Application of Continued Process Verification (CPV) to New Products

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IVT: Statistics In Validation Conference

The views and opinions expressed are those of the speaker and not necessarily of AstraZeneca.

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Objectives

Continued Process Validation Overview
Application of CPV to New Products
Review of a Case Study for CPV of a New Product
Revised Approach for CPV
Summary
The AstraZeneca/MedImmune Frederick Manufacturing Center

Manufacturing Facility (~350,000 ft$^2$)

ISPE’s Facility of the Year - 2011
Validation in General

Planning and Knowledge are EVERYTHING

✓ Documenting the established approaches and terms, process monitoring, testing methods, acceptance criteria, etc. prior to initiating validation studies is absolutely required.

✓ Demonstrating true understanding of the systems, equipment and processes is key to Success.
<table>
<thead>
<tr>
<th>How the process was developed</th>
<th>How the Project was described at kick-off</th>
<th>How the Receiving Site understood it</th>
<th>How the Manufacturing team heard it</th>
<th>How Project Management planned it</th>
</tr>
</thead>
<tbody>
<tr>
<td>How the Project was really supported</td>
<td>How it was actually put into the plant</td>
<td>What QA and Reg Affairs expected</td>
<td>How the Project was documented</td>
<td>What was required for licensure</td>
</tr>
</tbody>
</table>
ICH Q10 Pharmaceutical Quality System

Process control is key in producing a quality product

Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement.

- Quality risk management to establish the control strategy
- Measure and assess parameters and attributes identified in the control strategy
- Verify continued operation within a state of control
- Identify sources of variation
- Provide knowledge to enhance process understanding
Process Validation Overview – FDA

Focuses on the validated state at commercial-scale


*Process Validation* is defined as 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 products.

Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes process validation activities in three stages.
Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use.

Process validation should **not** be viewed as a **one-off event**:

The *lifecycle concept* links product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a *state of control* during routine commercial production.

A product lifecycle concept follows the International Conference on Harmonisation (ICH) guidances for industry, *Q8(R2) Pharmaceutical Development*, *Q9 Quality Risk Management*, and *Q10 Pharmaceutical Quality System*. 

Process Validation occurs throughout the Product Life Cycle

Stage 1 Process Design

1.1 Identification of process variables

Stage 2 Process Performance Qualification

2.1 IQ, OQ, PQ

2.2 PV (PPQ)

Stage 3 Continued Process Verification


Retirement
Process Validation Life Cycle

• Stage 1 – *Process Design*: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
  - Demonstrate a Understanding of the Process

• Stage 2 – *Process Performance Qualification (PPQ)* or traditional *Process Validation*: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
  - Demonstrate Process Robustness at Commercial-scale

• Stage 3 – Continued Process Verification (CPV): Assuring that during routine production the process remains in a state of control.
  - Demonstrate Understanding of Process Variability at Commercial-Scale

Process Life Cycle – Stage 3

Maintaining the validated state at commercial-scale includes the following:

- Maintain the validated state of the facility, utilities and equipment
- Maintain the validated state of the process
- Perform ongoing process monitoring (CPV)
  - statistically analyze the data as appropriate
Stage 3: Process Life Cycle Maintenance

Two Phases:

Initial, Short-term: Stage 3a
- General trending of data (non-statistical)
- Accumulate batch data to set limits based on statistical significance
- Review parameters and update risks

Long-term: Stage 3b
- Introduce SPC with rules for alerts
- Continue ongoing process verification
- Understand variation and trends
- Identify opportunities to continuously improve process
Stage 3: Process Life Cycle

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FDA Expectations for CPV

An ongoing program for collecting and analyzing product and process data that relate to product quality

- Procedures for data collection and trending
- Data collected should verify that the quality attributes
- Intra-batch and inter-batch variation
- Data should be collected to evaluate process stability and capability
- Data should be statistically trended
- It is recommended that a statistician or person with adequate statistical training develop the data collection plans and methods for analysis

Must have a system for detecting unplanned departures from the process

- Evaluate the performance of the process
- Identify Problems
- Determine if corrective action is necessary
- Anticipate and Prevent problems to ensure control
FDA Benefits for CPV

Recommend that CPV monitoring and sampling mirror the PPQ stage until sufficient data are available to generate significant variability estimates.

- Monitoring can be adjusted to a statistically appropriate and representative level.
- Process variability should be periodically assessed and monitoring adjusted accordingly.

