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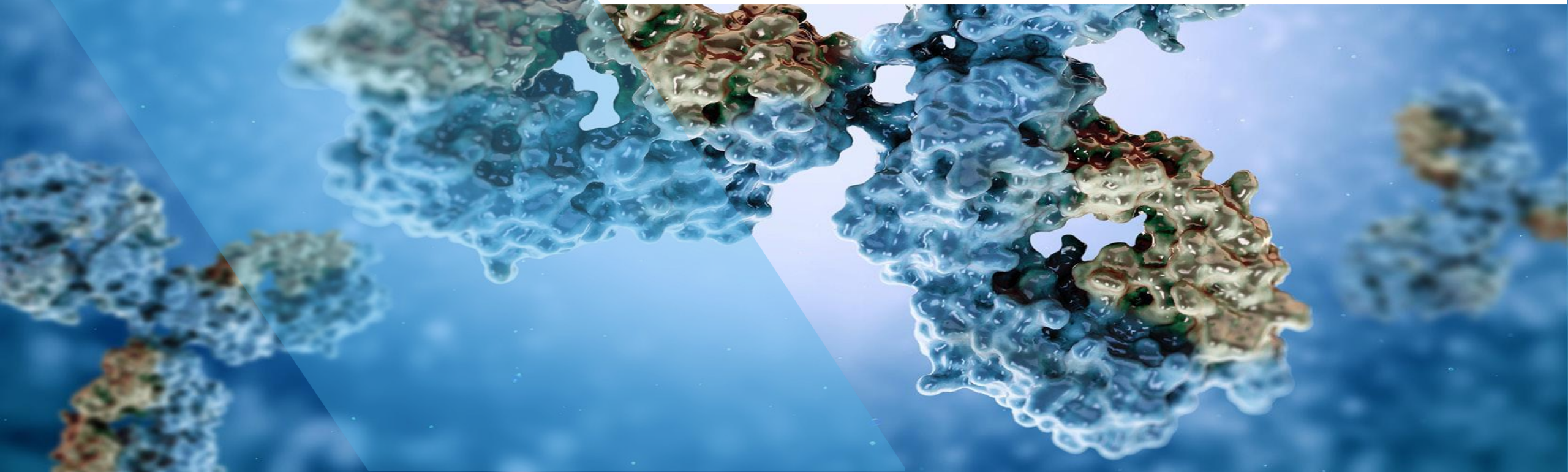
Lecture 9: Continuous Process Verification

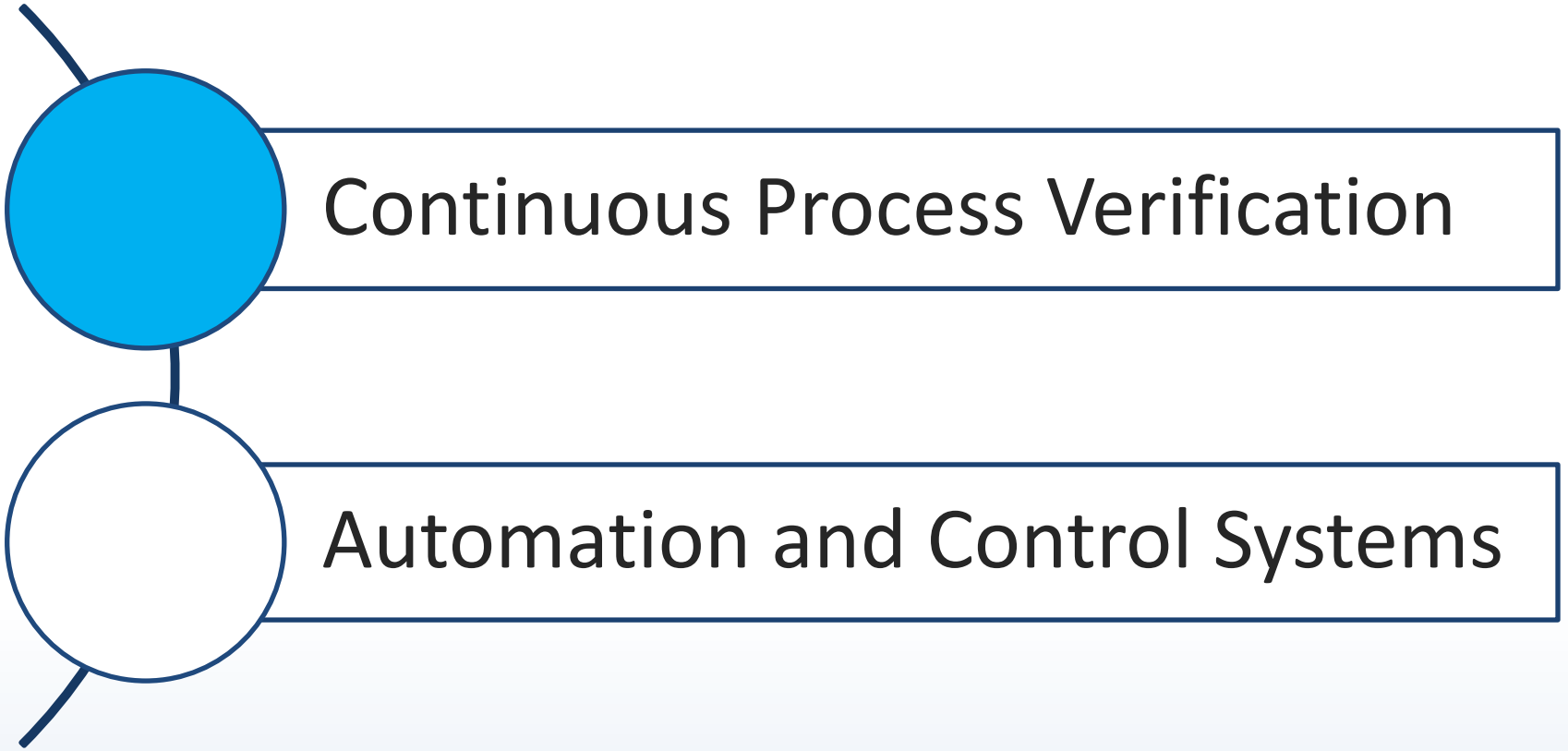


End of Module Info

- **Long Answer Question (LAQ) assessment – Wednesday 16th April**
  - 30% of overall grade
  - Answer **3** of 4 questions. There is no word count.
  - The assessment will be available on Moodle from 7.30am on 16th April to 7.30am on 17th April
  - Once started you will have 1.5 hours to complete it

