Process Validation: Fundamentals for Success

SoCal PDA Chapter Technical Symposium
October 11th, 2018
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Topic Outline:

- What is Process Validation?
- What do the Guidelines require?
- What are key elements for success?
- What can we learn from history?

What is Process Validation?

"The collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products" – FDA 2011 Guidance for Industry

"The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting predetermined specifications and quality attributes. – Annex 15 (2015 revision)

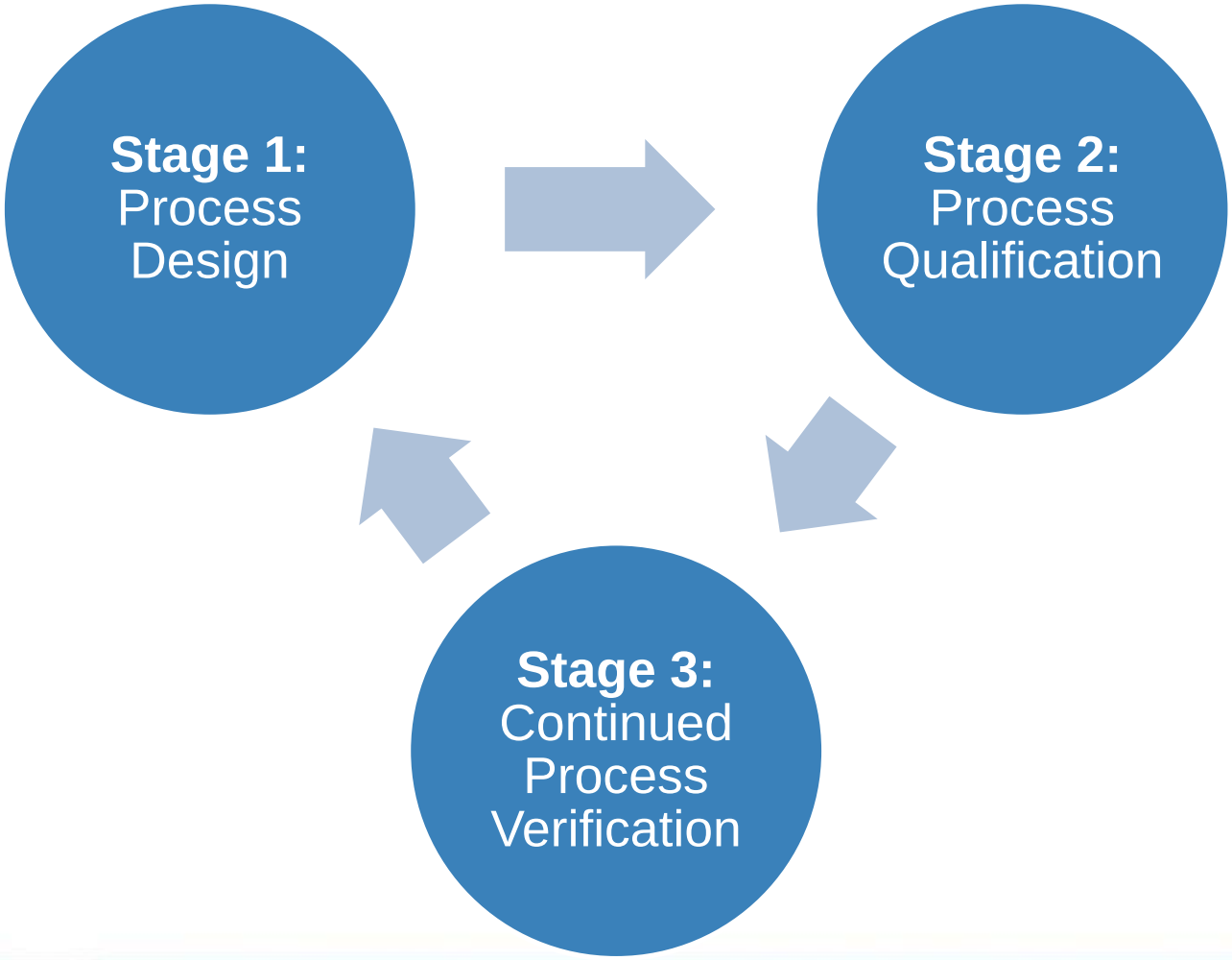
Why do Process Validation?

- “Qualify a system, then validate a process”
- Need assurance that what you built, is the right thing!
- Implementation of Quality by Design
- Knowledge / understanding of process is needed to demonstrate state of control
- Safety of the Process/Product
- Impact of operators, environment

Why do Process Validation?

- Business sense:
  - Less complaints due to process related failures
  - Reduced testing from in-process/finished product
  - Consistent quality with reduced risk
  - Increased throughput / reduced rework
- Regulations
  - Development of 1978 first major revision to cGMP, broad spectrum without details, proof of safety
  - 1987 Guidelines – 3 runs and done, became industry standard