Data gathered might suggest ways to improve the process

Must document description of the planned change

Additional process design and process qualification activities could be warranted

Maintenance of the facility is an important aspect of ensuring controlled process.

Qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules
CPV Overview – EMA

- Monitor product quality
- Ensure a state of control
- Provide assurance of the continued capability of the process
- Relevant process trends, non-conformances, and defect reporting should be collected and assessed
- Periodic review should be performed
- Consider the level of process understanding and performance
- Possible period of enhanced sampling/monitoring
- Increase process understanding

EMA Guideline on process validation for finished products:

EMA Guideline on Process Validation for Finished Products – Information and Data to be Provided in Regulatory Submissions (27Feb 2014)
Establishing a Strategy for Process Control

Control Strategy is required to go into Process Validation/PPQ

Control Strategy – A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to active substance and finished product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Design Space – The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. (ICH Q8)

Proven Acceptable Range (PAR) – A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria. (ICH Q8 R2)

Normal Operating Range (NOR) – A region around the target operating conditions that contains typical operational variability and is within the claimed acceptable ranges. (EMA 25Apr2014 Draft guideline on process validation for the manufacture of biotechnology-derived active substances)
Stage 1: Control Strategy Development

Finally, the normal operating range
Control Strategy - Input and Output Parameters

Process Parameter
- Critical Process Parameter (CPP)
- Non-Critical Process Parameter (NCPP)

Output Parameter
- Critical Quality Attribute (CQA)
- In-Process Control (IPC)
- Key Process Attribute (KPA)

Key Operational Parameter (KOP)
- Non-Key Operational Parameter (NKOP)
Process and Product Monitoring

Process Monitoring
- A strategy
- Proactive
- Assessing output parameters for the extent to which they conform to requirements
- Assess control

Product Monitoring
- A snapshot
- Retrospective
- Assessing any parameter for the extent to which it is stable
- Assess capability
Selection of Attributes and Parameters to be Monitored

Determined based on current understanding of the manufacturing process and systems in relation to quality attributes.

This can be based on:
- Prior knowledge
- Statistical Models based on DOE
- Understanding based on Manufacturing experience

The number of parameters and/or extent of testing may increase/decrease as:
- Knowledge is gained
- Specific residual risks are reduced or
- New risks are identified
Selection of Attributes and Parameters to be Monitored for New Products

- Developed according to QbD principles.
- Scientifically and statistically justified.
- Based on process understanding and QRM.
- Enhanced sampling during Stage 2 of PV.
- Consider intra- and inter-batch variability.
- Consider the number of batches to calculate Process capability.
- Impact of each process variable on CQA.
Data Analysis and Review

Develop a process to collect, analyze, report and store data

Use appropriate collection and analysis tools

Consider normality of data (Normal vs Non-normal)

Use Statistical tools
Control Charts

Developed by Walter Shewhart (Bell Labs ~1924)

- Company needed to improve reliability of their telephony system:
- Need to reduce variability in their manufacturing process
- Stressed that bringing a process into a state of statistical control, where there is only common-cause variation, and keeping it in control is necessary to predict future output
  - typically produce a normal distribution curve

W. Edwards Deming - became the foremost champion and proponent of Shewhart's work.

- Served as statistical consultant to the Supreme Commander for the Allied Powers following WWII.
- His influence lead to the use control charts widely in Japanese manufacturing industry throughout the 1950s and 1960s.
Control Charts

- pH
- Lower Specification Limit
- Lower Warning Limit
- Upper Specification Limit
- Upper Warning Limit
- Center
## Differences between Cpk and Ppk

<table>
<thead>
<tr>
<th>Cpk</th>
<th>Ppk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Capability Indices</td>
<td>Process Performance Indices</td>
</tr>
<tr>
<td>Short term Capability (snap shot)</td>
<td>Long Term Capability (reflects the future)</td>
</tr>
<tr>
<td>Focused on Inherent (common-cause) variation</td>
<td>Focused on Total Process (Common and special-cause) Variation</td>
</tr>
</tbody>
</table>

- **Cpk**: Process Capability Indices focus on short-term capability, reflecting inherent variation (common-cause). It provides a snapshot of the current state of the process.
- **Ppk**: Process Performance Indices focus on long-term capability, reflecting total process variation (both common-cause and special-cause). It reflects the future performance of the process.
Define and Analyze Process Capability and Process Performance – Cp and Cpk