- **Assignment due Friday 25th April 2025**
  - Written report to be submitted on Moodle. Turnitin link now available.
  - A trial Turnitin link is available on Moodle to check for plagiarism before your final submission. You have **ONE ATTEMPT** using this link.
  - 10-15 minute pre-recorded presentation must also be submitted on Moodle by 28th April. This link is also now available.

Topics


Continuous Process Verification
Automation and Control Systems

Continuous Process Verification

- Continuous Process Verification: “An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated” (ICH Q8).

- The goal of Continuous Process Verification is to continually assure that the process remains in a state of control (i.e. the validated state) during commercial manufacture.

- An ongoing program to collect and analyze product and process data that relate to product quality must be established.

Continuous Process Verification

- Continuous Process Verification is:
  - An approach to process validation in which manufacturing process performance is continuously monitored and evaluated.
  - Demonstration that the process is validated (under specified control)
  - Based around a control strategy and process knowledge
  - Composite of data from lab and various scale manufacturing
  - Can include multiple data sources (IPC, batch, in-line, at line, off-line analysis)

- After the process has been “validated”, the validated state is “continuously verified” by monitoring the Critical Process Parameters (CPP) and ensuring that they are continuously maintained in a state of validated control.

Continuous Process Verification

- Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits.

- It is recommended that continued monitoring and/or sampling is carried out at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates.

- Variation can also be detected by the timely assessment of risk analyses, defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports.

Continuous Process Verification

- Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product, such as the 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

Differences in Terminology

- It is important to keep in mind that this stage is known by different names depending on the regulatory body in force.
  - FDA and WHO call it **Continued/Continuous Process Verification .**
  - EMA uses **Ongoing Process Verification.**

- Regardless of the terminology, the intent of the regulators is the same: manufacturers need to monitor the state of process control, verify the impact of variability, and identify potential issues.

- This helps to determine the best course of action to ensure that the process remains in control. A process that is “in control” has a greater assurance of producing a safe product for the patient.

Key Features of CPV

- A successful continuous process verification strategy should incorporate the following:

1. Integrated:
   - Design based on process knowledge
   - Testing and monitoring designed to assess control and maintenance of validated state
2. Measurement:
   - In-line/At-line/Off-line
   - Attribute and Parameter
   - Established control, alert, reject limits
3. Analysis:
   - Statistical analysis
   - Link to plant and lab automation systems
4. Actively managed:
   - Continuous monitoring and review
   - Continuous improvement

Role of Scaled-down Models

Benefits:

- Cost: lower fixed assets needed for experimentation
- Time: Faster turnaround between runs. More data.
- Data density: Higher number of runs using multiple identical equipment sets
- Flexibility: Easy to improvise and experiment

This allows for:

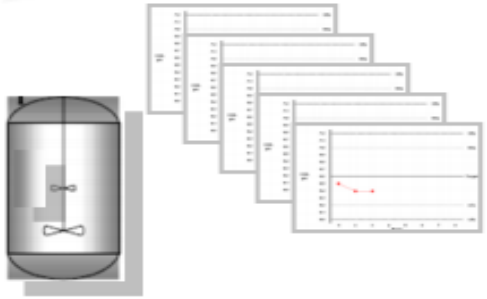
- Complex interaction studies
- Replication of statistical validity
- Data-rich process knowledge

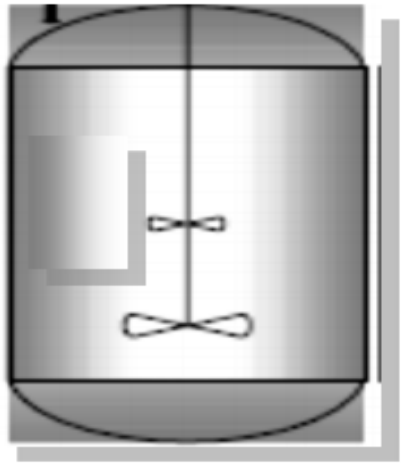
Challenge: Extrapolation of rich database of knowledge to full-scale

Small to Large Scale

- Multiple runs
- Information density
- Interaction data

- Limited number runs
- At-scale data for all Unit Ops
- Key stage in confirmation of PV





- Extensive evidence of process performance
- Examination of performance at multiple parameter set points Forms the basis for Continuous Process Verification

- Limited number of runs at full-scale
- Focus on confirmation of control strategy at scale
- Limited ranges explored
- Selection of set-points and testing to maximise value of at-scale-data
- Cannot directly test edges of Design Space at scale

