Process Validation Lifecycle Approach: A Return to Science

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Woburn, MA
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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](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

0. Knowledge Acquisition (Stage 1 PV and/or Manufacturing History)

1. Product Knowledge and Process Understanding Risk Assessment

2. Control Strategy Risk Assessment

3. Determine Overall Residual Risk

Risk Unacceptable

Risk Acceptable
Stage 2 PV – Number of PPQ Batches - Workflow

4. Translate Risk into Number of PPQ Batches

5. Perform PPQ

6. Review PPQ Data / Verify Risk Assessment Conclusion

7. PPQ Reports / Commercial Manufacturing / Start CPV

PPQ Criteria Not Met: Go Back
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

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

<table>
<thead>
<tr>
<th>Residual Risk</th>
<th># of PPQ Batches</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Not Ready</td>
<td>Process change or additional control needed</td>
</tr>
<tr>
<td>High</td>
<td>10</td>
<td>Large number of batches needed to show consistency</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
<td>Additional batches due to higher residual risk</td>
</tr>
<tr>
<td>Low</td>
<td>3</td>
<td>Historically shown to be appropriate</td>
</tr>
<tr>
<td>Minimal</td>
<td>1-2</td>
<td>Strong knowledge &amp; high degree of control = minimal risk</td>
</tr>
</tbody>
</table>
Approach 2: Target Process Confidence and Capability

• By definition, $C_{pk}$ of a capable process is $\geq 1.0$
  
  (6 σ process, 3.4 defects / million opportunities)

• For low residual risk processes, $C_{pk} \geq 1.0$ 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

<table>
<thead>
<tr>
<th>Residual Risk</th>
<th>Target Confidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>N/A</td>
<td>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.</td>
</tr>
<tr>
<td>High</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>95%</td>
<td>Target confidence levels provide reasonable assurance of process capability needed for commercial distribution</td>
</tr>
<tr>
<td>Low</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>N/A</td>
<td>Minimal residual risk indicates that a high confidence that there is already good process understanding and a robust control strategy</td>
</tr>
</tbody>
</table>
Approach 2: Number of PPQ Batches

<table>
<thead>
<tr>
<th>Residual Risk</th>
<th>Minimum # of PPQ Batches</th>
<th>Target Process Confidence for $C_{pk} \ 1.0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Not Ready</td>
<td>N/A</td>
</tr>
<tr>
<td>High</td>
<td>14</td>
<td>97%</td>
</tr>
<tr>
<td>Moderate</td>
<td>11</td>
<td>95%</td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>90%</td>
</tr>
<tr>
<td>Minimal</td>
<td>1-3</td>
<td>N/A</td>
</tr>
</tbody>
</table>

• 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 $1 \ldots n$ 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%)

<table>
<thead>
<tr>
<th>$z$</th>
<th>$P_z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.333</td>
</tr>
<tr>
<td>3</td>
<td>0.500</td>
</tr>
<tr>
<td>5</td>
<td>0.667</td>
</tr>
<tr>
<td>10</td>
<td>0.818</td>
</tr>
<tr>
<td>50</td>
<td>0.961</td>
</tr>
<tr>
<td>100</td>
<td>0.980</td>
</tr>
<tr>
<td>1000</td>
<td>0.998</td>
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</table>
Approach 3: Expected Coverage

<table>
<thead>
<tr>
<th>Residual Risk</th>
<th>Expected Coverage from PPQ Batches Alone (50% confidence)</th>
<th>Number of PPQ Batches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>N/A</td>
<td>Not ready for PPQ</td>
</tr>
<tr>
<td>High</td>
<td>80%</td>
<td>9</td>
</tr>
<tr>
<td>Moderate</td>
<td>70%</td>
<td>6</td>
</tr>
<tr>
<td>Low</td>
<td>50%</td>
<td>3</td>
</tr>
<tr>
<td>Minimal</td>
<td>N/A</td>
<td>1-3</td>
</tr>
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- When this approach is used, the between-batch variability should be evaluated (narrow gauge limits)
## Summary of Approaches

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
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<td>7</td>
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</tr>
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<td>1-3</td>
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</table>
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

1. Establish Monitoring / Sampling Plan for each CQA
2. Collect Data
3. Data Review & Analysis
   - No
   - Update process knowledge as appropriate
   - Yes
   - CAPA needed?
     - Yes
     - Continuous Improvement; Change Management / PV if needed
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??