Lifecycle Approach

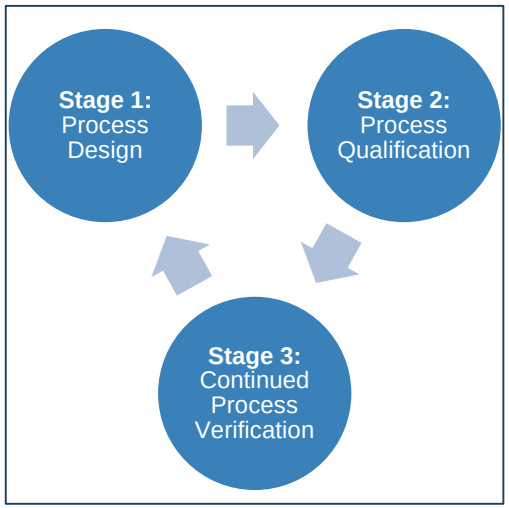


Lifecycle Approach

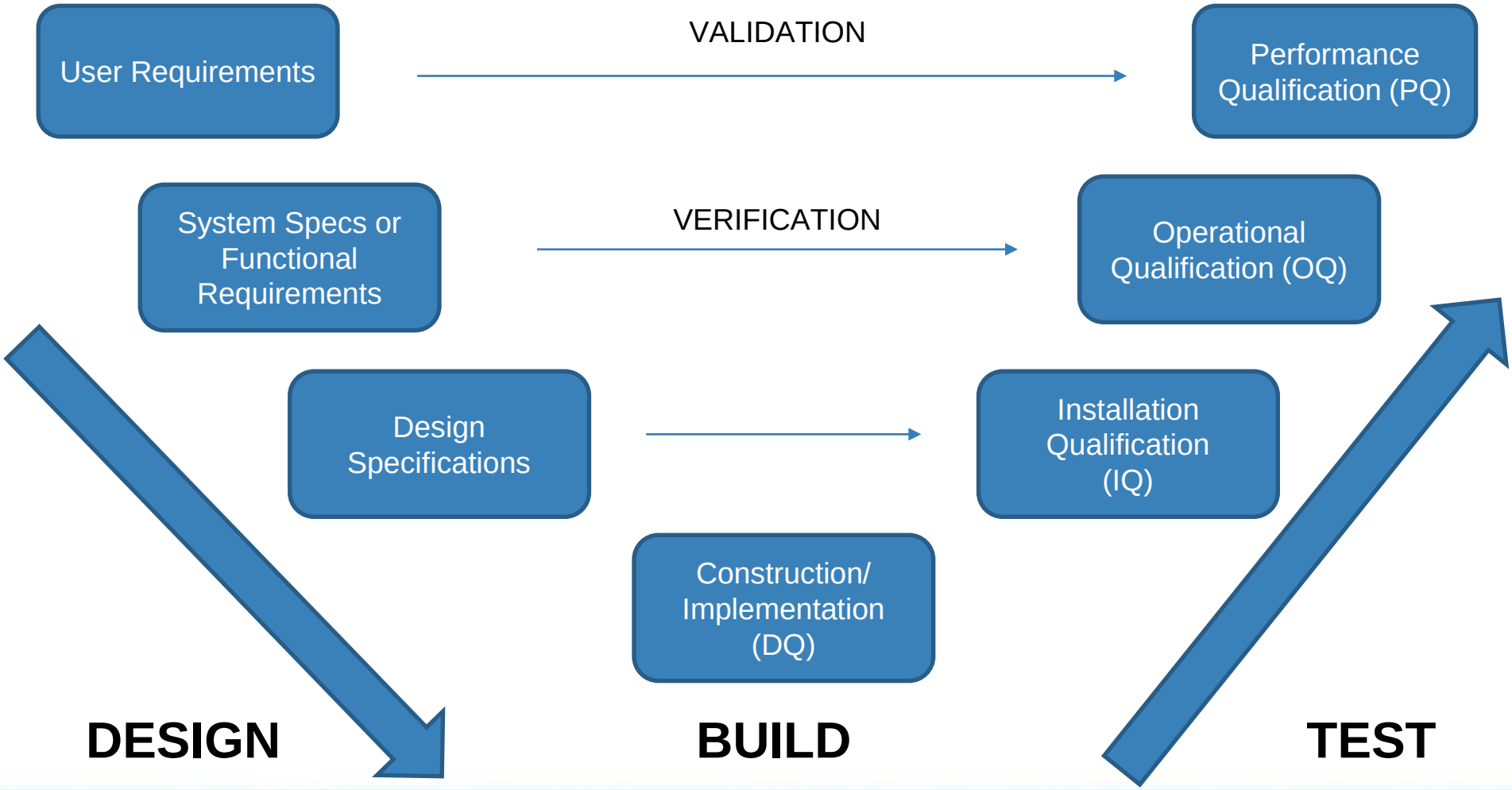
ICH Q8: Planning and Design

ICH Q9: Implementation and Qualification

ICH Q9: Continuous Verification & Improvement



Validation V-Model



Four Stages to Qualification

- **Stage 1: Design Qualification (DQ)**
  - Equipment design and selection based on your needs
  - Define user, functional, and operational requirements
  - Ensure the equipment is designed correctly and will have the appropriate functionality
  - Lack of DQ = deficient equipment that can have issues (technical, compliance, business)
  - Responsibilities: IT, Engineering, Validation, and QA

USER REQ.	FUNCTIONAL REQ.	OPERATIONAL REQ.	VENDOR QUAL.
1. Intended Use	1. URS response	1. Features	1. QMS-Designed
2. Environment	2. Define technical	2. Highly Numerical	2. Questionnaire
3. User needs	3. User knowledge	3. User needs	3. Auditing

Four Stages to Qualification

- **Stage 2: Installation Qualification (IQ)**
  - Successfully installed
  - Example: Design called out 5hp motor
  - Equipment is installed as defined by Design Specs.
  - Reference documents archived (manuals, spare parts, certificates)
  - Pre-approved activities

"Documented evidence that provides high degree of assurance that the equipment is installed in the correct environment and suitable for it's intended use."

