Product, Process Knowledge & SPC: PV Lifecycle Approach

IFPAC January 2016, Arlington, VA

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Stage 1 Process Design
The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities - "process understanding".

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

Stage 3 Continued
Process Verification
Ongoing assurance is gained during routine production that the process remains in a state of control - "maintaining state of control".
Process Validation Life Cycle Overview

1. **Formulation Development**
   - Product Development Report
2. **Risk Assessment**
3. **Scale up/Demonstration**
4. **Data Analysis**
5. **Pre-PPQ Risk Assessment**
6. **Process Performance Qualification**
   - PPQ Report
7. **Data Analysis**
8. **Commercial Distribution**
9. **Continued Process Verification**
   - CPV Stage 3A Report
10. **Commercial Manufacturing**
11. **Continued Verification**

**Stage 1**

- QTPP, Design Space, MV DoE
- Identifying KPPs, CPPs, CQAs, IPC
- Technical Risk Assessment (formulation, process, scale up)
- Sources of variation, Control Strategy, PAR
- Determine # of Batches
- Verify CPPs, NOR
- Probability of Acceptance (Pa), Process Capability

**Stage 2**

- Establish trending limits
- PpK, SPC, MVA, prediction profiling
- Trending, Signal detection
- Automated notification, action

**Stage 3A**

**Stage 3B**

**Knowledge Management**

**Sources of Variation:**
- Control Strategy, PAR

**Establishing Limits:**
- PpK, SPC, MVA, prediction profiling

**Trending:**
- Trending, Signal detection

**Automated Notification:**
- Automated notification, action
Risk Assessment Tool

Formulation Risk – CMAs* vs. CQAs
Process Risk – PP* vs. CQA
Scale up Risk – PP* vs. CQA

*and other attributes

Criticalities are set for each process, calculation based on equation:

\[
\text{Risk Ratio} = \frac{(\text{Critical/Not Evaluated} + \text{Critical/Not Mitigated})}{\text{Sum}(\text{Critical/Mitigated, Critical/Not Evaluated, Critical/Not Mitigated})}
\]

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Factor Count</th>
<th>Rating</th>
<th>total</th>
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<tr>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not Critical/ Evaluated</td>
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<td>1</td>
<td>12</td>
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<tr>
<td>Not Critical/ Not Evaluated</td>
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<td>2</td>
<td>34</td>
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<tr>
<td>Critical/ Mitigated</td>
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<td>3</td>
<td>30</td>
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<tr>
<td>Critical/ Not Evaluated</td>
<td>21</td>
<td>4</td>
<td>84</td>
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<tr>
<td>Critical/ Not Mitigated</td>
<td>26</td>
<td>5</td>
<td>130</td>
</tr>
<tr>
<td><strong>Total Risk Score</strong></td>
<td><strong>26</strong></td>
<td><strong>5</strong></td>
<td><strong>290</strong></td>
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<tr>
<td><strong>Risk Ratio</strong></td>
<td><strong>0.8246</strong></td>
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</table>

**Risk Ratio**

<table>
<thead>
<tr>
<th>Risk Ratio</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 0.25</td>
<td>Low Risk</td>
</tr>
<tr>
<td>0.25 - 0.75</td>
<td>Medium Risk</td>
</tr>
<tr>
<td>Higher than 0.75</td>
<td>High Risk</td>
</tr>
</tbody>
</table>

Edge factor: Data driven objective analysis

FIT FOR PHARMA
"The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches" FDA 2011 PV Guidance

# of PPQ batches required is the number of batches when the projected “best estimate” confidence interval of the product quality attribute measurements (which is a combination of the CI of the process mean and the CI of the process standard deviation) resides completely in the specification range. Approach considers critical CQAs (Assay, dissolution, CU). Since each quality attribute has its distinct requirements, the equation to determine CI is tailored per quality attribute.