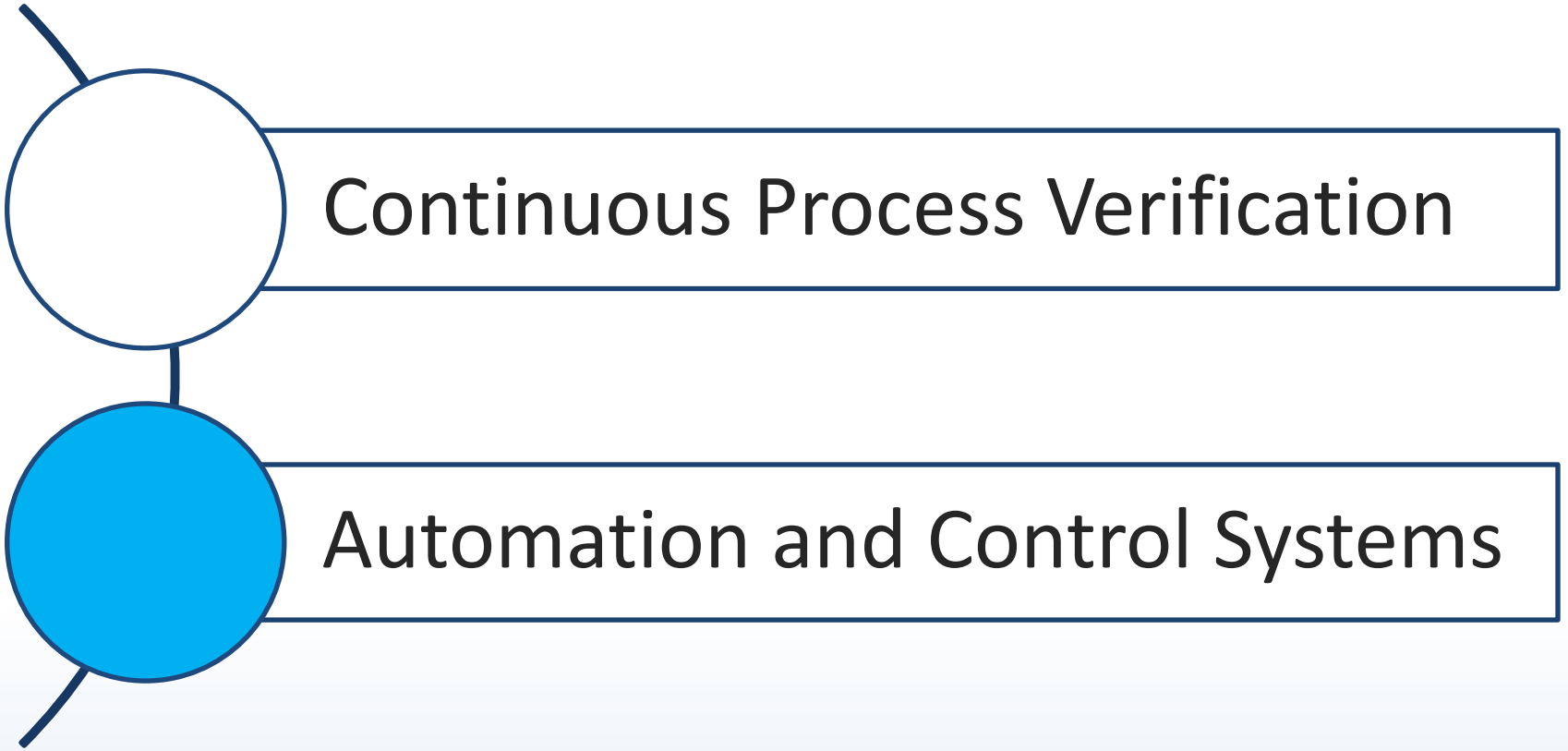
In Summary

- Successful Process Performance Qualification/Validation (Stage 2) confirms the effectiveness of the process design and control strategy (Stage 1) and demonstrates that the commercial manufacturing process performs as expected and is capable of consistently delivering quality product.

- The main purpose of Continuous Process Verification (Stage 3) is to provide assurance that throughout the commercial phase of the lifecycle, the process remains in a state of control.

- A period of enhanced monitoring after completion of PPQ may be required for certain attributes or parameters to further increase the level of confidence in the process

Topics


Continuous Process Verification
Automation and Control Systems

What is Process Automation?

- Automation refers to the development of processes or machines to be **self-acting or self-moving.**