Four Stages to Qualification

- **Stage 3: Operational Qualification (OQ)**
  - Conforms to pre-established requirements
  - Example: Mixer operates at 50-200rpm.
  - Alarms for out of range parameters
  - Calibrations are complete
  - Pre-approved activities
    - Verification of functional requirements (V-model)

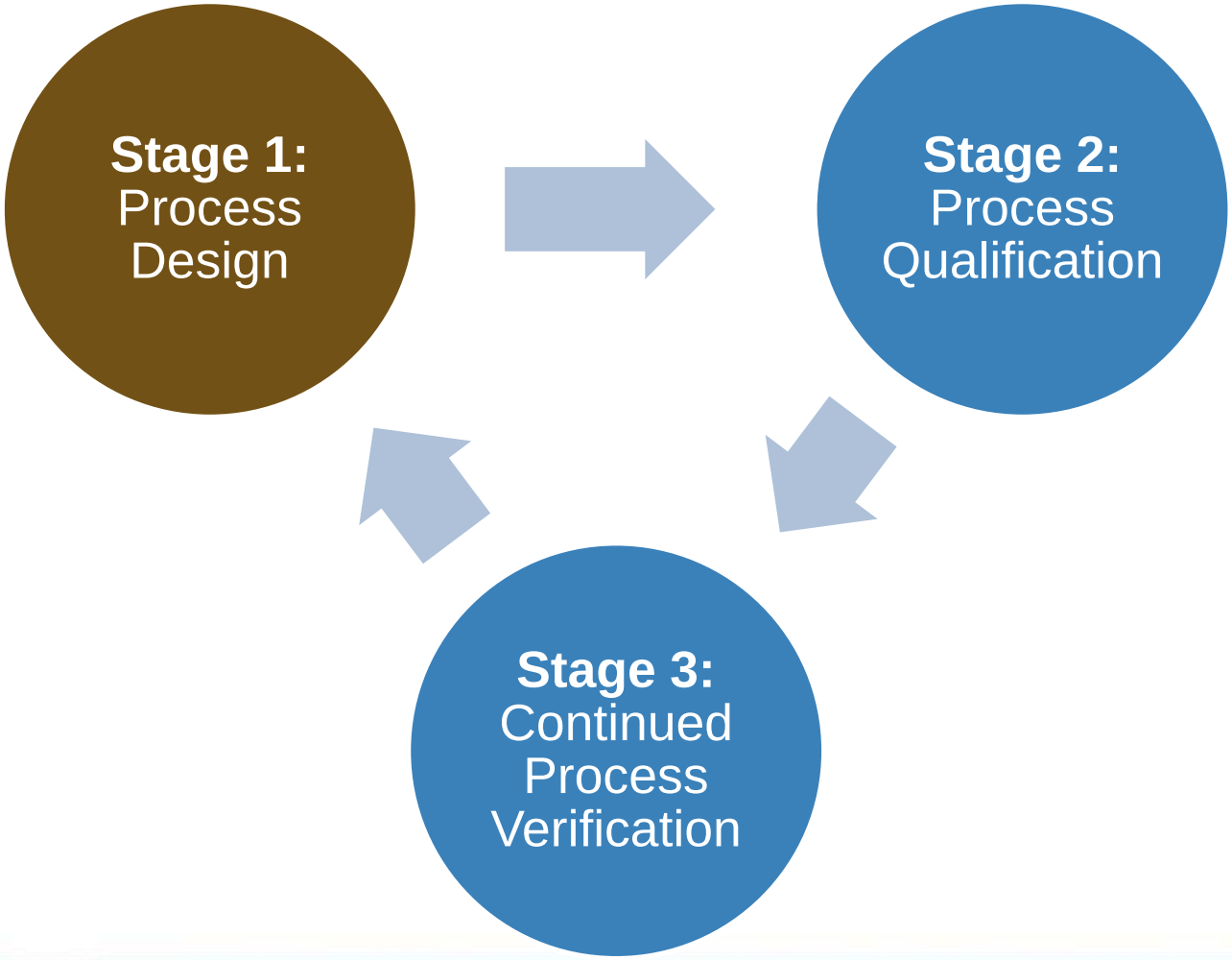
"Documented evidence that provides high degree of assurance that specific process equipment will consistently operate to established specifications."

Four Stages to Qualification

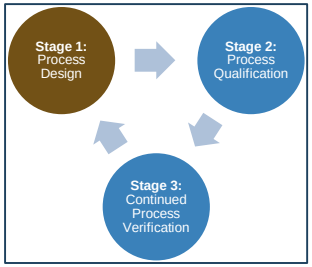
- **Stage 4: Performance Qualification (PQ)**
  - All systems are in place (PM, etc.)
  - Reproducibly meets normal operating conditions
  - Systems to control the process documented
  - Pre-approved activities
    - Validation user requirements satisfied (V-model)

"Documented evidence that provides high degree of assurance that process equipment will consistently perform to specifications appropriate for it's routine use."

