
- Valves open and close
- Alarm signals work
- Control systems and display units function
- Recipes and phases operate as intended
- Recording and report generation systems are functional

- OQ normally follows IQ but for less complex equipment they may be combined (IOQ).

Performance Qualification (PQ)

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).

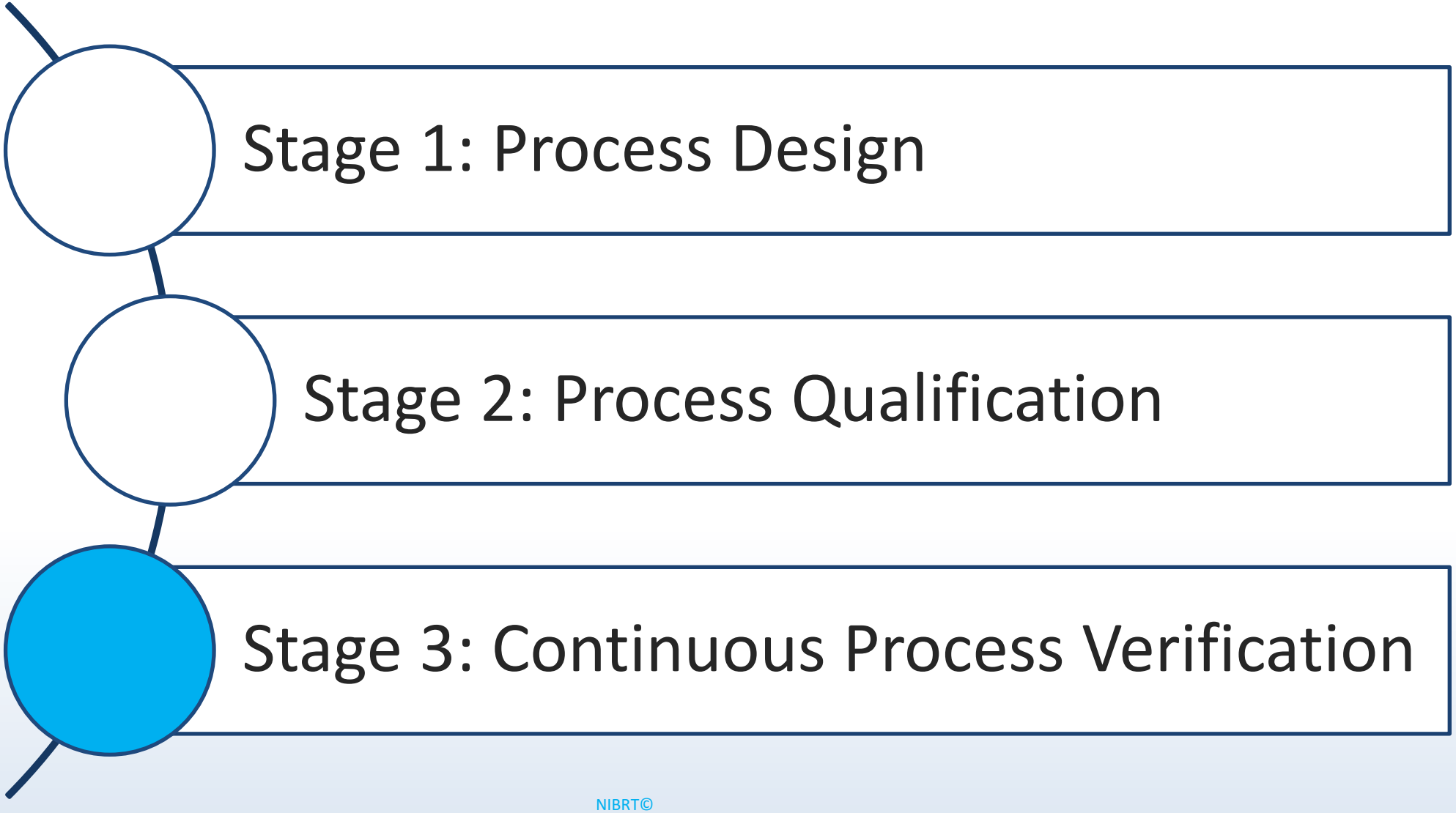
- A collection of tests used to verify that a piece of equipment can perform consistently under **simulated, in-process conditions**.
- OQ – all components of the equipment are fully operational, but:
  - Does introducing physical and systematic load reveal issues which may have been missed during OQ?
- PQ is also a final verification that all the requirements specified in the User Requirements Specification (URS) have been met.