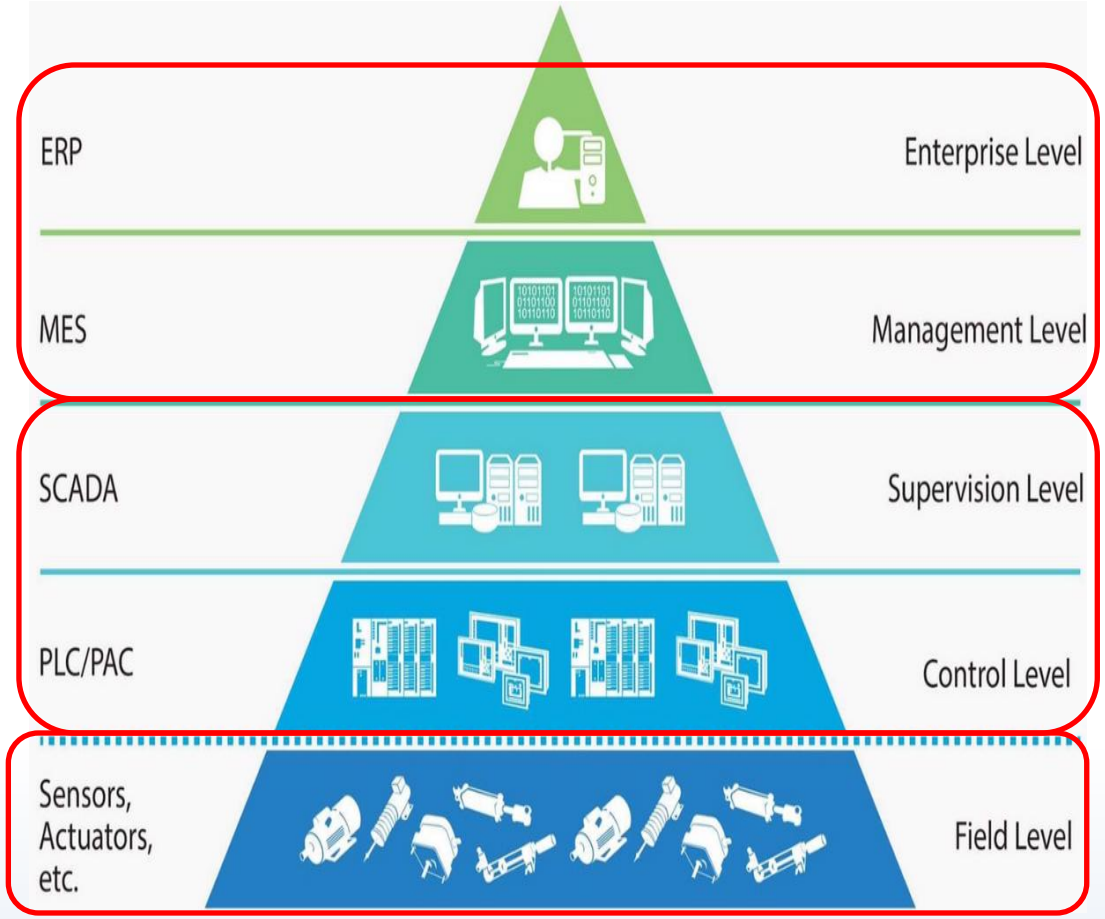
- The first programmable controllers (PLC) were developed in the late 1960s and replaced existing hard-wired relay systems that controlled manufacturing lines.

- The application of programmable controllers and systems enables the operation of processes that require:
  - High levels of control and modulation
  - High degree of precision
  - Involve hazardous chemicals or operations

The Automation Pyramid

- A graphical example of the different levels of automation & control found in a manufacturing facility.

- It ranges from:
  - Sensors, probes, and actuators at the lowest level, which measure/affect individual parameters or equipment components.
  - Computers and control systems at mid-level, which monitor the information relayed from field equipment, cause other system components to react, and maintain specific equipment/operations in a state of control.
  - Management systems at top-level, which gather data across an entire process/facility/company in order to manage business functions and overall operation success.



Data and control flows vertically

Process Automation – Advantages and Disadvantages

Advantages

- Less variation from batch to batch
- Can improve throughput, quality, yield and energy efficiency
- Improves Safety
- Improves control of batch parameters / variables
- Data capture and storage
- Improved process adherence
- Facilitates investigations when things do not operate as expected

Disadvantages

- High cost and complexity to implement
- Can lead to less understanding of the process
- Troubleshooting may take longer when problems arise
- Hard to integrate SU systems as they require significant manual interaction

Sensors, Actuators, and Motors

- **Sensors, Actuators, and Motors** interact directly with our process. These devices connect our process to our process control systems
- Traditionally considered “Dumb” devices

Conductivity

Capacitance

PH

DO

Pumps/Agitators

Valves

Process Analytical Technology (PAT)

PAT: “a mechanism to design, analyse, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA)” FDA.

- **Process Analytical Technology (PAT)** is typically composed of in-line, on-line, or at line probes and sensors (e.g. pH, DO, pressure, temperature, weight, flow, etc.)

- In-line PAT can:
  - continuously monitor important parameters (e.g. CPPs)
  - relay this information to a controller, which assesses the parameter state and compares it to a set-point/range
  - this may cause another system component to react in order to adjust or maintain the system in an acceptable state.

Process Validation and PAT

FDA 2011 Process Validation Guidance:

- "More advanced strategies, which may involve the use of process analytical technology (PAT), can include timely analysis and control loops to adjust the processing conditions so that the output remains constant.

- Manufacturing systems of this type can provide a higher degree of process control than non-PAT systems. In the case of a strategy using PAT, the approach to process qualification will differ from that used in other process designs.

- Further information on PAT processes can be found in FDA's guidance for industry on PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance."

Process Control Systems (PCS)

