Process Validation Lifecycle Approach: A Return to Science

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ISPE's PQLI Initiative

- PQLI® = Product Quality Lifecycle Implementation®
- Global effort to identify & share a practical approach to implementation of ICH Q8, Q9, Q10, and Q11
- http://www.ispe.org/pqli-resources
- ISPE and PDA have reviewed PQLI versus PDA's Paradigm Change in Manufacturing Operations (PCMO) and found the following:
  - Programs are different
  - Programs are complementary
  - Efforts are not in competition

ISPE PV Initiative – Strategy and Deliverables

- Goal: Assist in practical implementation of PV guidance
- Use previously-developed PQLI work products where possible
- PV Group Activities
  - Process Validation-focused conferences

    Next Conference: October 7-8, 2015; Silver Spring, MD
  - Online discussions
  - Discussion papers
- Volunteer Opportunity

ISPE PV Discussion Papers

- Topic 1: Stage 2 PV – Determining and Justifying the Number of PPQ Batches
- Topic 2: Stage 3 PV – Applying Continued Process Verification Expectations to New and Existing Products
- Topic 3: Lifecycle Approach to Biotech Process Validation
- Topic 4: Evaluation of Impact of Statistical Tools on PPQ Outcomes

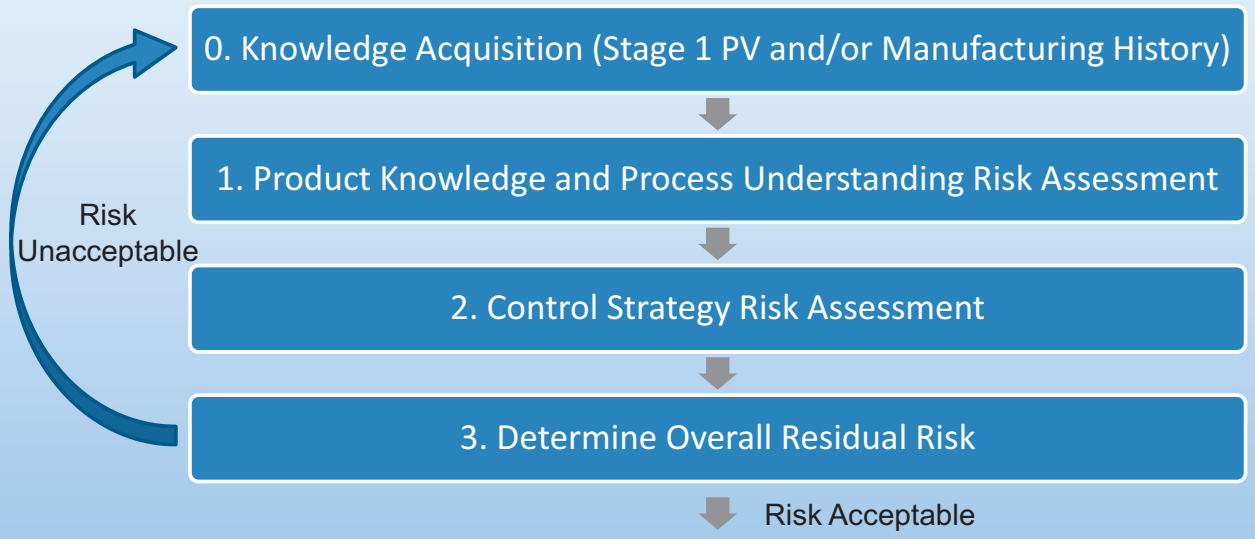
Available online at http://www.ispe.org/publications/discussion-papers