Process Validation – PPQ Batches

Process Performance Qualification (PPQ) "Confirming that the manufacturing process … is capable of reproducible commercial manufacturing" (FDA).

- The PPQ stage tests that the process, when operated as a whole, can consistently produce a drug that meets its requirements i.e. the process is validated.
- Typically, 3 consecutive PPQ batches are required to prove Process Validation, but an alternative number of batches can be scientifically justified.
- PPQ brings together the entire manufacturing process, utilities, facility, personnel and procedures to demonstrate a **Validated Process.**

Topics



Stage 3 – Continuous Process Verification

- Aim: To continually assure that the process remains in a state of control (i.e., the validated state) during commercial manufacture.

- Continuous Process Verification:
  - Continuously monitors and evaluates process performance
  - Demonstrates that the process is validated (under specified control).
  - Based on control strategy and process knowledge.
  - Can include multiple data sources **(in-line, off-line)**

- Good process design and development should anticipate variability and establish appropriate detection, control, and mitigation strategies.

Process Monitoring and Control

Acceptable operating ranges were established in the Design Space. Systems for monitoring and maintaining these parameters within specification throughout operation must be developed.

- Where possible, this should be done in “real-time” using in-line or at-line probes
- This concept is known as **Process Analytical Technology (PAT).**
- PAT is a fundamental component of the process control strategy.

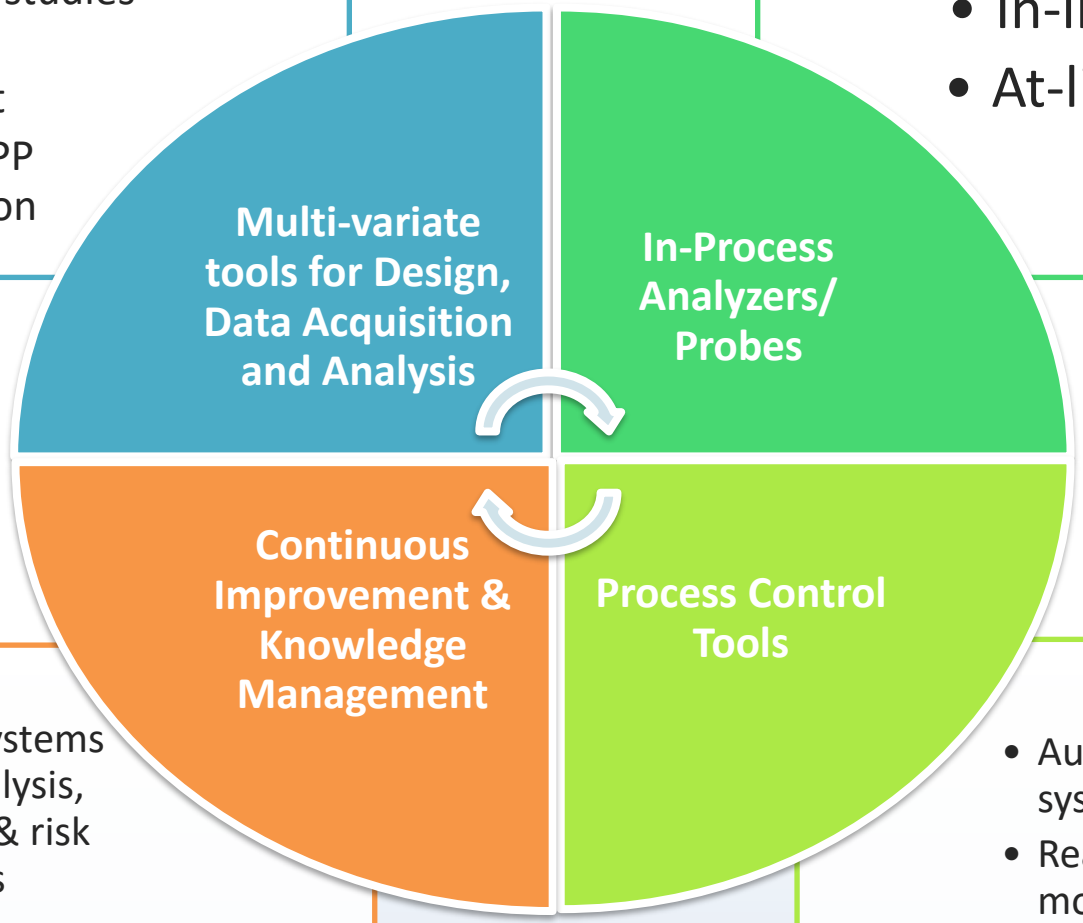
Process Analytical Technology (PAT)

- **Process Analytical Technology** (**PAT**) has been defined by the FDA as:
  "a mechanism to design, analyse, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA)".