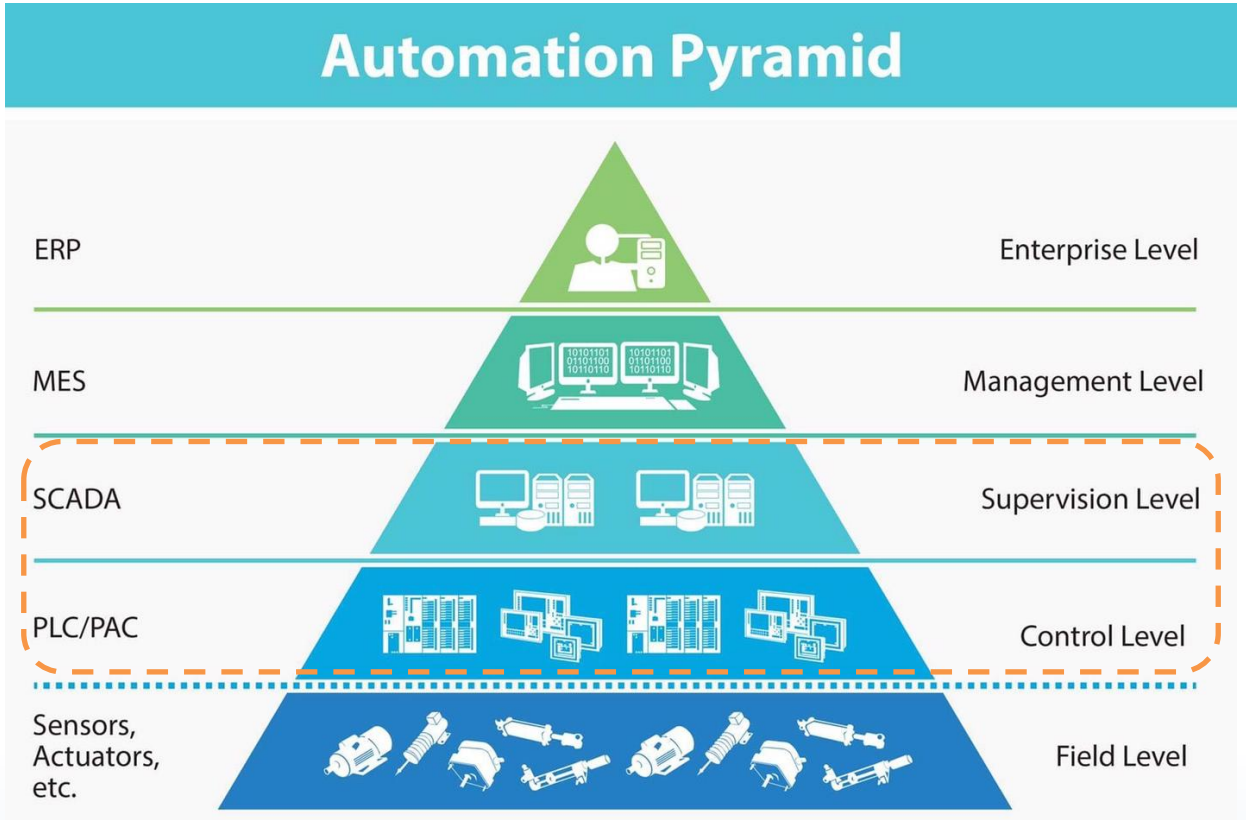
- A process control system is designed to automate and manage complex processes to a high degree of consistency and accuracy
- A PCS works to gather and transmit data obtained during the manufacturing process
- Many types of process control systems exist, including:

Programmable Logic Controllers (PLC)

Supervisory Control and Data Acquisition (SCADA)

Distributed/Decentralized Control Systems (DCS)

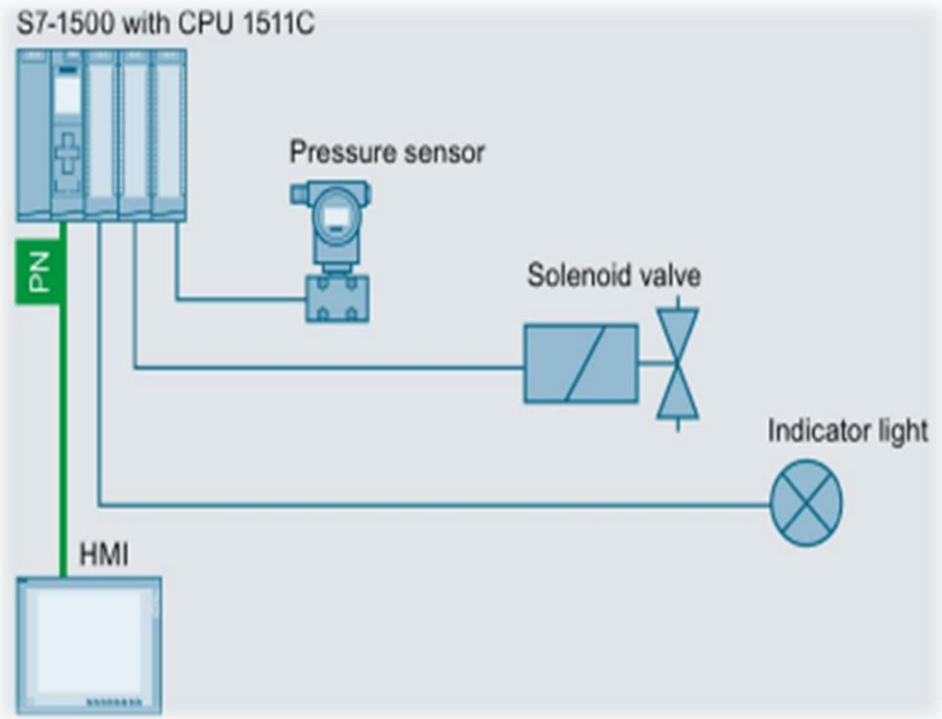
Process Control Systems



- **Process Control Systems** operate on the Control and/or Supervisory level of the Automation pyramid.

