EMA and FDA Approaches to Process Validation

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PharmOut

Regulatory Knowledge, Practically Applied.

Agenda

A quick overview of the new FDA and EMA process validation approaches

- What are the main changes from the previous approaches?
- Are you going to require significant change and investment to comply?

What are the key differences between the EMA and FDA approaches for process validation?

- Where do the EMA and FDA disagree?
- Where do they ask for different requirements?

How you can navigate the two approaches to present an integrated, compliant strategy.

- How you can develop a single approach to be compliant across both regulators

Part 1: Overview of the New Process Validation Requirements

FDA Approach to Process Validation

Emphasised in the FDA's 2011 guidance document – Process Validation: General Principles and Practices.

Process Validation is "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."

FDA Approach to Process Validation

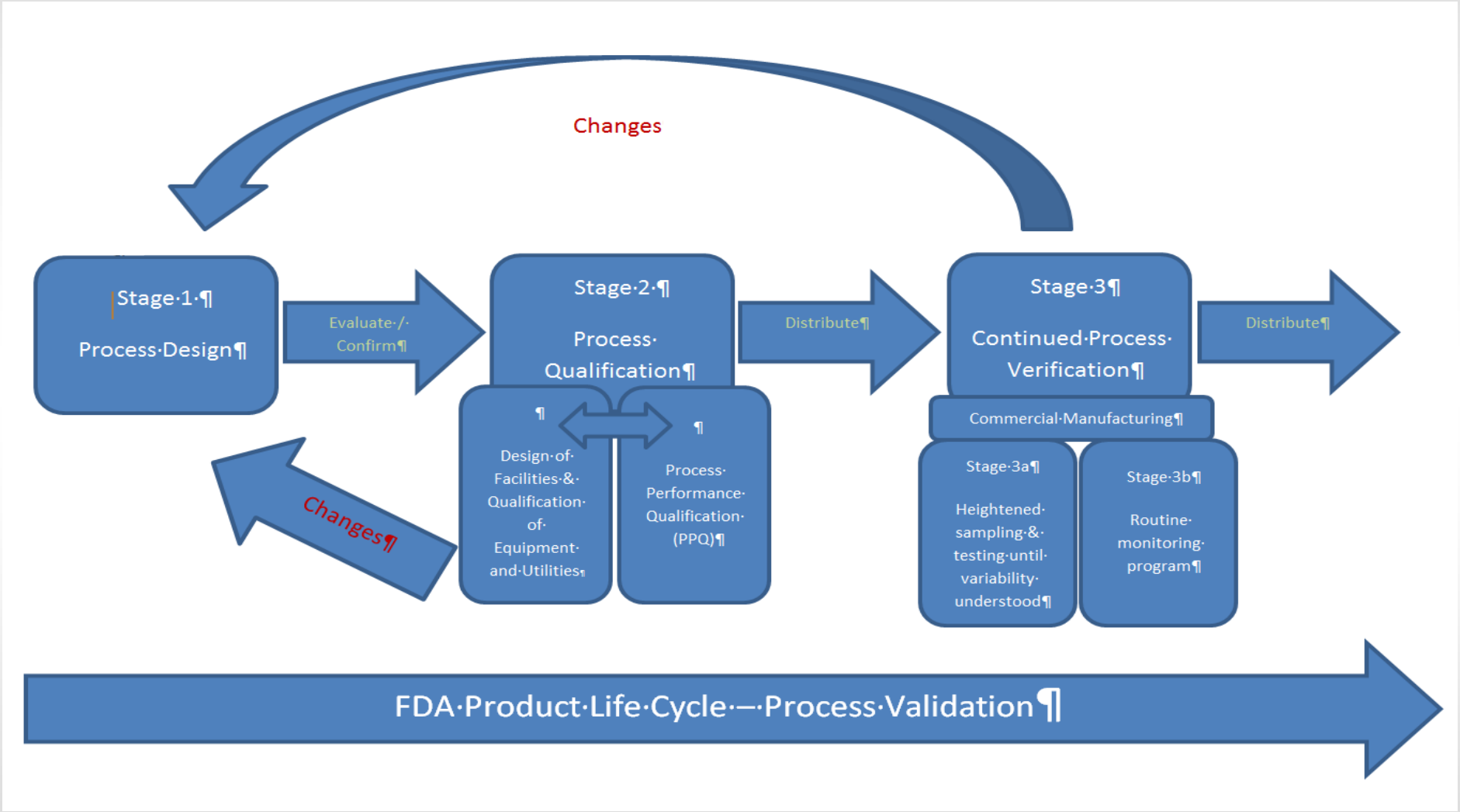
Objective

To understand and control input **variability** impact and manufacturing process to assure consistent product quality and reliable supply.

- Science and Risk based PV / PPQ – product and process understanding, good science, statistical confidence.
  - Statistically based sampling plans and acceptance criteria for PPQ / PV and release.

- Understanding the impact of variability and demonstrating control strategy is robust beyond the variability
  - Variability in raw materials / excipients, parameter control, operators, shifts, equipment sets, etc.

FDA Process Validation Lifecycle



FDA Approach to Process Validation

PV Stage 3a (Establishing initial process variability)

- "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**."

PV Stage 3b (After variability established)

- "**Monitoring can then be adjusted to a statistically appropriate and representative level**."

EMA Approach to Process Validation

- "A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes."
- A robust product development process is required to enable successful process validation.
- Before product is released to the market, the process must be shown to be robust and ensure consistent product quality irrespective of the approach used.

EMA Approach to Process Validation

- Retrospective validation no longer acceptable.
- Concurrent validation only acceptable where there is a strong benefit-risk ration for the patient.
- Appropriate quality oversight over the whole validation life cycle is essential.

EMA Approach to Process Validation

- The V-model concept is still appropriate.
- Testing completed during FAT / SAT can be leveraged provided that:
  - The strategy is defined up front.
  - Good documentation practice and data integrity practices are followed throughout the testing.
  - Appropriate quality oversight is applied to the testing.

Part 2: Key differences between the EMA and FDA approaches for process validation

EMA vs. FDA – Differences

- The differences in the guidance documents are not significant. Properly developed processes / products should meet the expectations of both EMA & FDA.
- The core expectations of both EMA & FDA with respect to process validation overall are nearly identical and likely to be more closely aligned in the future.
- FDA – Currently effective
- EMA – Final version released 30th March 2015
  Effective 1st October 2015

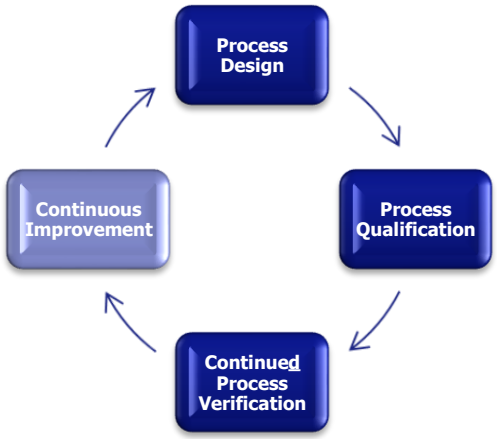
EMA vs. FDA – The Focus

- FDA focuses on understanding and controlling variability.
- EMA focuses on science based, quality risk management.
- EMA tends to be more apprehensive with respect to novelty and identifies specific products / processes where additional products / processes where additional concerns are present.
- There is substantially less mention in the EMA guidance with respect to the use of statistics.

EMA vs. FDA – Process Validation Life Cycle

- FDA uses the term "Process Validation" to refer to the life cycle of validation, from process design to routine manufacture.

- EMA uses the term "Process Validation" to represent the life cycle of the product. "Qualification and Validation" is used to define processes applicable to facilities, services and equipment.



EMA vs. FDA – Number of PV / PPQ batches

- EMA – "it is generally considered acceptable that a minimum of three consecutive batches manufactured under routine conditions could constitute a validation of the process."

- FDA – "Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product"

Continued vs Continuous vs Ongoing Process Verification

FDA

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Continued Process Verification.

Continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.

Continuous Process Verification.

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

Ongoing Process Verification (aka continued process verification).

Documented evidence that the process remains in a state of control during commercial manufacture.

Continued vs Continuous vs Ongoing Process Verification

- Continuous Process Verification is usually done by some form of Process Analytical Technology (PAT).
- FDA requires that data from Continuous Process Verification is assessed **after every batch.**
- EMA states that "there should be a regular evaluation of the control strategy".

Part 3: Navigating the two approaches to present an integrated, compliant strategy

A paradigm shift

A new direction towards a:

- Science-Based
- Risk-Based
- Cost Effective approach

to ensuring patient safety & product quality during pharmaceutical development and manufacturing

International Conference on Harmonization (ICH)

In Brussels, 2008 the International Conference on Harmonization established the following goal:

"Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science."