- Traditional pharmaceutical manufacturing: laboratory testing conducted on collected samples to evaluate quality – outdated!

- By monitoring CPPs in real-time, processes can react to changes before they have an impact on product quality, thus maintaining consistent, high-level control.

PAT Tools



- Small scale studies
- Design of Experiment
- CQA and CPP identification

- In-line
- At-line

- Software and paper systems for data storage & analysis, quality investigations & risk mitigation, continuous improvement

- Automated control systems & alarms
- Reactive process monitoring/control

<u>Regulatory documents:</u>

- FDA: Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
- EU: Generally refers to ICH guidelines on PAT

Analyse Your Data

https://stock.adobe.com/ie/search?k=analyse&search_type=usertyped

- Data obtained from real-time process monitoring should be stored and evaluated on a regular basis.
- This data provides a greater insight and understanding of the process.
- Analysing this data for trends can help identify sub-optimal aspects of the process which can be improved to enhance product quality assurance.

Investigate & Manage Risk

- Analysis of process data allows for the identification of quality/process deviations and nonconformities.
- These instances should be investigated promptly and strategies for future mitigation should be established.
- Regulators expect manufacturers to employ Root Cause Analysis (RCA) and Corrective Action, Preventative Action (CAPA) methodologies to investigate and manage risks.

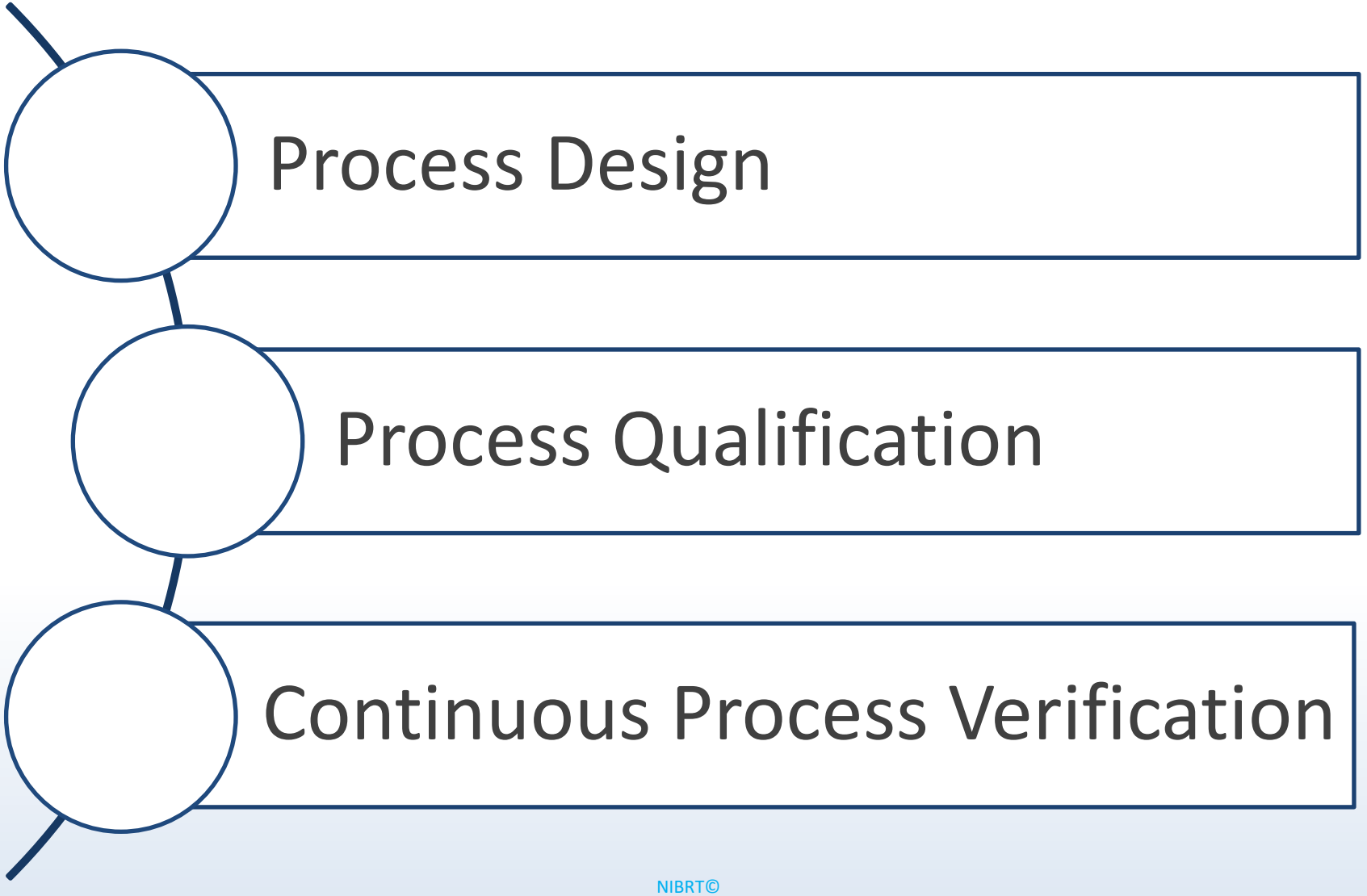
Continuously Try To Improve!