Lifecycle Approach

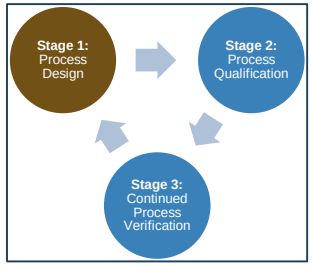


PV Lifecycle Approach



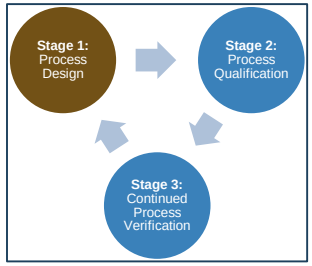
- **Stage 1: Design Phase**
  - Knowledge Gathering:
    - Prior experience with a similar process
    - Clinical/Pre-clinical process understanding
    - Analytical characterization
    - Literature
    - Engineering studies / batches
    - Clinical Manufacturing
    - Process development / characterization studies

PV Lifecycle Approach



- **Stage 1: Design Phase**
  - Output from Efforts:
    - Quality Target Product Profile (**QTPP**)
    - Critical Quality Attributes (**CQAs**) assessed
    - Process Design
      - Inputs/Outputs, in-process controls, setpoints/ranges
      - Compatibility Requirements (product contact considerations)
    - Analytical methods
    - Quality Risk Assessment
    - Process Characterization
      - Evaluate varying parameters to determine effect on product
      - If lab scale / scale-down model, qualify it for full-scale
      - General rule: 10% of commercial scale is representative
      - If well understood, can be used to support PPQ

PV Lifecycle Approach



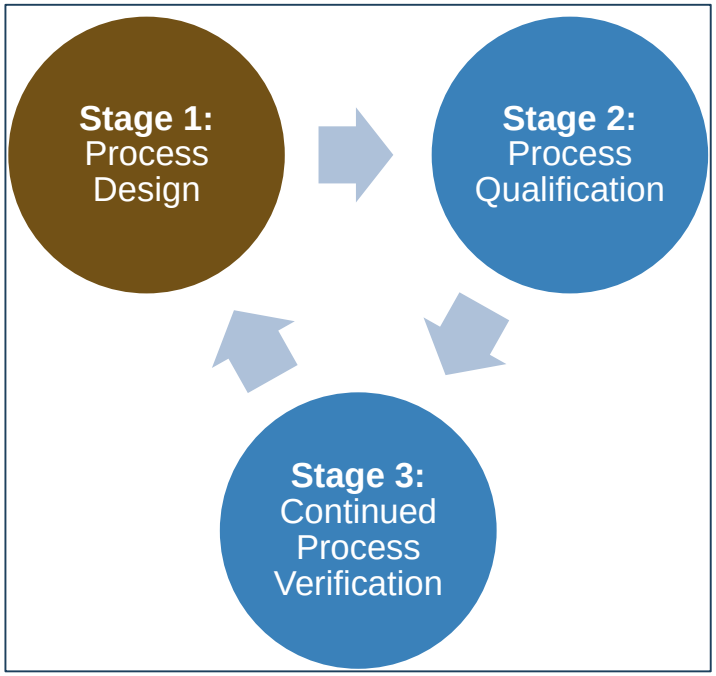
- **Stage 1: Design Phase**
  - Output from Efforts:
    - Process Control Strategy

Raw Materials Manage inputs for consistent output	**In-Process / Release Specs.** Testing is appropriately defined	**In-Process Controls** Adjustments / monitoring to meet CQAs	**Performance Parameters** Indicators that process is performing
Setpoints / Ranges Acceptable vs. normal	**Process Monitoring** Measurement data, sampling, testing	**Hold Times** Stability!	**PAT** Real-time adjustment of CPPs

PV Lifecycle Approach

- **Stage 1: Design Phase**

"Stage 1 will establish CQAs, process flow, inputs/outputs with controls and test criteria / specifications. Process parameters will be classed by risk, ranges will support design space."



PV Lifecycle Approach

- **Stage 1 Complete, ready for Stage 2?**
- **Process Validation Master Plan**
  - **Organizes your PPQ strategy**

Equipment and Facilities

Analytical Methods

Sampling Plan

Protocols

Timeline / Schedule

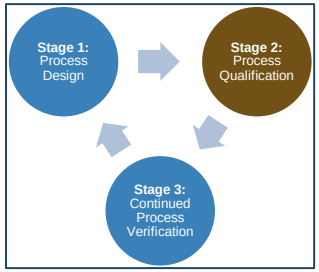
Deviation Management

Continued Process Verification Plan (CPV)

PV Lifecycle Approach

- **Process Validation Master Plan**
  - **Your Quality Document**
    - **Establishes qualification policies**
    - **Identifies what to perform**
    - **Document when activities completed**
  - **Stakeholders**
    - **Upper Management**
    - **Validation**
    - **Engineering**
    - **Project Manager(s)**
    - **Regulatory / Compliance**

PV Lifecycle Approach



- **Stage 2: Process Qualification (PPQ)**

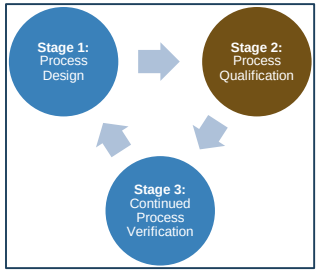
Two Elements:

1. Design and qualification of the facility, equipment, and utilities (suitable to its intended use)

2. Process Performance Qualification (PPQ)

"Documented evidence that there is a high degree of assurance that the Process Control Strategy can be executed during routine manufacturing and it is reproducible and consistent."