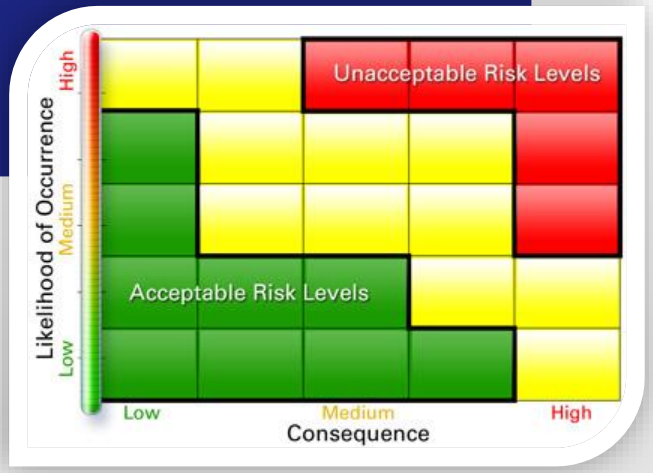
ICH Q8 Pharmaceutical Development

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 Q9 Quality Risk Management

"The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk."

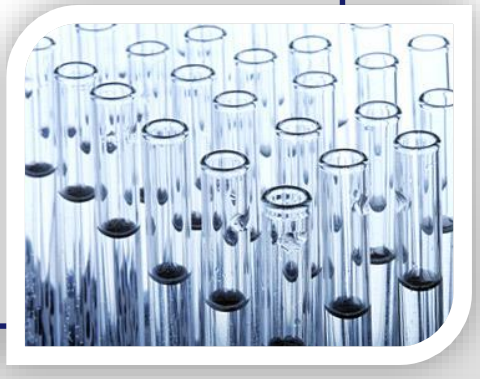


ICH Q11 Development & Manufacture of Drug Substances

"A company can choose to follow different approaches in developing a drug substance. For the purpose of this guideline, the terms "traditional" and "enhanced" are used to differentiate two possible approaches."

Traditional approach:

Set points and operating ranges for process parameters are defined and the drug substance **control strategy** is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria.



ICH Q11 Development & Manufacture of Drug Substances

Enhanced approach:

Risk management and **scientific knowledge** are used more extensively to identify and understand process parameters and unit operations that impact critical quality attributes (CQAs) and develop appropriate **control strategies** applicable over the lifecycle of the drug substance which **may** include the establishment of design space(s).

FDA (& EU) Process Validation Stages

Stage 1 – Process Design: The process is defined during this stage based on knowledge gained through development and scale-up activities.

Identify sources of Variability

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Control of Variability

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

Monitoring Variability-remains "in control"

Stage 1 – Process Design: The process is defined during this stage based on knowledge gained through development and scale-up activities.

Identify sources of Variability

Quality Risk Management (QRM)

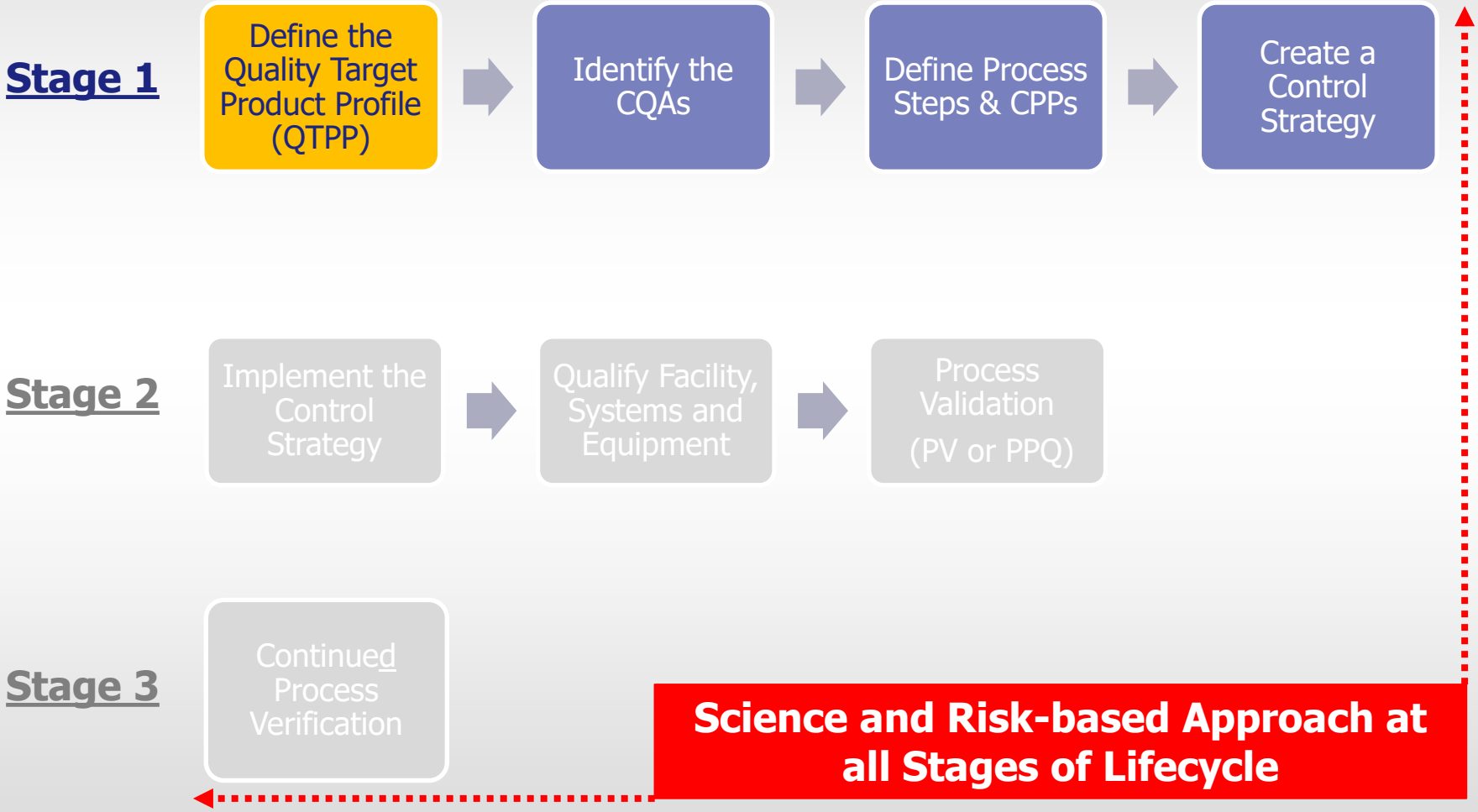
The QRM process must be systematic with defined policies and procedures

Must operate across the lifecycle

Principles and methodologies should be clear

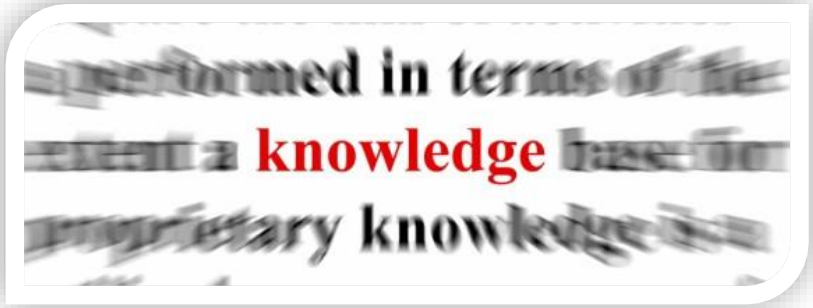
Criteria and decisions from assessments should be documented

Product realisation by QbD



Stage 1- Process & Product Knowledge

- Process & Product Knowledge gathered to develop a Control Strategy.
- Robust process with low variability.
- Effort focussed using Risk Assessment.
- Efficient Planning ensures success through the entire Lifecycle.



Define the Quality Target Product Profile (QTPP)

Stage 1- Process & Product Knowledge

Product & Process Knowledge can come from a variety of sources:

- Previous experience with the process or a similar process.
- Analytical and product data from clinical studies.
- Process Development information.
- Small scale or engineering studies/batches.
- Clinical manufacturing.
- Technology Transfer

Define the Quality Target Product Profile (QTPP)

Quality Target Product Profile (QTPP)

"A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product".

(ICH Q8)

Define the Quality Target Product Profile (QTPP)

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Quality Target Product Profile (QTPP)

Pharmaceutical Development goals are to design a quality product.

Establish pre-defined objectives and document the summary as a QTPP:

- Summarise the quality attributes that ensures safety and efficacy.
- Starting point for understanding and assessing criticality of product quality attributes.