Topic 1: Stage 2 PV – Determining and Justifying the Number of PPQ Batches

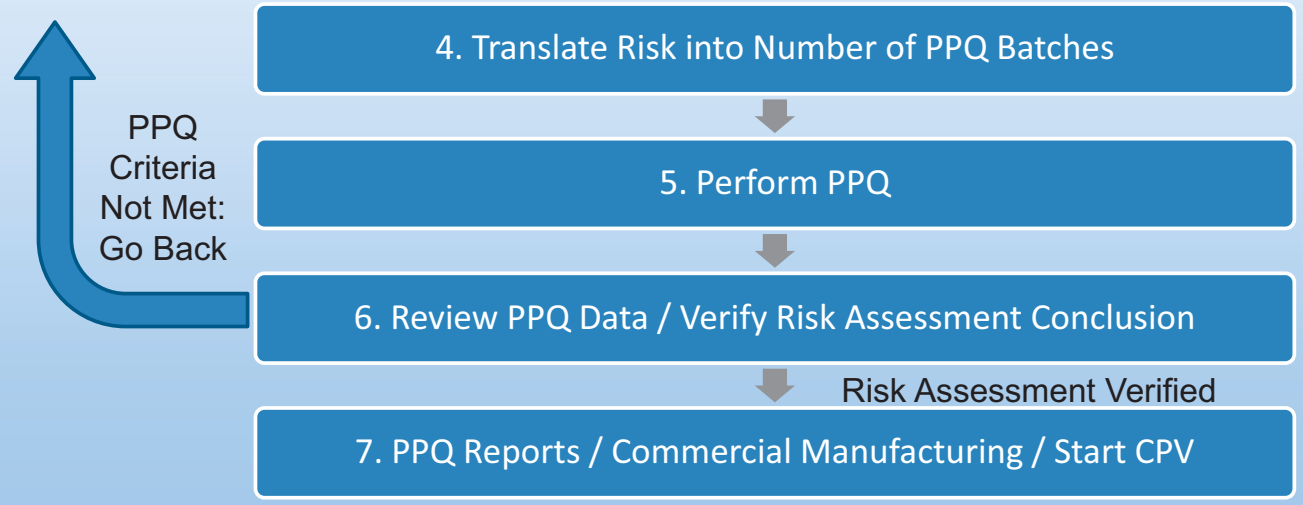
Topic 1: Stage 2 PV – Number of PPQ Batches

- Key Question: How many PPQ batches (including consideration of Stage 1 activities) are needed to demonstrate that the process implementation and control strategies are sufficiently robust?
- Key Concepts
  - Use knowledge from development and historical performance
  - More knowledge & more control = lower risk → fewer PPQ batches required

Stage 2 PV – Number of PPQ Batches - Workflow



Stage 2 PV – Number of PPQ Batches - Workflow



Assess Product Knowledge (Step 1a)

- ICH Q8: Quality Target Product Profile
- CQAs
- Risk Assessment should include severity & probability
- Basis of acceptable ranges for CQAs should be assessed

Assess Process Understanding (Step 1b)

- What is the relationship between material attributes, process parameters, and CQAs?
- How does variation without control affect CQAs?
- Potential sources of information
  - Development information
  - Other prior knowledge
  - Degree of process understanding by unit operation
  - Process predictability and models
  - Effects of scale change / scale down models

Assess Control Strategy (Step 2)

Purpose: Control input material and process variability to maintain a consistent output

- Must monitor (measure) both inputs and outputs to achieve control

Potential factors to consider

- Raw material variability
- Equipment capability
- Previous experience with process performance

Determine Residual Risk (Step 3)

- Use QRM methods (such as FMEA) to determine residual risk
- Five residual risk levels proposed

Residual Risk	Description
Severe (5)	Multiple factors have high risk ratings
High (4)	Few factors have high risk ratings or all have medium
Moderate (3)	Multiple medium risk factors or one high risk factor
Low (2)	Medium risk for a few factors; others are low
Minimal (1)	All risk factors are low

Determine Number of PPQ Batches (Step 4)

Key Question: How many PPQ batches (including consideration of Stage 1 activities) are needed to demonstrate that the process implementation and control strategies are sufficiently robust?