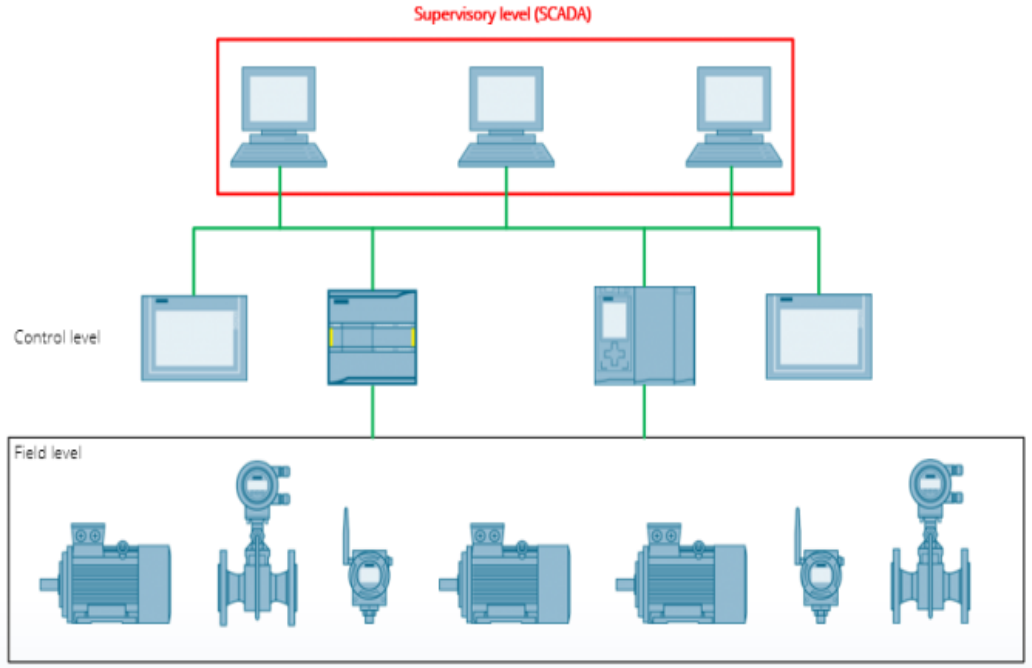
Programmable Logic Controller (PLC)

- A ***Programmable Logic Controller*** (***PLC***) is a modular industrial computer.
- PLCs are used to automate and control individual or multiple pieces of process equipment.
- A control PC/device must be used to program the PLC.
- Input/Output (I/O) feeds from field devices (e.g. probes and actuators) connect directly to the PLC.
- PLC is a relatively simple example of a control system.



2. SCADA

- ***Supervisory Control and Data Acquisition (SCADA)*** is a centralized system that can monitor multiple processes with varying levels of control.
- SCADA systems are made up of the following:
  - Human Machine Interface (HMI)
  - Supervisory system
  - Remote Terminal Units (RTUs)/Programmable Logic Controllers (PLCs)
  - Communication infrastructures (typically slower than DCS).



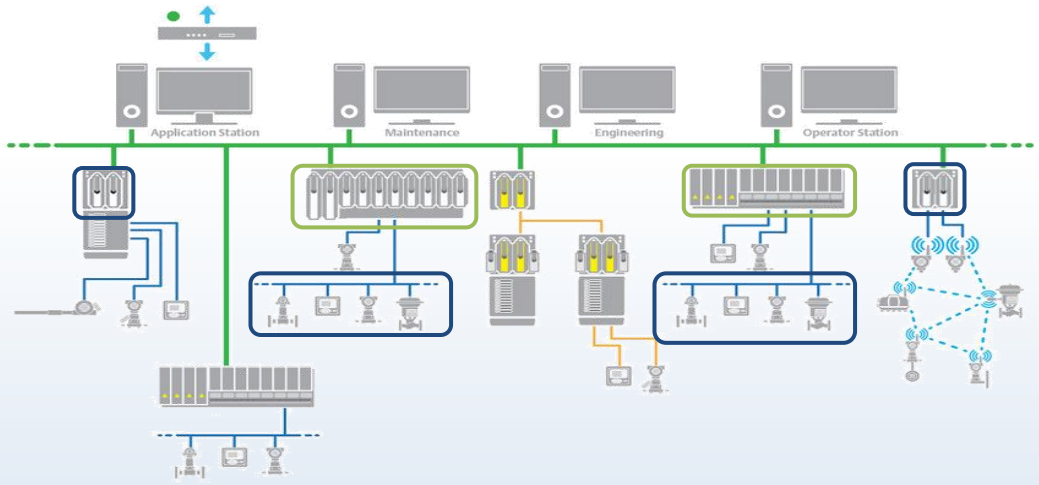
- Typically data driven, so not process-specific. Like a blank slate that is programmed as needed.

3. Distributed Control System (DCS)

- DeltaV is an example of a ***Distributed Control System (DCS)***. Very similar to SCADA systems. Usually contains a SCADA element.

- DCS is typically process-oriented i.e. the program is designed for the specific process. Designed with more processing power and allowing for more complex control algorithms.

- Servers, Equipment, and Controllers are connected via a high-speed communication network.



Controllers are industrial computers similar to PLCs

Device I/O is manged by each controller

Basic Control Theory – Terminology

- **Process variable (PV)** is a condition of the process (e.g. temperature)
- **Set-point (SP)** is the desired value for the process variable (e.g. 37°C for mammalian cell culture)

- **Manipulated variable** is the variable changed so that the PV reaches the SP (e.g. jacket temperature)
- **Error** is the difference between the process variable and the set-point
  - The error has a magnitude, duration and rate of change
- **Offset** is a sustained deviation of the PV from the SP
- **Load disturbance** is an undesired change in one of the factors that affects the PV
- **Control algorithm** is the sequence of measurements, calculations and actions required to control PVs

Development of a Control Strategy

- Fundamentally exists to describe and manage the influence of CPPs on CQAs. Should be comprehensive and contain quantitative criteria which allows for control of:
  - Raw material
  - Process intermediates
  - Process parameters

- Should understand the multi-factor CPP impact for single and multiple attributes and contain a multi-step control strategy for same.

- Risk-based criticality assessment, along with process characterization studies, allows a CS to be established which is subsequently verified during PPQ. The CS should ensure required product quality and a consistent and robust process.

- Here, CPPs must be controlled within limits and in-process controls must be within specified ranges to ensure drug safety and efficacy.

What to Measure?

- The Critical Process Parameters and Critical Quality Attributes which were identified during process and product development.

- Is there any value in measuring attributes shown to be non-critical?
  - Markers of process consistency
  - Only if they have indicator status
  - Knowledge develops over time and batch manufacture experience
  - Material and intermediate attributes linked to CQA outcomes
    - Indirect or indicator parameter or attributes can demonstrate/indicate drift or loss of control

Statistical Procedures/Sampling

- FDA 21 CFR 211.110 “Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specification”.