Define the Quality Target Product Profile (QTPP)

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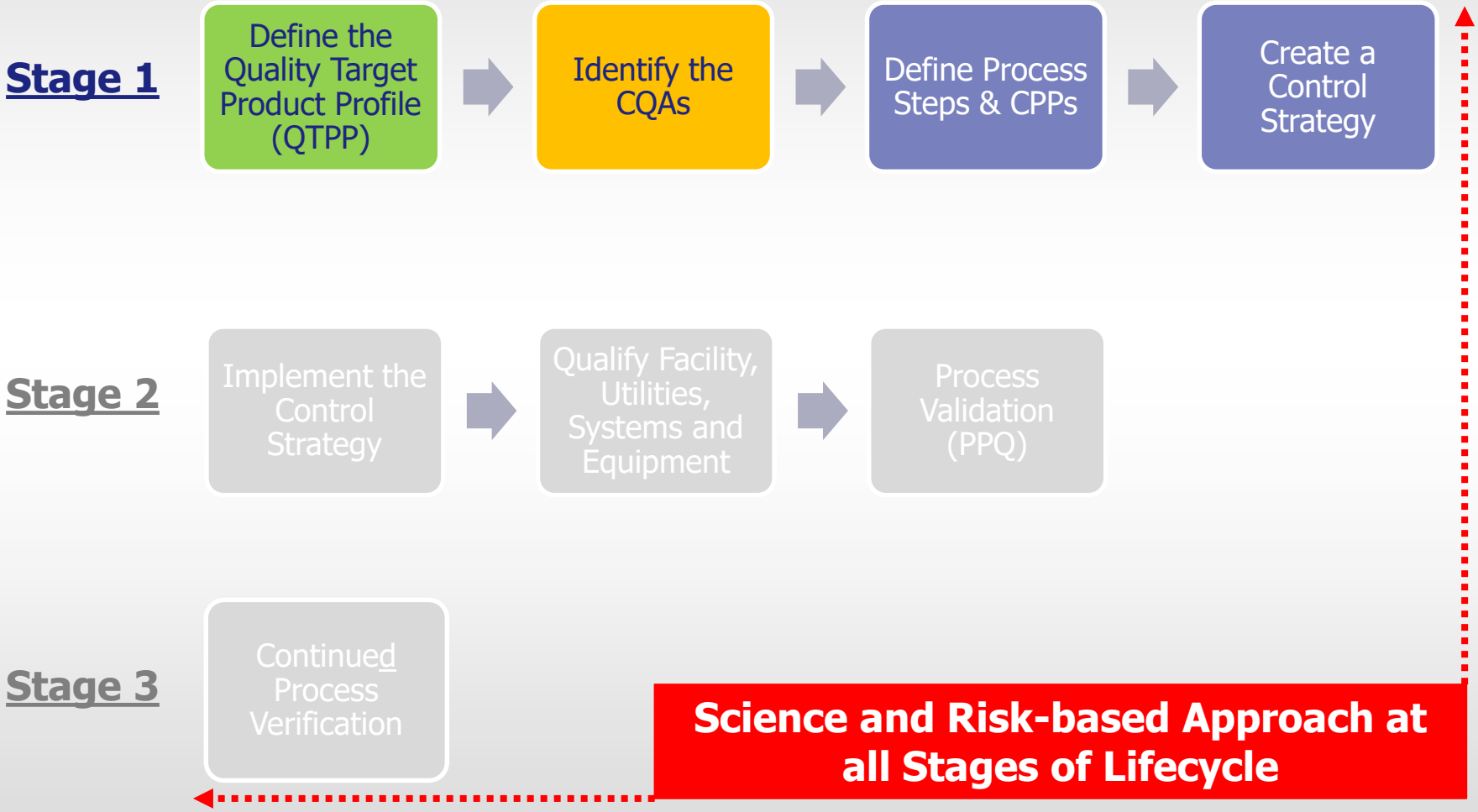
Quality Target Product Profile (QTPP)

Example: 500mg paracetamol tablet

Tablet Attribute*	Tablet QTPP
Dose	500mg Paracetamol tablet
Subjective properties	Appearance, uniform, no off taste or odour
Patient safety – chemical purity	Impurities and / or degradation products below ICH or to be qualified
Patient safety – biological purity	Acceptable level of non-pathogenic microorganisms, free from yeast or moulds or below the specified limit
Patient efficacy – particle size distribution (PSD)	PSD that does not impact bioperformance or pharmaceutical processing
Chemical and drug product stability:2 year shelf life, below 30˚C	Degradation products below ICH or to be qualified and no changes in bioperformance over expiry period

**Only a few Paracetamol TPPs discussed here*

Process Flow



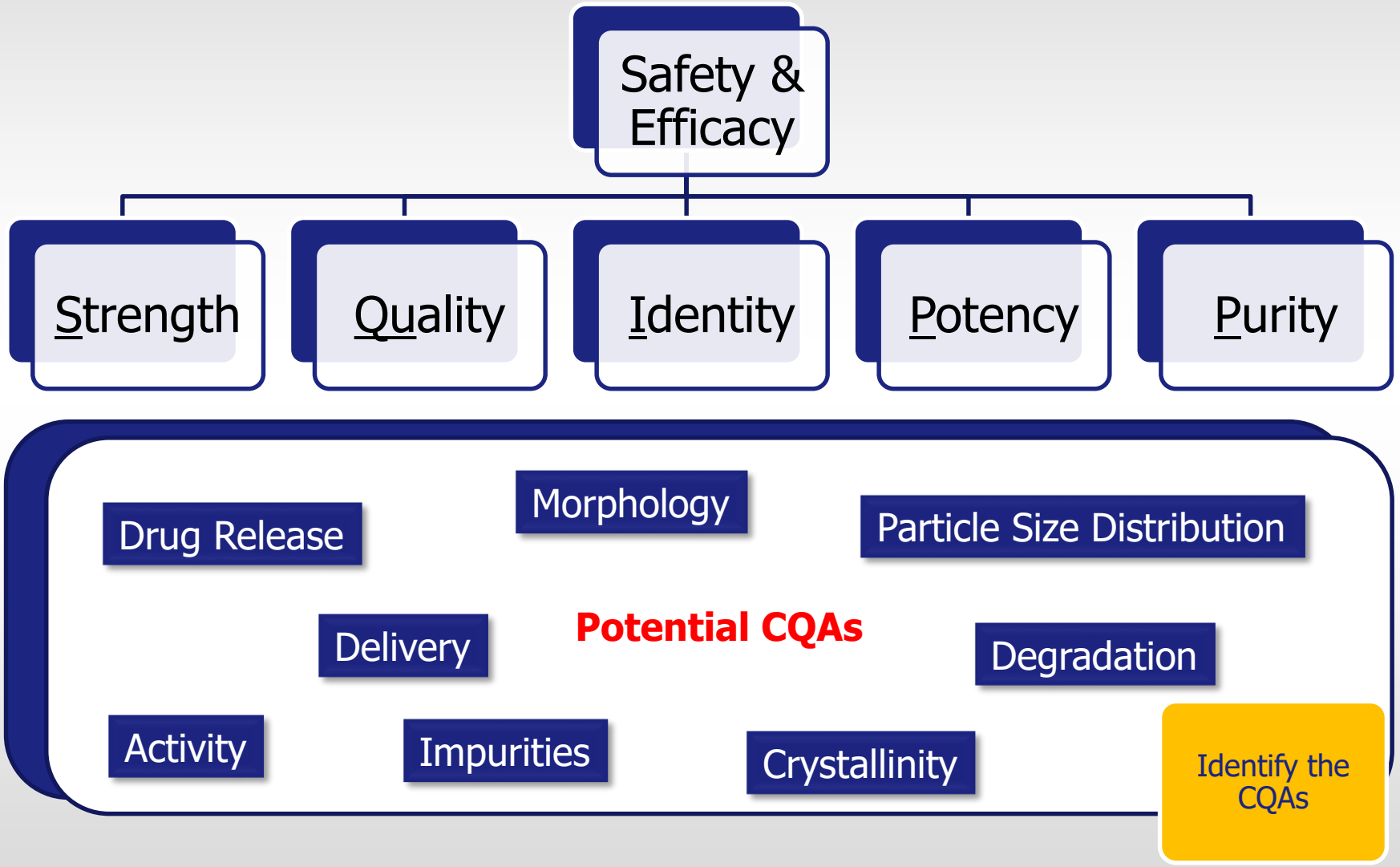
Critical Quality Attributes (CQA)

"A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality".