Data might suggest ways to improve or optimize the process by altering operating conditions (ranges and set-points), process controls, components, or in-process material characteristics.

Such findings should encourage the manufacturer to make improvements to the process (if they arise) over the product lifecycle – Continuous Improvement.

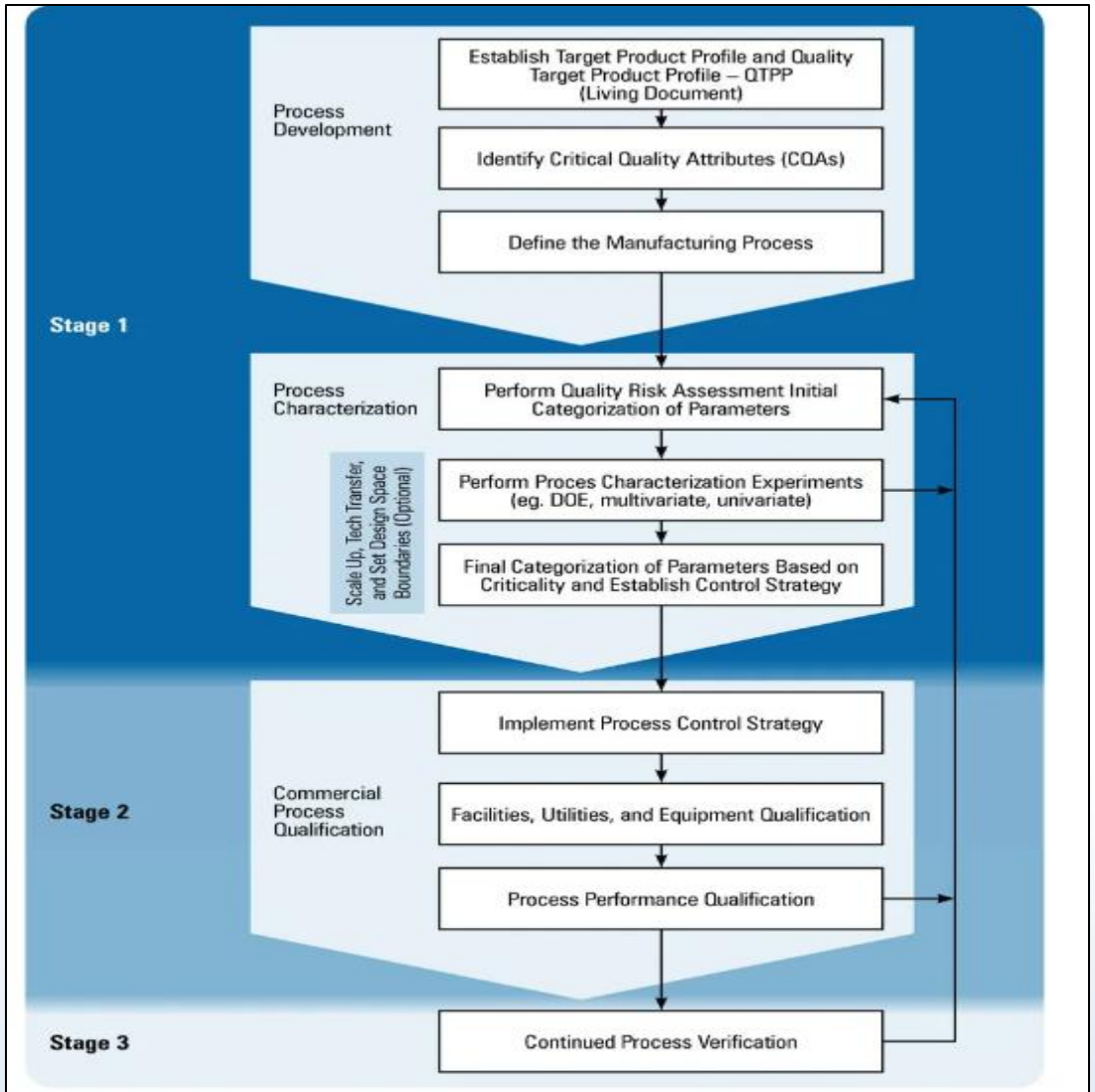
This provides a high-level of assurance that a process can consistently produce the highest levels of product quality, safety, and efficacy for the patient!