PV Lifecycle Approach



- **Stage 2: Process Qualification (PPQ)**

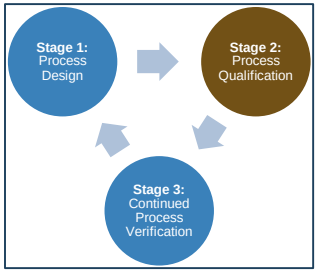
  Number of batches:

  FDA 2011 Guidance – *"sufficient understanding to provide a high degree of assurance"*

  ICH Q7 (12.50) – *"3 consecutive batches should be used as a guide, but…"*

  EMA / Annex 15 – *"minimum of 3 consecutive could constitute a validation of the process"*

PV Lifecycle Approach



- **Stage 2: Process Qualification (PPQ)**

  Number of batches: Considerations

Statistical Methods

Unit Operations Complexity

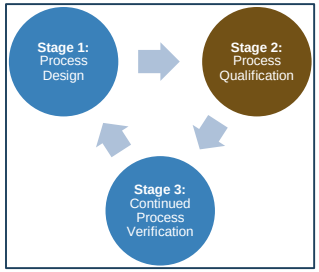
Risk Analysis

Raw Material Variability

Back to Stage 1

Elevated sampling / testing Post-PPQ

PV Lifecycle Approach

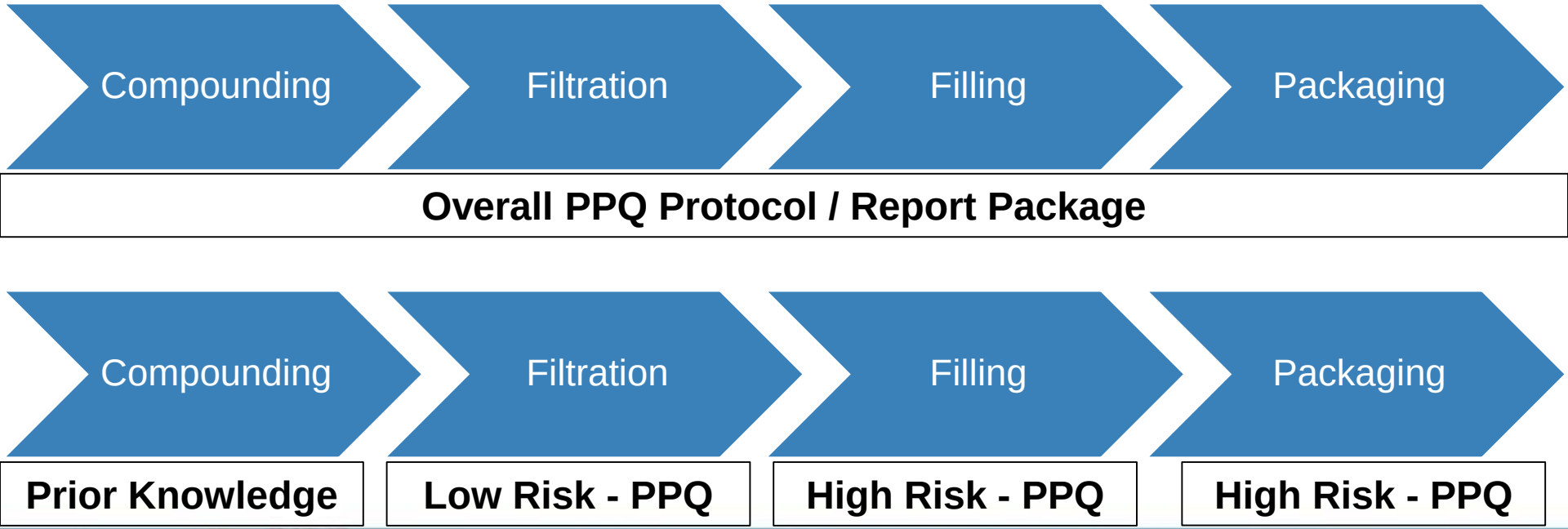


- **Stage 2: Process Qualification (PPQ)**

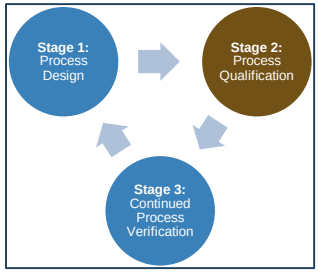
  Approaches:

  Unit Operation PPQ vs Overall Process PPQ

  Modulation of scope for each unit



PV Lifecycle Approach



- **Stage 2: Process Qualification (PPQ)**

  Approaches:

Prospective / Traditional

Preplanned PPQ activities

Examples:
- **Site transfers**
- **Development to Production**

Concurrent

PPQ Based on Production

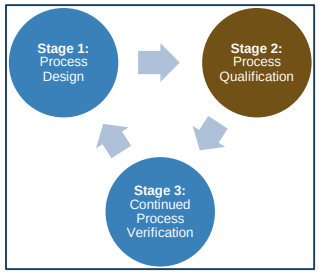
Examples:
- **Infrequent Batch**
- **Low-volume**
- **Orphan drug**

Retrospective

Historical Data documents control

- **FDA no longer mentions**
- **EU allows for unique situations**

PV Lifecycle Approach



- **Stage 2: Process Qualification (PPQ)**

  Approaches:

Bracketing

Qualify processes representing the extremes

Examples:
Common solution
Different fill volume
Different container

Matrix

Qualify configurations with many variables

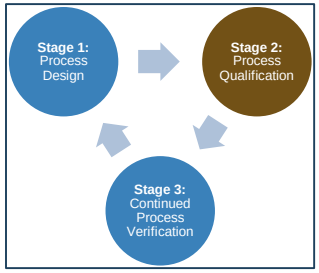
Examples:
Different Fill, Bulk Strength, & Product Strength

Family (Grouping)

Qualify based on cluster of 'similar enough'

Examples:
Equipment Family
Buffer Family

PV Lifecycle Approach



- **Stage 2: Process Qualification (PPQ)**
  General Considerations

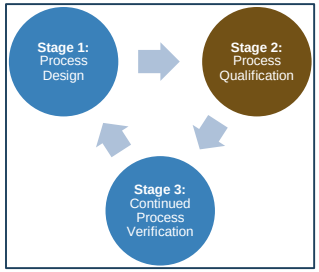
Successful Stage 1:

Risk assessments used to define CQA; Approved Batch Records

PAT (Process Analytical Technology):

Critical to demonstrate CPP adjustments lead to consistent, passing product quality attributes.

PV Lifecycle Approach



- **Stage 2: Process Qualification (PPQ)**
  General Considerations

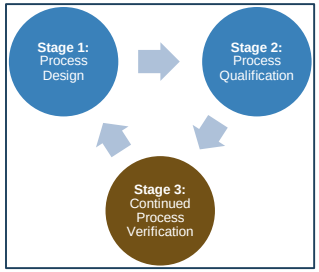
Sampling Strategy:

INCREASED sampling and analytical testing is expected!

Acceptance Criteria:

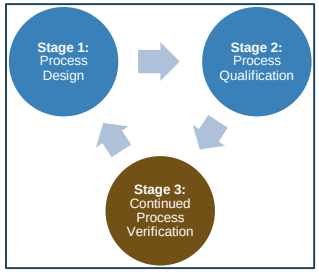
Consider incoming material, CPPs (within normal range), and attributes

PV Lifecycle Approach



- **Stage 3: Continued Process Verification**
  - **Purpose: A means of ensuring the process(es) remain in a state of control following successful PPQ.**
  - **FDA 2011 Guidance:**
    "Continual assurance that the process remains in a state of control during commercial manufacture"
  - **Continued monitoring allows for adjustments to inputs, and compensates for process variability to ensure output is consistent.**

PV Lifecycle Approach



- **Stage 3: Continued Process Verification**
  - **When do you start Stage 3?**

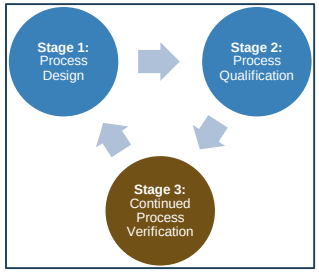
CPV Drafting:
Data to be trended
Statistical methods
Frequency

CPV Polishing:
PPQ Lessons Learned
Adjustments

CPV Formalized:
Periodic Review

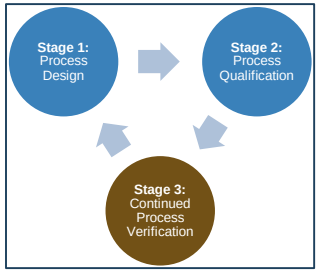
Stage 1 → Stage 2 → Stage 3 → Post-PPQ

PV Lifecycle Approach



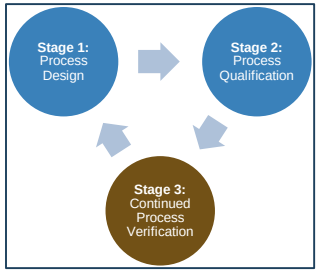
- **Stage 3: Continued Process Verification**
  - **<u>CPV Plan Considerations:</u>**
    - **Roles and Responsibilities**
    - **Sampling / Testing**
    - **Data Analysis Methods**
    - **Acceptance Criteria**
    - **Strategy for Handling OOS/OOT**
    - **Re-evaluation of CPV**
    - **Method of Identifying Changes**

PV Lifecycle Approach



- **Stage 3: Continued Process Verification**
  - **<u>What about Legacy Facilities?</u>**
    - **Facility:**
      - **Fully qualified equipment**
      - **Partially qualified equipment**
      - **Unqualified, older equipment**
    - **Validation Master Plan**
      - **Risk assessment**
      - **Qualification matrix**

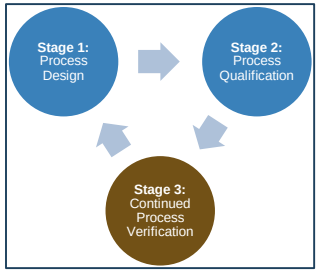
PV Lifecycle Approach



- **Stage 3: Continued Process Verification**
  - **<u>How do you know if your CPV is working?</u>**
    - **Knowledge Base:**
      - **Process Parameters / Quality Indicators**
      - **Variability not within CPPs**

    - **Lifecycle Approach:**
    - **Stage 1 – Captures critical inputs/outputs**
    - **Stage 2 – Confirms control strategy functions**

PV Lifecycle Approach



- **Stage 3: Continued Process Verification**
  - **<u>Take-home: Case-by-Case!</u>**
    - **Do I have enough information gathered?**
    - **Can I use PPQ to support monitoring?**
      - **Process Parameters / Quality Indicators**
        - **Limited data? High variability?**
    - **CPV Plan is dynamic = Lifecycle**
      - **Frequency of sampling static?**
      - **Information only?**
      - **Special scenarios with heightened testing?**