Three approaches described:

1. Rationales and experience
2. Target process confidence and process capability
3. Expected coverage

Approach 1: Rationales and Experience

- Assumption: For low risk processes, three PPQ batches is appropriate
  - This approach has historically been used successfully
  - More or less PPQ batches for other residual risk levels

Residual Risk	# of PPQ Batches	Rationale
Severe	Not Ready	Process change or additional control needed
High	10	Large number of batches needed to show consistency
Moderate	5	Additional batches due to higher residual risk
Low	3	Historically shown to be appropriate
Minimal	1-2	Strong knowledge & high degree of control = minimal risk

Approach 2: Target Process Confidence and Capability

- By definition, C_{pk} of a capable process is ≥ 1.0
  (6 σ process, 3.4 defects / million opportunities)
- For low residual risk processes, C_{pk} ≥ 1.0 at 90% confidence is set as "baseline"
- Degree of confidence should be greater for higher residual risk processes

Approach 2: Target Process Confidence and Capability

Residual Risk	Target Confidence	Comments
Severe	N/A	Severe or high indicate major gaps in knowledge and understanding. For High risk, a high degree of confidence (97%) is needed with respect to the process capability.
High	97%	
Moderate	95%	Target confidence levels provide reasonable assurance of process capability needed for commercial distribution
Low	90%	
Minimal	N/A	Minimal residual risk indicates that a high confidence that there is already good process understanding and a robust control strategy

Approach 2: Number of PPQ Batches

Residual Risk	Minimum # of PPQ Batches	Target Process Confidence for C_{pk} 1.0
Severe	Not Ready	N/A
High	14	97%
Moderate	11	95%
Low	7	90%
Minimal	1-3	N/A

- Readily Pass, Marginally Pass, and Fail C_{pk} values are also provided in paper (not shown here)
- Other combinations of confidence and C_{pk} thresholds may be appropriate

Approach 3: Expected Coverage

- Order statistics: the more observations you have, the more likely future observations will fall within the range of the existing observations (the "coverage")
- Mathematically, the probability that value m is within the range of values $1....n$ is

$$P_m = \frac{m}{n+1}$$

Approach 3: Expected Coverage

- Probability of a future observation z within the range of the n existing observations:

$$P_z = \frac{n-1}{n+1}$$

- As n increases, P_z approaches 1 (100%)

z	P_z
2	0.333
3	0.500
5	0.667
10	0.818
50	0.961
100	0.980
1000	0.998

Approach 3: Expected Coverage

Residual Risk	Expected Coverage from PPQ Batches Alone (50% confidence)	Number of PPQ Batches
Severe	N/A	Not ready for PPQ
High	80%	9
Moderate	70%	6
Low	50%	3
Minimal	N/A	1-3

- When this approach is used, the between-batch variability should be evaluated (narrow gauge limits)

Summary of Approaches

Residual Risk	Approach		
	1. Rationales and experience	2. Target Process Confidence and Capability	3. Expected Coverage
Severe	Not Ready	Not Ready	Not ready
High	10	14	9
Moderate	5	11	6
Low	3	7	3
Minimal	1-2	1-3	1-3

Appendices (from Discussion Paper)

#1: Risk Assessment Example

#2: Number of PPQ runs to provide confidence that process capability exceeds a desired Target Process Performance

#3: Number of PPQ batches based on PQLI Example

Topic 2: Stage 3 PV – Applying Continued Process Verification Expectations to New and Existing Products