\[
S_{\text{total}}^2 = S_{\text{batch-batch}}^2 + S_{\text{inrabatch}}^2 (S_{\text{sampling}}^2 + S_{\text{analytical}}^2 + \ldots )
\]

historical batch-to-batch variability for comparable product/processes based on highest correlation factor: active content

product specific information (e.g. data generated from Stage 1 batches produced for the purpose of clinical trials, submission, stability, process scale-up/demonstration)
Determining Number of PPQ batches

Advantages

- Compliance to regulatory requirement of justifying number of batches selected.
- Tool prevents excessive data collection and further gains confidence in process verification.
- Tool can be used to develop and justify sampling plans for product development, scale-up and investigations.

Other Applications

- Methodology may be applied to determine Stage 3A Continued Process Verification batches.
- Methodology can be extended to Analytical, Equipment, Systems, Utility-performance qualifications

Edge factor

Incorporates Stage 1 performance and similar product/process knowledge into overall risk assessment based on within batch and between batch variability as intended by 2011 FDA PV guidance

Acceptance criteria for Pharmaceuticals are typically multi-level and more intricate than other industries

- Traditional SPC strategies ($C_{pk}$, $P_{pk}$, control charts) may give erroneous indications or fall short in providing a suitable assessment of product risk.
- A more applicable analysis method is required to provide a reliable understanding of the ability of the product to fulfill the requirements for quality attributes.
- An “improved” concept, described herein as the Probability of Acceptance ($P_a$), provides a clear measure of assurance and risk based on presently measured statistics.
  - $C_{pk}$ typically provides information about a future single unit, the improved concept, $P_a$, is designed to provide the probability that a future produced batch will meet the specification.
  - $P_a$ is considerably more distinctive than capability indices. The meaning of a 99.93% probability that a future batch will meet the requirements is easily understood than $C_{pk}$

**PPQ:** “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 2011 Guidance
This approach permits a risk-based assessment of future batch performance of the critical quality attributes. It cannot supplant for product release specifications.

Examples when Pa can be applied to solid dose: Dissolution, Content Uniformity, Assay, Compression In-Process testing results (Hardness, Thickness etc.)

The concept has also been applied to sterile/non sterile liquid dose and transdermal products. Quality attributes such as Deliverable Volume and Assay per Spray have stage-wise acceptance that can be converted into an acceptance probability.

Accepted statistical guidelines indicate processes with $C_{pk} > 1.33$ as performing well within statistical control with a centered process that will statistically produce less than 63 defective units per million. This is equivalent to an acceptance probability of $>99.99%$. 
Stage 3 - Continued Process Verification

- Program that builds upon Process Knowledge acquired in Stage 1 & Stage 2 of PV lifecycle
- Ongoing assurance is gained during routine production that the process remains in a state of control
- Two staged- Stage 3A, 3B (A Case for Stage 3 – Continued Process Verification, Pharmaceutical Manufacturing, May 2014)

Stage 3A is to allow close monitoring and evaluation of parameters and quality attributes and to detect any undesirable process variability post launch
- The results of IP CQA and FP CQAs are collected and utilized for statistical analysis (CpK, PpK, Pa, SPC where applicable for CPPs and CQAs)
- Appropriate actions, relevant trends and intra-batch variability is discussed.
- Where process performance does not meet the requirements appropriate actions is discussed (investigations, Change control, remediation activities) or may be taken
- Based on results of CQAs obtained from these batches, recommendations for CQA limits is made for Stage 3B CPV monitoring

Stage 3B is routine Continued Process Verification and trending of IP and FP CQAs and CPPs within established alert limits
# Stage 3A – Statistical Analysis