Data and Trending Activities

- **Continued Process Verification**
  - **What data is required?**
  - **How is it collected?**
  - **How is it analyzed?**
- **Out-of-{Trend / Control / Specification}**
  - **Limits exceeded?**
  - **What action is triggered?**
- **Incorporate Feedback Mechanism**
  - **What events, and when? Inter/Intra Batch?**

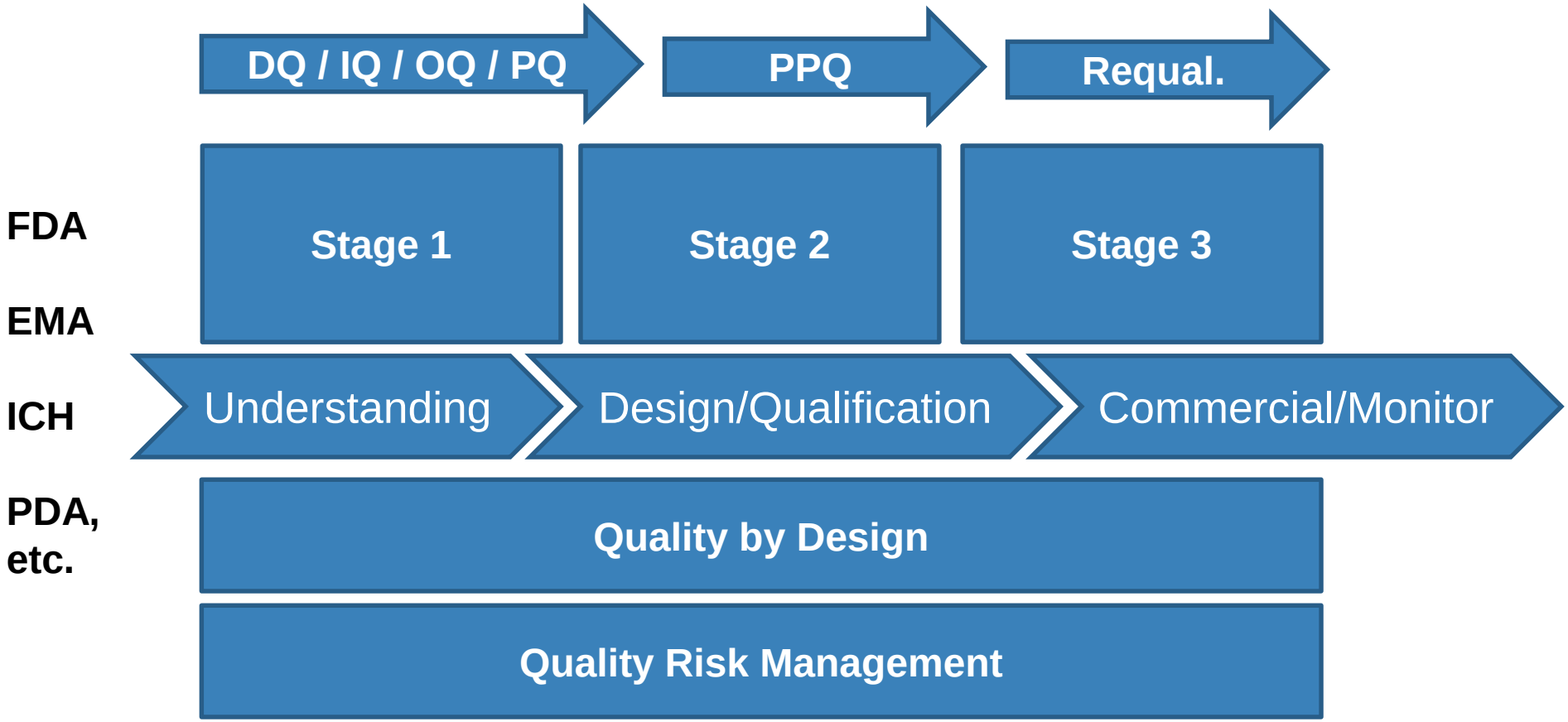
Data and Trending Activities

- **Statistical Tools**
  - **Capability studies**
  - **Sample size determination**
  - **SPC Charts**
  - **Gauge R&R**
  - **Design of Experiments**
  - **Tolerance Analysis**
  - **Regression/Correlation**
  - **ANOVA**
  - **Pareto**

Setting up for Success

- **Features of a smooth PV process:**
  - **Multi-disciplinary Team**
  - **Quality is built into the design**
  - **Commitment to process understanding**

Setting up for Success



Setting up for Success

- **Quality by Design (QbD)**
  - **Characterization of Component/Material**
  - **Risk table captures impact of unit/component on final product / process**

- **Advantages**
  - **Less dependent on in-process and finished product**
  - **Cost-efficient – increased output**

Setting up for Success

- **Quality Risk Management (QRM)**
  - **Identifying and assessing**
- **Advantages**
  - **Less dependent on in-process and finished product**
  - **Cost-efficient – increased output**

Learning from History

- **March 26th, 2018**
- **Tris Pharma Inc. – Batch Failures**
  - **Improper investigation of failures**
  - **Lack of addressing product / dissolution failures**
  - **Root cause, and CAPA procedures not prompt/effective**
- **"Response is inadequate because you did not promptly and thoroughly investigate variables in the process that may be responsible for inconsistent product quality (e.g. dissolution performance."**
- **"Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport."**

