Drug Product Continuous Process Verification – A Case Study

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Drug Product CPV In Practice - 3 Levels

1. Drug Product Manufacturing Site
- Approximately Monthly interbatch data reviews
- Voice of the Process at the Shop Floor
- Site Focused...but also feeds data upward

2. End to End Product Reviews
- Cross functional team across Drug Substance, Drug Product, Analytical, Stability and Quality
- Deeper Statistical Analysis applied to Hot Spots

3. Quarterly Portfolio - Sr. Management Scorecard looking at all sites and products

<table>
<thead>
<tr>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACME</td>
<td>ACME</td>
</tr>
<tr>
<td>% Ppk &gt; 1.3</td>
<td>2/50</td>
</tr>
<tr>
<td>% Ppk &gt; 1.0</td>
<td>80%</td>
</tr>
<tr>
<td>Yield</td>
<td></td>
</tr>
</tbody>
</table>

Product A Product B
ACME ACME CMO
% Ppk > 1.3 2/50 0/20
% Ppk > 1.0 80% 80%
Rejection Rate 2/50 0/20
1. Manufacturing Site CPV- Getting Started

1. Procedures and training
   • Statistical software and Training
   • Data mining practices- Manual, Automated, or Hybrid
   • Statistical Alert Rules And Procedures
   • Data review frequency and participants

2. Initial Monitoring – Beginning of Stage III Process Validation
   • Monitoring Plan Established Based on Risk Assessment
   • Monitor 1st ~ 30 lots, generate Time Series plots (too soon for CpK)
   • Lock Control Limits

3. Continuous Process Verification
   • Visualize Data using Time series, histograms, and PpK/CpK analysis
   • Generate statistical alert event reports where needed
   • Utilize Heat Map, and apply multivariate analyses when needed (Generally multivariate utilized less for DP than in DS)
   • Data Feed upwards into E2E Product Reviews and Portfolio scorecards
Drug Product Monitoring Plan - Typical Profile

Critical Quality Attributes
- pH
- Concentration
- HMW/LMW
- Bioanalytical impurities
- Particulate
- Potency
- Moisture (lyo)
- Etc.

In Process Control
- pH
- Fill weight Performance

100 % Visual inspection Process – Valuable, often overlooked
- % Particle defects
- % Critical defects found
- % Overall

Less is more at the start. Automated data capture and analysis enables larger data sets with faster alert response
pH – 2 Learnings From a Basic Assay

N=30 Batches
PpK = 1.07 (Borderline Capable)

Most Recent 15 Batches – PpK Increases to 1.63

Learning 1:
Data visualization is King...PpK is a lagging indicator.

Learning 2:
Assays with low sig figs, while scientifically correct, often drive non-normal data sets.
Fill Weight Control

Boxplot of Net Fill Weight Checks by Lot

- Box Plots are ideal...but data-intensive
- Per lot sigma is another measure
- Automated data acquisition from OEM check weigh system can be a challenge due to proprietary software
- Use side-by-side to compare 2 different DP sites
Visual Inspection - Example Defect Trend

I Chart of Major Defects

Simple but powerful tool to reduce complaint/quality risk
- Lot defect rates compared to in-process control limits (not specs)
- Further defect pareto can be explored in regions of concern (e.g. scratch, product on stopper)
- Side by side control charts used for comparing performance of 2 different DP sites.

Statistical Alert

- UCL = 1.461407%
- NMT = 1.0%
- $\bar{X} = 0.335201$
- LCL = -0.791005%
Example – Product Related Impurity

Variability..... Method or Process...or Both?