(ICH Q8)

Identify the CQAs

QTPP to Potential CQAs



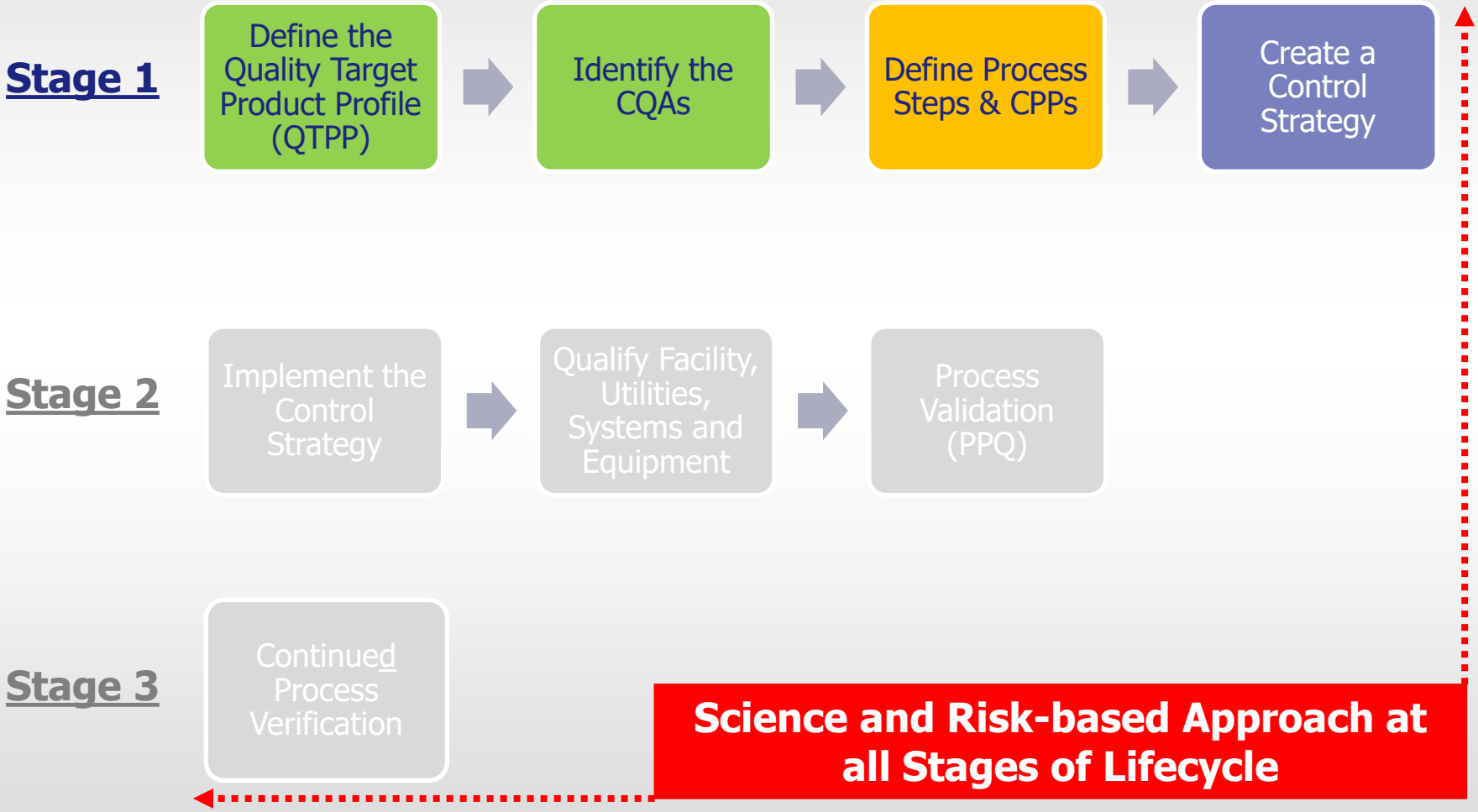
From QTPP to CQAs

Example: 500mg paracetamol tablet

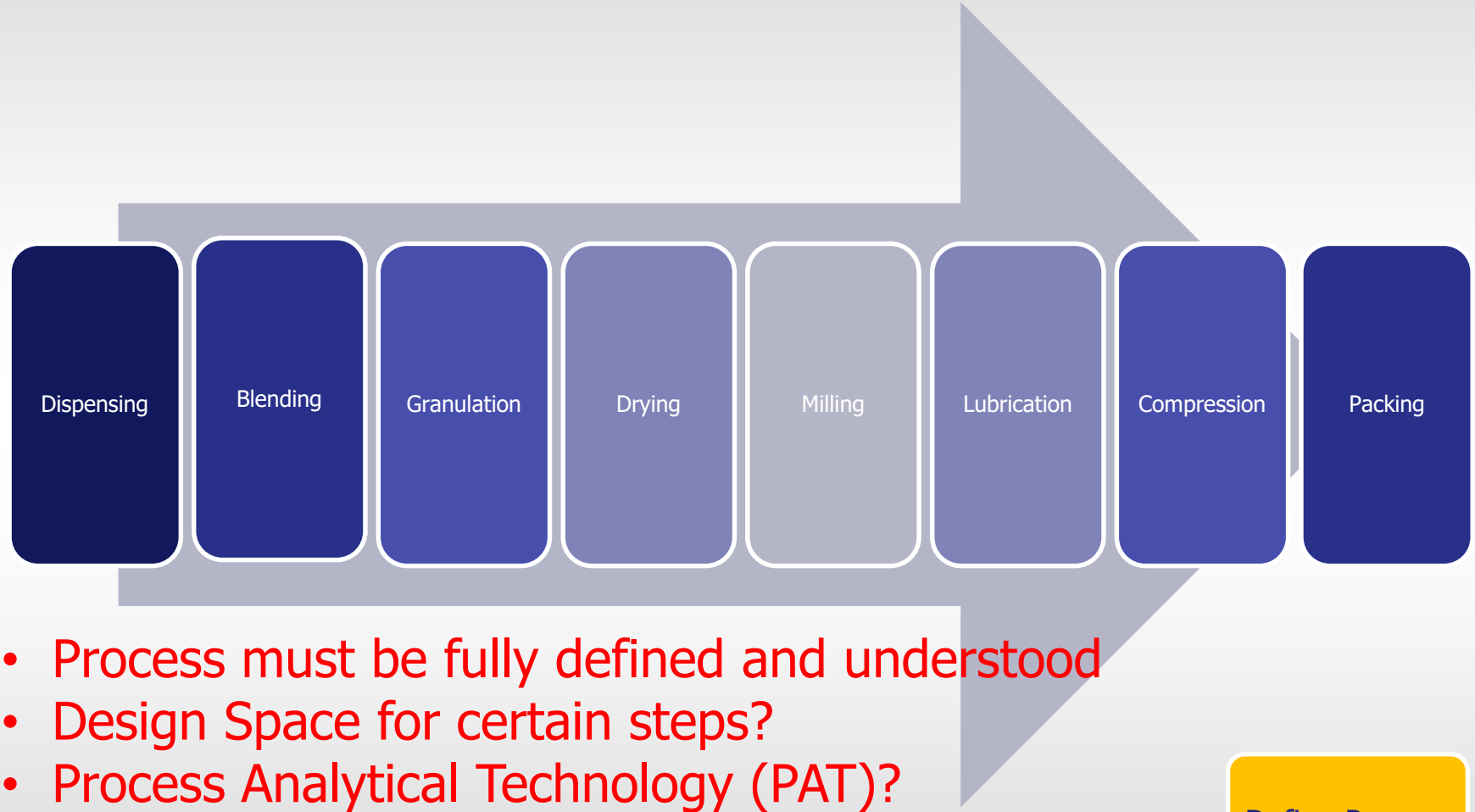
Paracetamol Product	Paracetamol QTPP*	Translation to CQA
Dose	500mg tablet	Identity, Assay, Uniformity of Dosage Units
Subjective properties	Appearance, uniform, no off taste or odour	All blisters filled, correct number of strips in pack, unit Integrity and other characteristics
Patient safety – chemical purity	Impurities and/or degradation products below ICH	Appearance and other characteristics Absence of defects
Patient safety – biological purity	Acceptable level of non-pathogenic microorganisms, free from yeast or moulds or below the limit	Acceptable degradation product levels at release, appropriate manufacturing environment controls, input raw material quality. Degradation controlled by packaging.

**Only a few Paracetamol QTPPs included here*

Process Flow



Process for manufacture of 500mg Paracetamol



- Process must be fully defined and understood
- Design Space for certain steps?
- Process Analytical Technology (PAT)?
- Real-time Release Testing (RTRT)?

Define Process Steps & CPPs

Process Description

Each step of the process should have the following information available:

Inputs	Processes	Outputs
• Raw Materials • Excipients • Intermediates • Utilities	• Steps/scale • FSE* • Set-points • Ranges • Sampling • Testing	• Product • Intermediate • Waste • Data

*FSE = Facilities, Systems (& Utilities) & Equipment

Define Process Steps & CPPs

Overall Process Assessment

CQA	Dispensing	Blending	Granulation	Drying	Milling	Lubrication	Compression	Packing
Identity								
Appearance								
Assay								
Content Uniformity								
Purity								
Hardness								
Friability								
Dissolution								

Known or Potential impact to CQA

Potential impact to CQA

No impact to CQA

Define the highest risk parameters and identify the CPPs

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Critical Process Parameters (CPPs)

"A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality".