- FDA 21 CFR 211.16 “Samples must represent the batch under analysis”
- and 211.165 “meet specifications & statistical quality control criteria as condition of approval & release”

FDA Sampling/Monitoring Recommendations

- Recommendation for sampling/monitoring after Stage 2
  - "We recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates.
  - These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process.
  - Monitoring can then be adjusted to a statistically appropriate and representative level.
  - Process variability should be periodically assessed, and monitoring adjusted accordingly."

Data Analysis

- Data analysis from continuous monitoring allows for the following:
  - Trending and analysis
    - In-specification
    - In-trend
  - Alert and action limits
    - Maintenance of product quality
  - Continuous improvement
    - Ensuring process performance is optimal
  - Process change and improvement
    - Using Continuous process verification to demonstrate maintenance of control following process change

Process Capability Index

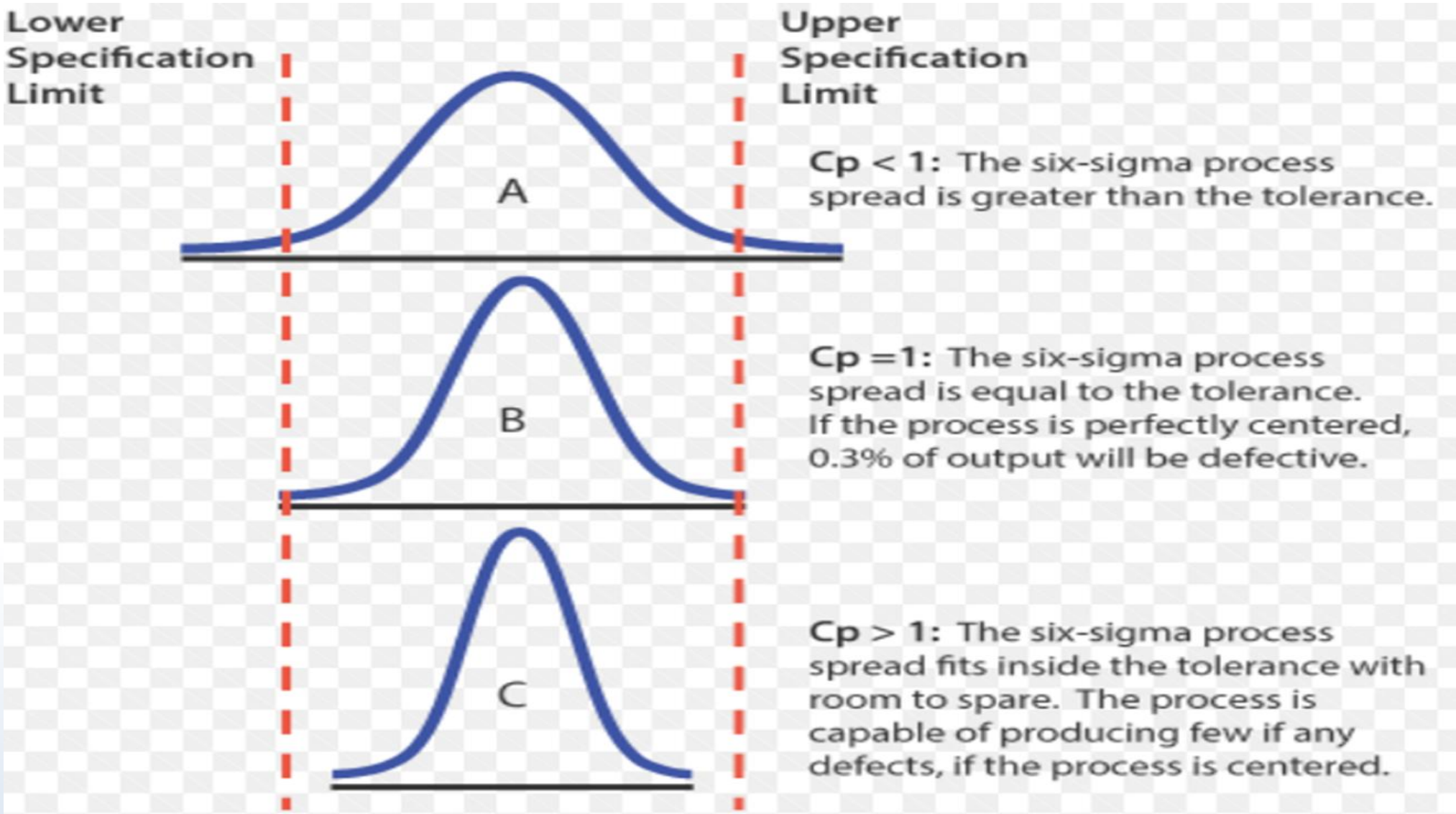
- Process capability assessment evaluates the risk that an attribute will fail to meet specifications; in other words, it quantifies the likelihood that an attribute will routinely meet specifications.

- Any assessment of process capability requires the assumption that the same sources of variation that affected previous results will continue to affect future results, and the expected range of variability does not change.

Cp, CpK and PpK

- There are many indices that measure process capability, but two are especially popular: Ppk and Cpk.
- Both indices compare the width of the specification range to the width of the typical variation range.
- The key difference between Cpk and PpK is that CpK uses a short-term estimate of variation, whereas Ppk uses a long-term.
- These indices take into account the centering of the process within the specification range, and higher values of either index indicates higher process capability (or lower risk of missing specifications). Cp ignores this centering.