Learning from History

- **June 8th, 2018**
- **Biologique Recherche (B.R.). – Deficient cGMP**
  - **Inadequate testing for identity and strength**
  - **Reliance on CoA from Suppliers not qualified**
  - **No procedures to investigate deviations**
  - **No PPQ studies performed**
  - **No ongoing program for monitoring process control**

- **"Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport."**

Learning from History

- **August 24th, 2018**
- **Zimmer Biomet – Remediation project**
  - **Increased monitoring while interim control implemented.**
  - **Statement only that tested was worst case**
  - **Production staff not following procedures**

- **"Failure to adequately ensure that when the results of a process cannot be fully verified…that the process shall be validated with a high degree of assurance."**
- **"Failure to develop, conduct, control, and monitor production processes to ensure that product conforms to specifications, including the monitoring and control of process parameters during Production.**

Learning from History

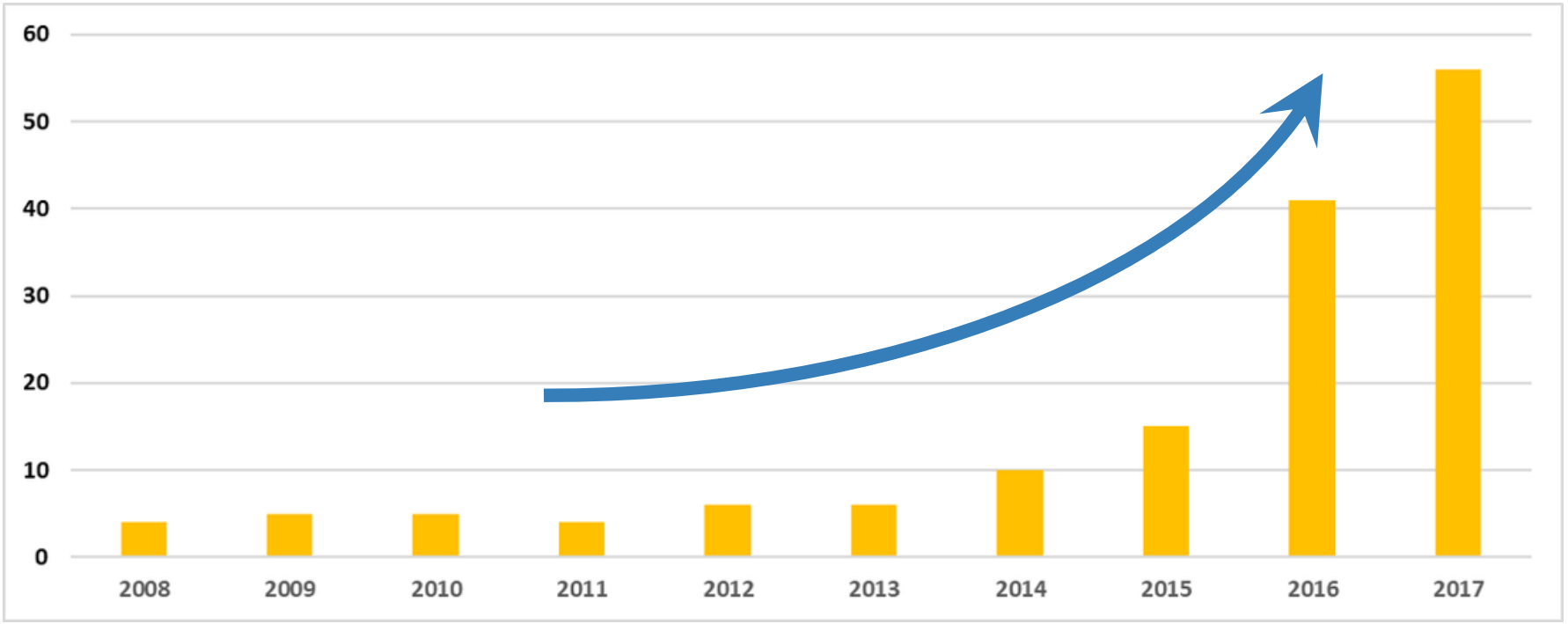
Table 4: Warning Letters Citing Data Integrity Deficiencies (Excluding Compounding Pharmacies)

	FY2013	FY2014	FY2015	FY2016
Total warning letters	38	22	19	46
U.S. warning letter sites with data integrity citations	0 of 13 (0%)	0 of 4 (0%)	1 of 3 (33%)	8 of 11 (73%)
OUS sites with data integrity citations	10 of 25 (40%)	12 of 18 (67%)	13 of 16 (81%)	29 of 35 (81%)
Total number of warning letters citing data integrity	10 of 48 (26%)	12 of 22 (55%)	14 of 19 (74%)	37 of 46 (79%)

Unger, B. Analysis of FDA FY2016 Drug GMP Warning Letters
https://www.pharmaceuticalonline.com/doc/an-analysis-of-fda-fy-drug-gmp-warning-letters-0001

Learning from History

Figure 2: Data Integrity Associated Warning Letters, CY2008 – CY2017



Unger, B. Part 2: Drug GMP Warning Letters Data Governance and Data Integrity.
https://blog.fdazilla.com/2018/07/pharma-part-2-drug-gmp-warning-letters-data-governance-and-data-integrity/