(ICH Q8)

Define Process Steps & CPPs

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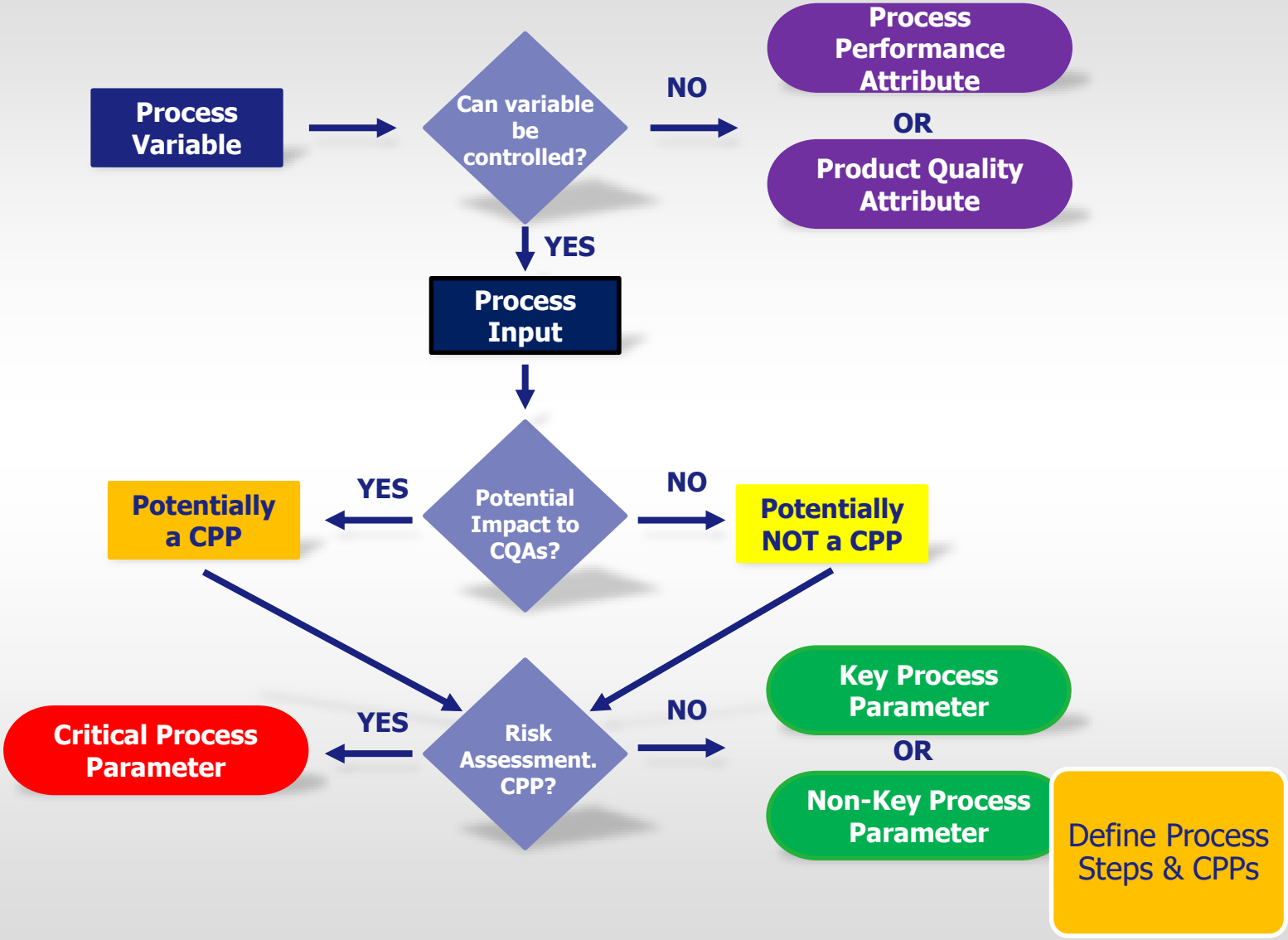
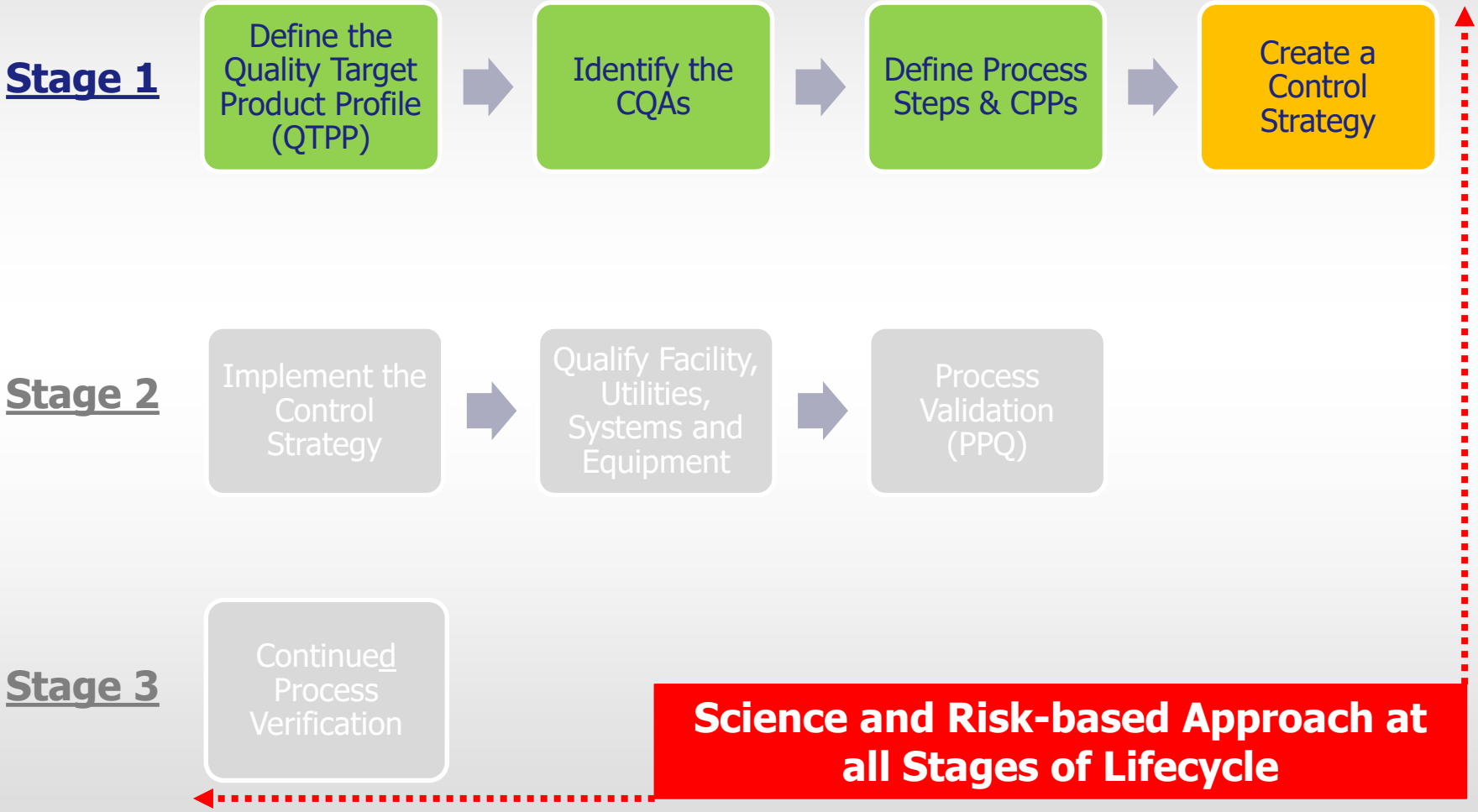
Defining CPPs



Process Flow



Control Strategy

"A planned set of controls, derived from current product and process understanding that ensures process performance and product quality."

(ICH Q10)

(definition continued on next slide)

Create a Control Strategy

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Control Strategy

"The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control".

(ICH Q10)

Create a Control Strategy

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Control Strategy

- Important output of Stage 1
- Will ensure that the process remains in control
- Created based on process knowledge gained and the application of science and risk-based approaches and techniques
- Encompasses all elements of each unit operation of the manufacturing process
- All product attributes and process parameters should be in a complete Process Control Strategy

Create a Control Strategy

Control Strategy for Blending

CQA	Process Step	Parameter	Specification	Control
Uniformity of Dosage Units	Blending	Time (min)	4-16 mins	5-8 mins
Uniformity of Dosage Units	Blending	Speed (rpm)	10-15 rpm	12-14rpm
Uniformity of Dosage Units	Blending	Load (Kg)	900-1200 Kg	1000-1100 Kg

**Only one Paracetamol Control Strategy included here*

Create a Control Strategy

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Control Strategy

Other Control Strategies and their rationale might include:

Control Strategy Elements	Rationale
Raw Materials	Control of input variability
Test Specifications	Related to product safety/efficacy
In-Process Controls	Monitor the process
Performance Parameters	Cannot be controlled but are indicators
Set Points & Ranges	Known acceptable variability
Process Monitoring	Data collection for all Stages
Processing & Hold Times	Time limits impact product quality
Process Analytical Technology (PAT)	Real-time monitoring/release

Create a Control Strategy

Process Design Completion

Stage 1 output should be a Report that justifies the Control Strategy:

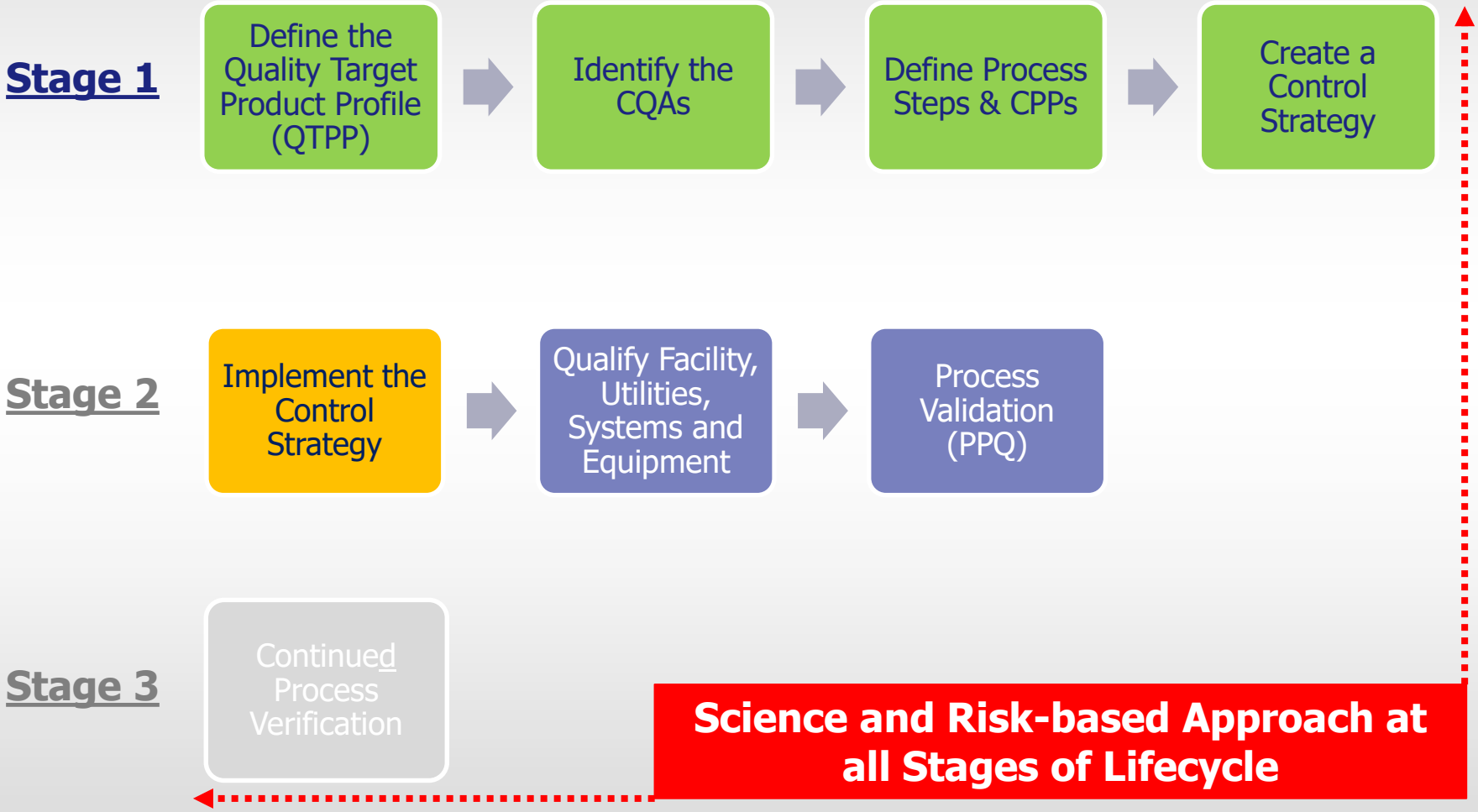
- Defined CQAs
- Risk Assessments
- Process Information (Inputs & Outputs)
- Parameters and Ranges
- Design Space Information (if applicable)

Create a Control Strategy

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

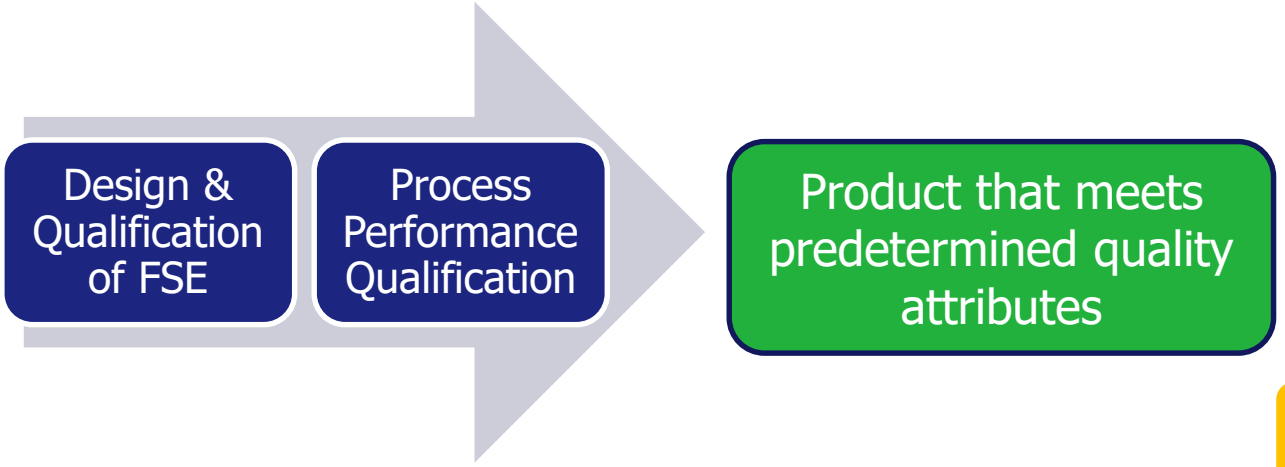
Control of Variability

Process Flow



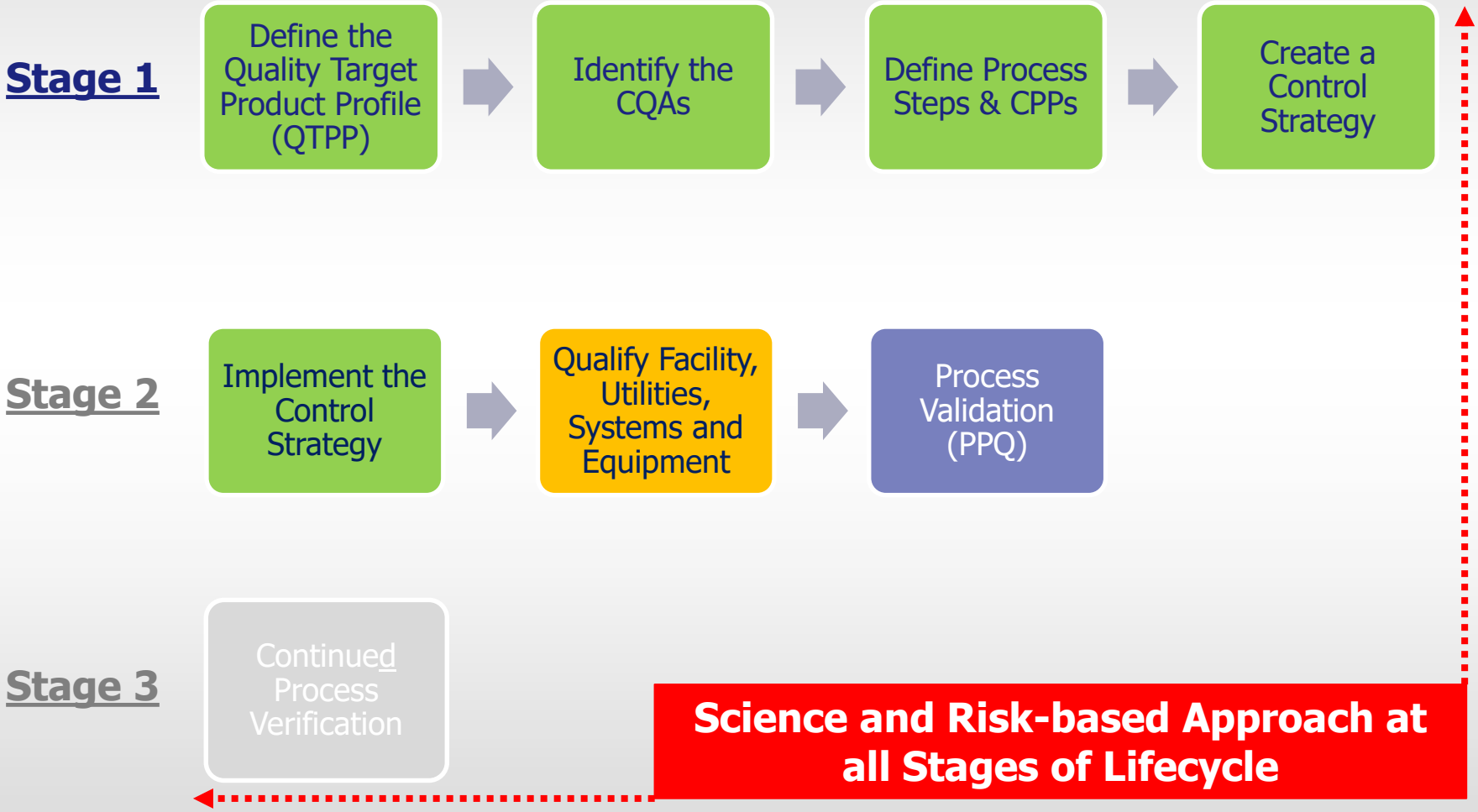
Stage 2 Process Qualification

- Demonstrate that the process is capable of reproducible commercial manufacture
- It should be completed before product is released commercially.
- Two parts to this Stage:

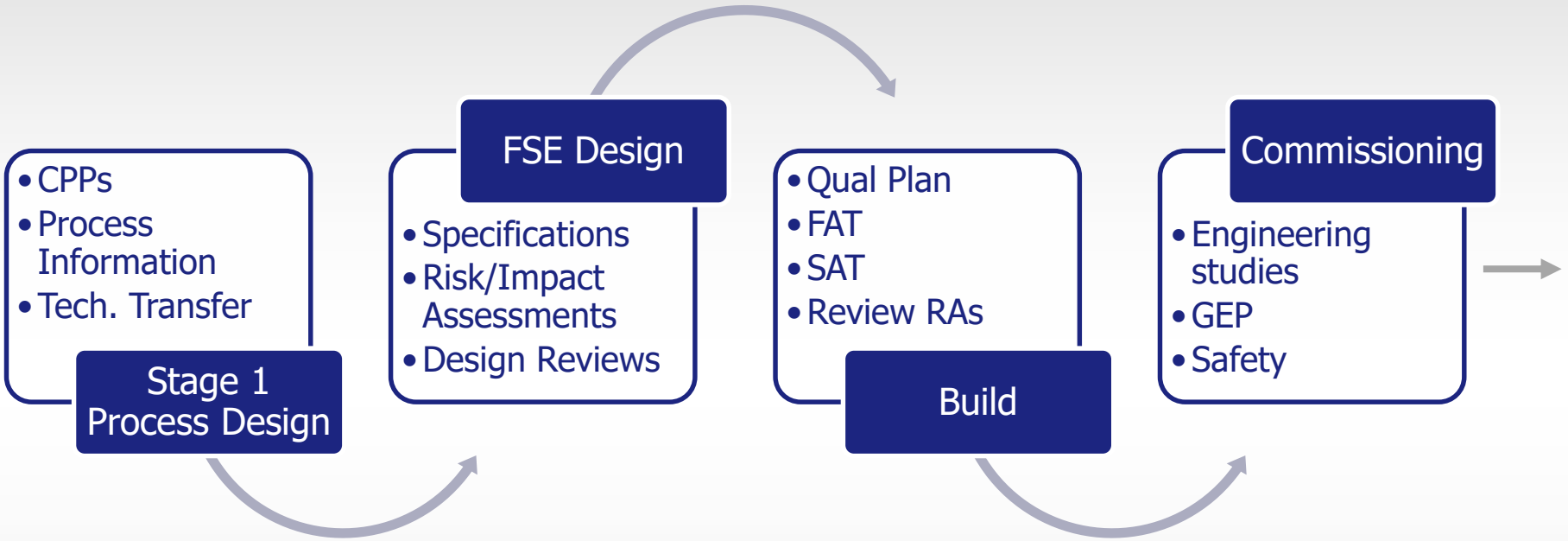


Implement the Control Strategy

Process Flow



Design & Qualification of FSE

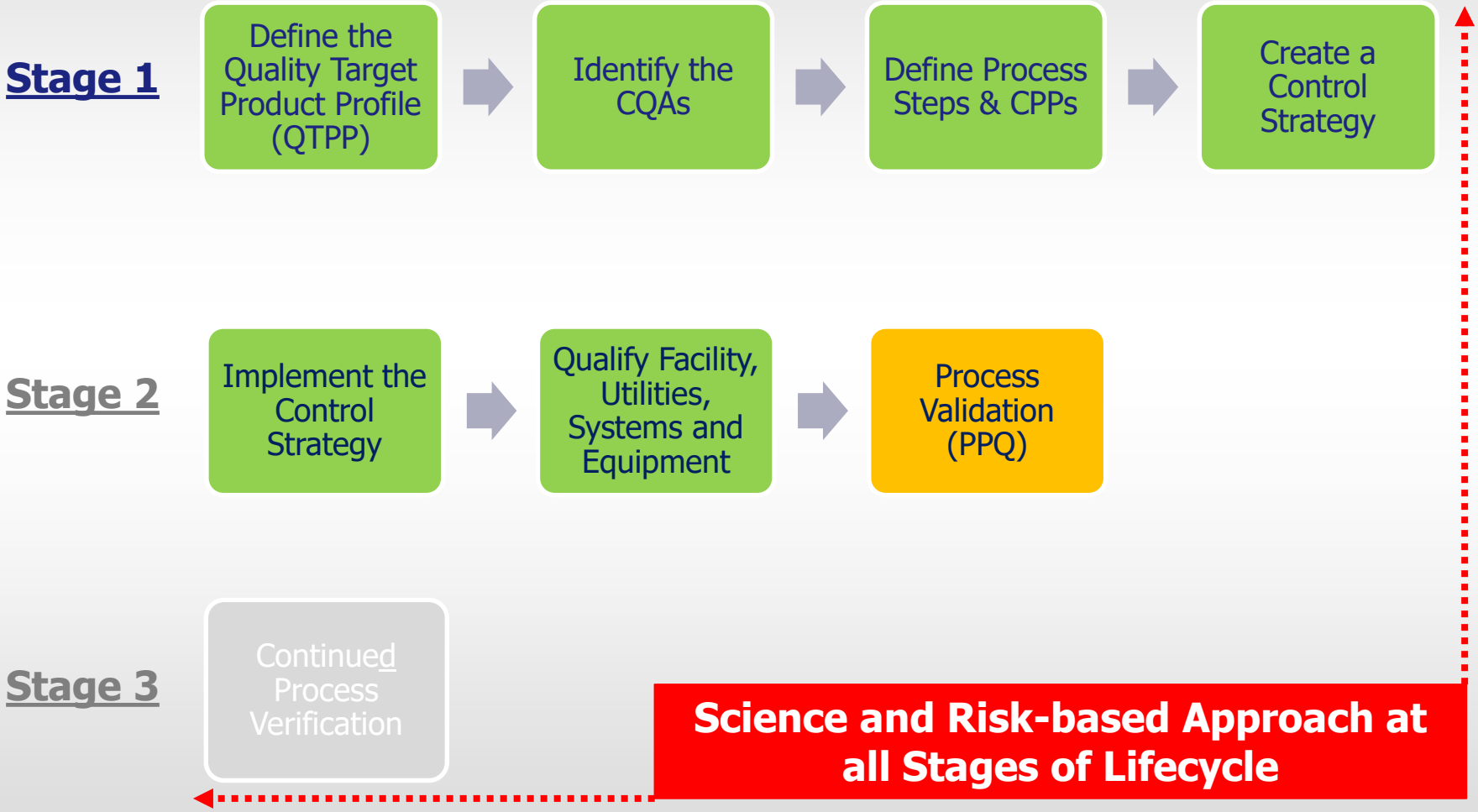


Qualify Facility, Utilities, Systems and Equipment

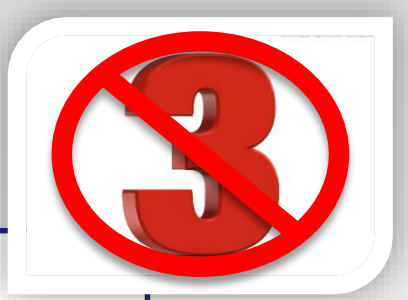
Design & Qualification of FSE

Qualify Facility, Utilities, Systems and Equipment

Process Flow



Process Validation



- Demonstrates the validity of the process design and the suitability of the process control strategy
- At full-scale (commercial manufacture)
- Provides confidence (documented evidence) that systems of monitoring, control and SOPs in production are capable of detecting and compensating for potential sources of process variability over the product lifecycle
- The number of PV batches to be produced should be justified

Process Validation (PPQ)

Knowledge vs # of PV batches

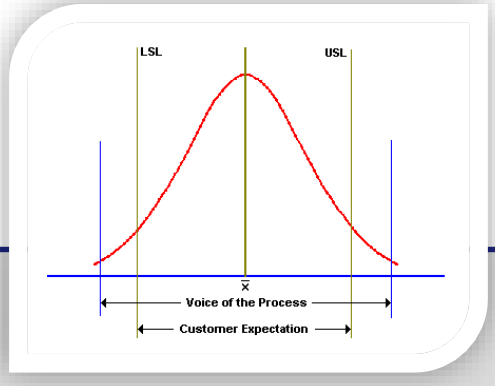
Comprehensive Prior Knowledge may support fewer PV batches

Limited Prior Knowledge may require more PV batches

How many PPQ batches?