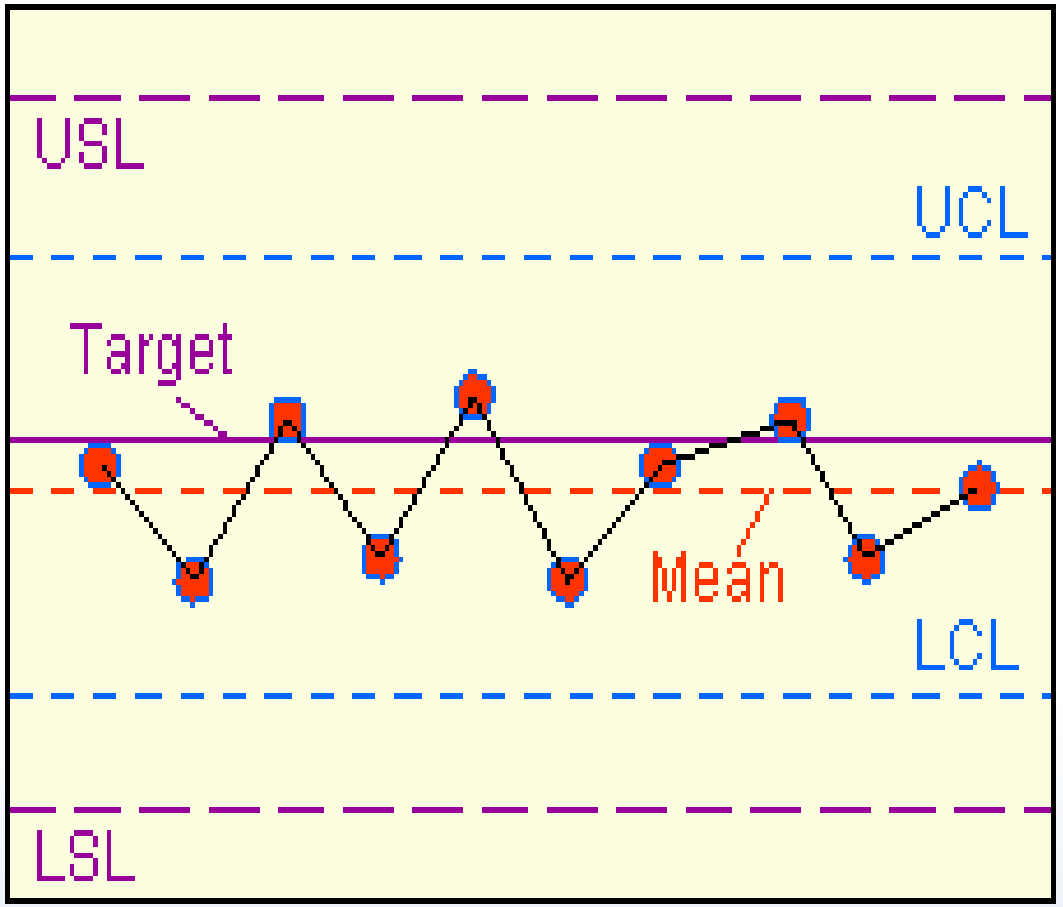
Cp, CpK and PpK



Control Charts

- Control charts consist of a few simple elements:
  - Results plotted in time order;
  - A centerline, usually at the average of the results;
  - Statistical control limits.

- There are many varieties of control charts. The type of chart should be selected based on the type of data to be plotted. Most attributes plotted for CPV are individual continuous measurements.



Responses to Shifts and Trends

- Continuous Process Verification (CPV) is intended to serve as an ‘early warning system’ where process drift can be detected before it can cause an OOS or failure that could otherwise impact product quality.

- Thus, responses to shifts and trends discovered during CPV typically include those that remain within specifications.

- Investigations or other activities may be triggered to identify the root cause of the process and/or quality shift; however, closure of the investigation triggered in this way is not typically tied to lot release; unless an ‘out-of-specification’ (OOS) situation has also occurred.

Responses to Shifts and Trends

- Shifts and trends that remain within specifications should be evaluated by trained personnel who are most familiar with the process or assay.

- The response to the shift or trend may be determined by the local engineering, process scientist, or technology function, with consultation from the quality, operations, and statistical functions.

- These investigations form part of the CPV Plan and in most cases, a formal quality investigation/deviation will not be required, as an OOS situation will not normally have occurred alongside a CPV trend.

Root Cause Analysis Following a Shift

- Establish that the results are valid;
  - Check for any indications of inconsistency, e.g. within a laboratory, during the timeframe the result was obtained;
  - Evaluate any other attributes that typically correlate with the result, to determine if all attributes trended together as expected, or if the particular result was exceptional;
  - Walk the process upstream from the sample point and collect process performance data to understand any unusual patterns in process operations during the timeframe the result was obtained.

- The explanation of within-specification shifts and trends should be documented in the routine CPV Report. If the reason for a shift or trend cannot be identified during CPV, it may be escalated to the status of an official quality deviation, for further investigation. It may be advantageous to define a ‘tiered’, risk-based approach linked to anticipated actions when a shift or trend is observed. This approach could be developed over time.

Change Management

- Changes to the control strategy need to consider the potential impact to the current status of the CPV plan.

- Facility, process, equipment, field measurements, or analytical laboratory method changes (examples of normal change controls) require a review of the control strategy, any related risk assessments, and the current monitoring plan for the steps being changed as well as the downstream steps that have linked parameters or attributes.

- If a process variable is re-classified in the control strategy based on new process understanding, changes to the CPV monitoring plan may also be needed and any impact to registered details of regulatory licenses need to be addressed.

Continued Process Verification

- 21 CFR 211.180 Stage 3 - Continued Process Verification:
  - "CGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability.
  - Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control".

Thank You