<table>
<thead>
<tr>
<th>ELEMENT</th>
<th>STAT ANALYSIS EXAMPLES</th>
<th>STAT ILLUSTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Batch Determination</td>
<td>Based on 3A # of batch calculator</td>
<td><img src="image1.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Determining additional 3A sampling and testing criteria</td>
<td>Determine heightened monitoring, sampling and testing points based on variability observed.</td>
<td><img src="image2.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Variability Trending for IP and FP CQAs, CPP</td>
<td>One way analysis- Box Plot, Distribution Analysis- Histogram, pooled Box Plot</td>
<td><img src="image3.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Correlation between CPPs and CQAs and impact</td>
<td>Least Squares Fit- Pareto plot, Multivariate Analysis- Prediction profiler</td>
<td><img src="image4.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Raw material evaluation</td>
<td>ANOVA, Correlation Analysis, Pareto Charts</td>
<td><img src="image5.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Equipment Specificity Evaluation</td>
<td>CQA and CPP Variance test, Cp</td>
<td><img src="image6.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Stability Data Analysis</td>
<td>Regression Analysis, Degradation Analysis</td>
<td><img src="image7.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Verify Dissolution Correlation</td>
<td>Similarity factor, Correlation Analysis</td>
<td><img src="image8.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Post Stage 3A Technical Risk Assessment</td>
<td>Criticality and data driven risk ratio assessment</td>
<td><img src="image9.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Estimate Inherent Process Variability (common cause)</td>
<td>Determine variability from all sources: testing, raw material, equipment, process</td>
<td><img src="image10.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Determining 3B trend/alert limits</td>
<td>Process performance with sufficient level of confidence within best estimate of process variability.</td>
<td><img src="image11.png" alt="Statistical Analysis Example" /></td>
</tr>
<tr>
<td>Monitoring</td>
<td>Apply Western Electric rules</td>
<td><img src="image12.png" alt="Statistical Analysis Example" /></td>
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</tbody>
</table>
Continued Process Verification provides an on-going assurance that routine production process remains in a state of control.

- Supports FDA Quality Metrics guidance recommendations
- Provides opportunity to correct/change without impacting subsequent process steps or additional batches
- Real time visibility to process shift and undesired process variability (OOT/OOSC)
- Reduce process failure rate
Stage 3B – Automation

- Automated data retrieval and assessment enables fast decision making.
- Enablement of trend notifications helps in reducing failures. Eliminates failure costs and associated loss of opportunity.
- Program helps in achieving a continuous supply chain and in planning.
- Knowledge Management (use of existing data by electronic data capturing and ad-hoc search/query/reporting functions of similar processes/formulations)
  - Dynamic query function- all fields are searchable, meta-data as well as information within a documents.
- Queries can be build ad-hoc and stored for future use
- Data is readily available (QA verified and approved in LIMS)
- Data that is OOT/OOSC/OOS is made visible in real-time via email notifications to users as well as being ‘flagged’ in the system.
- Data can be statistically evaluated within the software or exported to statistical software such as JMP.
- Periodic process review not required
FDA mandates a science based decision making process utilizing data from all three stages. Product and process knowledge of similar products for Stage 1 and SPC methodologies for Stage 3 (CPV) are key components for successful PV Lifecycle Management.

- **Stage 1** - Process Design includes Risk Assessment, Multivariate Design of Experiments to help reveal relationships and interactions to establish a design space. Use of prior knowledge for similar formulation/process is critical. This requires a Knowledge Management system that enables data queries and reporting functions.

- **Stage 2** - PPQ stage can utilize tools to determine number of batches required. This best estimate is based on statistical confidence and variability of similar products/processes and label claim. Pa is a novel statistical analysis tool applicable for multi-level acceptance criteria.

- **Stage 3** - CPV is an effective tool for detecting trends. Prevention of process related failures allows for uninterrupted supply, meeting patient needs and reduces cost of quality. An automated Stage 3 real time trending is key to the CPV program. SPC methodologies with automated signal detection, notification and escalation process are required to implement corrective measures.
Thank you

Special Acknowledgment:
Pradeep Sanghvi, Elisabeth Kovacs, Jana Spes, Ajay Pazhayattil