"The approach to PPQ should be based on sound science and the manufacturers overall level of product and process understanding and demonstrable control"

Process design is evaluated to determine if the process is capable of reproducible commercial manufacturing



Process Validation (PPQ)

How many PPQ batches?

This depends on the **risk** and the following elements could be applied to make the decision:

Process Validation (PPQ)

Statistical Acceptance Criteria for Validation

Provide X% confidence that each specified requirement has been met

- Requirements: process performance to consistently meet attributes related to SQuIPP (Strength, Quality, Identity, Purity, Potency).
- Level of statistical confidence required may be based on…
  - Risk
  - Criticality of the attribute
  - Scientific and engineering knowledge
  - *A priori* (beforehand) historical knowledge (Stage 1, similar processes, revalidation…)
- Document your strategy!!!

Process Validation (PPQ)

PV Acceptance Criteria for Attribute Types

Attribute Type	Comment
AQL attributes • Fill volume • Tablet defects • Extraneous matter, etc.	≥90% confidence that… • Nonconformance rate ≤assigned AQL
Statistical parameters • Mean / sigma / RSD • Cpk, Ppk	≥90% confidence that… • Mean / sigma / RSD in spec • Ppk ≥1.0, 1.33 or related to % coverage
No within batch variation expected • pH of a solution • Label copy test	Statistics not usually necessary • May consider 3X-10X testing • Assess between lot variation

Process Validation (PPQ)

What is confidence? Type I and Type II Error

- For validation:

		Test results…	
		Pass	Fail
Process is really…	In spec	Correct $(1-\alpha)$	Type I Error α Manufacturer's Risk
	Out of spec	Type II error β Consumer's Risk	Correct $(1-\beta)$

- Need to prove that the process is good – detect problem processes in validation
- "Guilty until proven guilty"
- Type II error usually β = 0.2, 0.1, or 0.05
- β = 0.1 ➔ 90% confidence an out of spec process will fail the process validation acceptance criteria

Process Validation (PPQ)

Impacts to Validation Sampling

- Ideally, all process variables would perform similarly across all runs of a product. However, products will often be impacted due to differences in:
  - Raw materials
  - Different plants of manufacture
  - Different process equipment for use with same processes
  - Different process operators
  - Different lab facilities and analyst capabilities

Process Validation (PPQ)

Sampling

1. **Simple Random Sampling** – Selecting samples so that each unit has an equal chance of being selected
2. **Stratified Random Sampling** – Selecting samples deliberately from each time period or location in a batch
3. **Nested Sampling** – Selecting units from locations within a batch and obtaining multiple samples from each location
4. **Systematic Sampling** – Selecting units periodically over time

Process Validation (PPQ)

Stratified Sampling

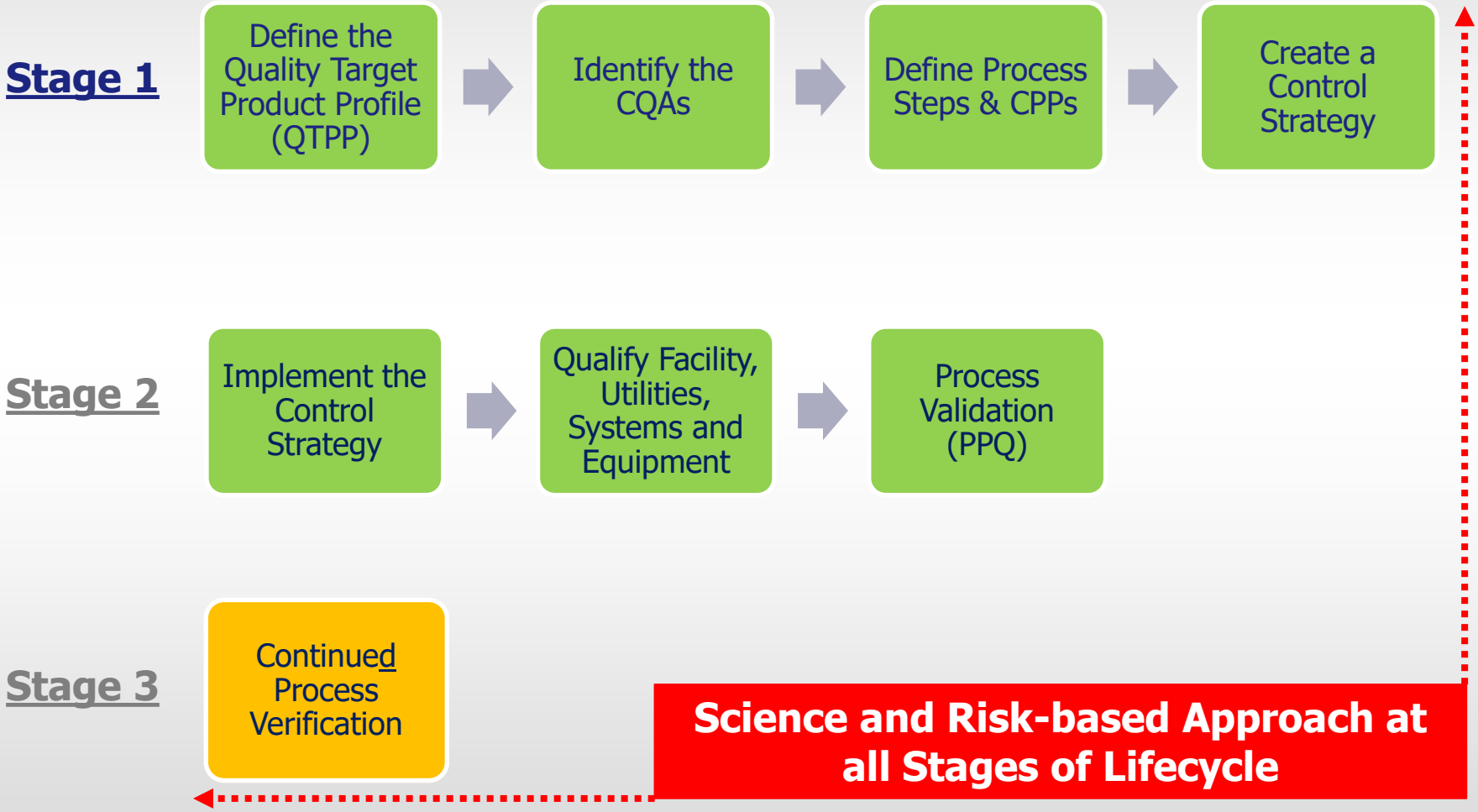
- What does stratified sampling do?
  - Assures you get units from each subgroup
- When would this be important?
  - To check identifiable (or potential) subgroups within the batch / process: top / middle / bottom; every hour; every fill nozzle, etc.
  - To prove we do NOT have uniformity problems, by sampling from higher risk physical locations or time points (worst case)
- How is this done?
  - Divide the population into "strata" or subpopulations
  - Take samples randomly from each stratum in the population

Process Validation (PPQ)

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

Monitoring Variability-remains "in control"

Process Flow



Maintenance of the Validated State

- "Continued Process Verification"
- Change in the validated state of the process could impact product
- Monitored via:
  - Change Control
  - Periodic Monitoring
  - Data Trending Review
  - Calibration and PM
- Knowledge of operational parameters (Control Strategy) and Design Space (if applicable)

Continued Process Verification

CPP's and Process Alarms

- Control range of Critical Parameters
- Control Strategy around critical process parameters
- Within the Design Space (if applicable)
- Easy to implement and control.
- Demonstrates proper performance of the process
- Measurement and control of parameters using PAT (if applicable)

Continued Process Verification

Change Control

- Maintain validated state via review and approval of changes made
- Review by cross-functional SME's
- Pre-approval by Quality
- All changes tracked & trended
- Planned & unplanned

Continued Process Verification

Routine Monitoring

- Demonstrates consistency of initial results
- Statistical Process Control
- Data from automation
- Risk-based Routing Monitoring Program

Continued Process Verification

Data Trending & Review

- Action & Alert levels
- Analytical Data from Routine Monitoring
- Process Parameters
- Process Alarms
- Helps identify potential issues
- CAPA system

Continued Process Verification

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Training

- Training on revised procedures & forms
- New staff
- Re-training of operators based on operator errors
- Re-training for processes
- All departments as applicable

Continued Process Verification

Periodic Review

- Overall Periodic Review of the Validated State
- Frequency of the review may be based on a risk assessment
- Review of regulations/CGMP
- Documented with Conclusions
- Recommend planned improvements

Continued Process Verification

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Regulatory Knowledge, Practically Applied.

Thank you for your time. Questions?

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