Topics

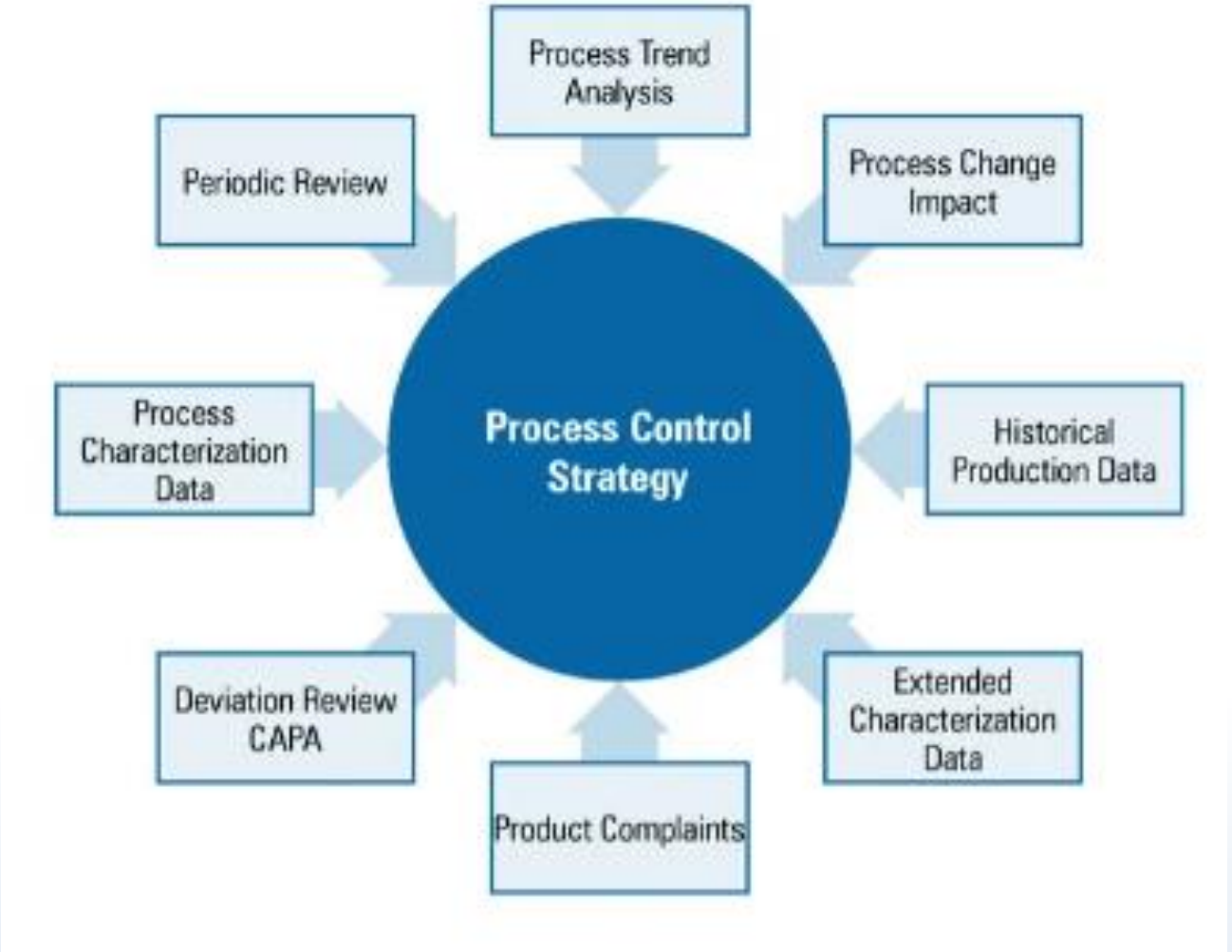


Thank You

Reference Info: Validation Stages/Activities



Reference Info: Process Control Data Sources



PDA TR 60 Process Validation: a Lifecycle Approach