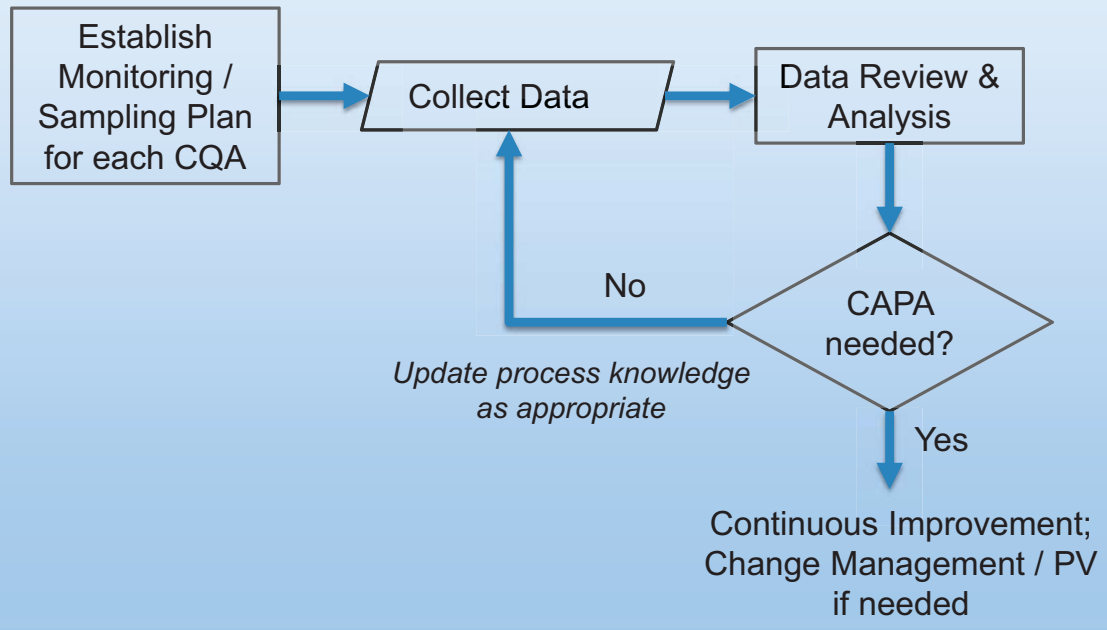
Stage 3: Scope

- New Products that have undergone Stage 1 and Stage 2 PV
- Legacy Products
- Facility, utility, equipment maintenance & periodic qualification status review / verification should not be overlooked

Stage 3: Continued Process Verification Monitoring Plan

- Purpose: Provide ongoing documentation throughout the commercial phase of the product lifecycle that the process remains in a state of control
  - Evaluate ongoing impact of variability in the process, materials, facility, and equipment
  - Continually increase process knowledge
  - Provide opportunities for improvement

Stage 3: Simplified Flow Chart



Stage 3: Selection of Parameters / Attributes to Monitor

- Based on process / product understanding
- As Stage 3 progresses, number and frequency of parameters may change as process & control strategy knowledge is gained
- Any decision to discontinue monitoring for a parameter should be based on confidence gained in the process from Stages 1, 2, and 3

Stage 3: Selection of Parameters: New / QBD Products

- Stage 3 based on Stages 1 and 2, including process understanding & quality risk management
  - Attribute criticality should have been assessed
- Starting point for Stage 3 attributes is Stage 2 (PPQ)
  - Stage 2 may have provided enough info about some parameters
  - May perform enhanced sampling at beginning of Stage 3
- Both inter-batch and intra-batch variability should be assessed

Stage 3: Selection of Parameters: Legacy Products

- First step: A criticality / risk assessment should be performed
- Based on both current process understanding and relevant experience
  - Quality System events: Deviations / CAPAs, Change Controls, complaints, etc.
  - Annual Product Reports
  - Etc.
- Some initial additional sampling may be indicated to gain additional process understanding

Stage 3: Review of Stage 3 Plan

- A periodic review (time-based or number of lots) should be performed on the monitoring plan
- Review should also consider facilities, utilities, and equipment

Stage 3: Data Analysis and Review

- A process for collecting, analyzing, reporting, reviewing, and storing data is required.
- Statistical tools should be used to verify that the process remains in control
- Examples
  - Time series plots
  - Histograms; box plots
  - Statistical Process Control (SPC) charting
  - Process capability monitoring (C_{pk}, etc).

Stage 3: Control / Action Limits

- Limits should be set to detect changes in parameter variability, to trigger further attention
- Statistically based limits should not be confused with specifications, PAR, in-process control limits ("quality" limits)
  - For a capable process, statistical limits will be tighter than other limits
- Control limits should be assessed when changes are made (process, equipment, testing)

Stage 3: Other Considerations

- Data Evaluation and Product Release
  - "Investigation" of statistical outliers should consider proximity of the data point to the specification limit
  - Out of statistical control limit results may not impact batch release, but should be assessed for possible trends or future impact
- Frequency of Process Analysis
  - Ongoing for trend detection
  - Periodically based on time or number of batches
- Knowledge Management
  - Learnings should be documented

Stage 3: Examples (from Discussion Paper)

#1: Selection of CQAs and PPs for New Small Molecule

#2: Large Molecule Example-Chromatography Step

Conclusions
Questions??