CpK = 1.0

To Be Continued....
# Example Process PpK Heat Map

## Parameter

<table>
<thead>
<tr>
<th>Drug Substance</th>
<th>Formulation</th>
<th>Filling</th>
<th>Capping / Sealing</th>
<th>100% Visual Inspection</th>
<th>Finished DP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thawing / Pooling</td>
<td>Mixing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein concentration</td>
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<tr>
<td>Purity</td>
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<td>pH</td>
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<tr>
<td>SEC</td>
<td></td>
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<tr>
<td>Moisture</td>
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<td>Reconstitution Time</td>
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<tr>
<td>Fill Dose</td>
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<tr>
<td>Machine Speed</td>
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<tr>
<td>Plunger Pressure</td>
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<tr>
<td>Height Adjustment</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical Defects</td>
<td></td>
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</tr>
<tr>
<td>Major Defects</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Defects</td>
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</table>

### Process Improvement Initiatives Focused Here

<table>
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<th>Highly capable</th>
<th>Ppk ≥ 1.33</th>
</tr>
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<tbody>
<tr>
<td>Barely capable</td>
<td>1.32 ≤ Ppk ≤ 1.0</td>
</tr>
<tr>
<td>Not capable</td>
<td>Ppk &lt; 0.99</td>
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3. Quarterly Portfolio - Sr. Management Scorecard comparing Products and Drug Substance and Drug Product Sites

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<td>2/50</td>
<td>0/20</td>
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Product A
- ACME
- % Cpk > 1.3
- % Cpk > 1.0
- Rejection Rate: 2/50
- Yield

Product B
- ACME
- % Cpk > 1.3
- % Cpk > 1.0
- Rejection Rate: 0/20
- Yield

CMO
- % Cpk > 1.3
- % Cpk > 1.0
- Rejection Rate
- Yield
End to End Product Reviews

Each Cross-Functional Product team presents data package to technical management, approximately 3-4X per year
  – Drug Substance
  – Drug Product
  – Analytical and Stability

• **End to End view provides powerful insights**
  – Most CQA’s are common from DS to DP
  – Analyses such as DS-to-DP genealogy assessments and Assay Variation Ratio provide insights to source of variation (Assay or Process?)
  – Selective multivariate analysis used as needed

• **Input into Annual Product Quality Review**
Variability not attributable to lab. Lower purity DS results in lower purity DP
2. DP mfg process contribution should be explored: shorter Time out of Refrigeration or light exposure?
3. Consider multivariate analysis
Random pattern of DS vs. DP result suggests analytical contribution
Method precision appears to be increasing with more recent lot history
Assay Variance Ratio (AVR)

- AVR is ratio of analytical system variance (based on reference standard results) to total process variance (DS or DP results)

- Indicates contribution of assay variability to total variability

\[
\text{Assay Variance Ratio} = \frac{\hat{\sigma}_A^2}{\hat{\sigma}_T^2}
\]

<table>
<thead>
<tr>
<th>Guideline</th>
<th>No Action Required</th>
<th>May need further evaluation of analytical method. Medium risk</th>
<th>Needs further evaluation of analytical method. High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpk &gt; 1.33 &amp; AVR &lt; 0.45</td>
<td>No Action Required</td>
<td>May need further evaluation of analytical method. Medium risk</td>
<td>Needs further evaluation of analytical method. High risk</td>
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<td>Cpk &gt; 1.33 &amp; AVR ≥ 0.45</td>
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Notes:
- 0.45 cut off derived on the basis that analytical variability should not contribute more than 50% of the variability compared to the process variability.
General Takeaways

- VP-level engagement and broad data transparency down to the shop floor are critical to a successful and sustainable CPV program.

- Centralized Process Analytics team, led by Statistician, helps drive end-to-end product view and provides second-level statistical support (multivariate).

- When in doubt—use time-series plots to visualize the data.

- CPK/PpK “heat maps” provide a good overview of process risk, and help drive further analyses and corrective actions.

- Investment in automated data capture and analysis platforms (e.g., Discoverant) provide the following benefits:
  - Decreased data lag
  - Less labor
  - Increased data integrity

- While automation is good, CPV can be resourced and executed with manual data capture when necessary.
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Questions?