- Cp measures the process capability with respect to its specification using USL and LSL.
- Process capability is determined by taking periodic samples from the process and calculating its standard deviation and sample mean.
- Cpk measures the process variation with respect to its sample mean, which is also considered to be the process mean.
- Cpk is used to evaluate the centering of the process.
- Normally Cp and Cpk target values should be determined by the company.
- These are “short-term” process variability indicators.

\[
C_p = \frac{USL - LSL}{6 \times \text{std. Dev}}
\]

\[
C_{pk} = \min \left( \frac{USL - \text{mean}}{3 \times \text{std. Dev}}, \frac{\text{mean} - LSL}{3 \times \text{std. Dev}} \right)
\]

USL: Upper Specification Limit
LSL: Lower Specification Limit
Define and Analyze Process Capability and Process Performance – Cp and Cpk

• Establish Control Limits and follow trending rules (e.g., Western Electric)
• These statistical tools are associated with a normally distributed dataset.
Define and Analyze Process Capability and Process Performance – Cp and Cpk

Process Capability Process Levels

<table>
<thead>
<tr>
<th>$C_{pk}$</th>
<th>“X”-Sigma Quality</th>
<th>% Out-of-Specification</th>
<th>PPM Out-of-Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.33</td>
<td>1</td>
<td>31.7%</td>
<td>~317,300</td>
</tr>
<tr>
<td>0.50</td>
<td>1½</td>
<td>13.4%</td>
<td>~133,600</td>
</tr>
<tr>
<td>0.67</td>
<td>2</td>
<td>4.6%</td>
<td>~45,500</td>
</tr>
<tr>
<td>0.83</td>
<td>2½</td>
<td>1.24%</td>
<td>~12,400</td>
</tr>
<tr>
<td>1.00</td>
<td>3</td>
<td>0.27%</td>
<td>~2,700</td>
</tr>
<tr>
<td>1.17</td>
<td>3½</td>
<td>0.047%</td>
<td>~465</td>
</tr>
<tr>
<td>1.33</td>
<td>4</td>
<td>0.0063%</td>
<td>~63</td>
</tr>
<tr>
<td>1.50</td>
<td>4½</td>
<td>6.8 x 10^{-4}%</td>
<td>6.8</td>
</tr>
<tr>
<td>1.67</td>
<td>5</td>
<td>5.7 x 10^{-5}%</td>
<td>0.57</td>
</tr>
<tr>
<td>1.83</td>
<td>5½</td>
<td>3.8 x 10^{-6}%</td>
<td>0.038</td>
</tr>
<tr>
<td>2.00</td>
<td>6</td>
<td>2.0 x 10^{-7}%</td>
<td>0.002</td>
</tr>
<tr>
<td>2.33</td>
<td>7</td>
<td>2.6 x 10^{-10}%</td>
<td>0.0000026</td>
</tr>
<tr>
<td>2.67</td>
<td>8</td>
<td>1.2 x 10^{-13}%</td>
<td>0.000000012</td>
</tr>
</tbody>
</table>
Define and Analyze Process Capability and Process Performance – Pp and Ppk

- These are “long-term” process variability indicators
- Relies on overall process variability
- The larger the index, the more capable the process is of meeting the specification limit
- Target values should be determined by the company
Western Electric Rules

**Rule 1:** 1 or more points fall outside a control limit.

**Rule 2:** 2 out of 3 successive values are outside of the warning limits on the same side of the central line.

**Rule 3:** 4 out of 5 successive values are outside of the inner limits on the same side of the central line.

**Rule 4:** 8 successive values fall on the same side of the central line.

**Rule 5:** 6 points in a row steadily increasing or decreasing
Response to Signals

Suggestions on what to watch for when noticing a trend:

- Common Cause Variation vs Special Cause Variation
- Sudden recent change(s) (violate WE rule 1 or 2)
- Step change around the beginning of the run (violate WE rule 3, 4, or 5)
- Correlation with other parameters
- Cycling (work shifts, seasons, changeovers)
Western Electric Rules Don’t Always Apply

- One data point outside ± 3 s
- Two out of last three points outside on same side of ± 2 s
- Four out of last five points outside on same side of ± 1 s
- Eight points in a row on same side of center line
- Six consecutive points in an increasing or decreasing direction
- Fifteen consecutive points within one sigma zone
- Fourteen consecutive points alternating direction
- Eight consecutive points outside one sigma zone
Setting Control and Action Limits for a New Product

Statistical Control Limits:
• Ideally are tighter than acceptance criteria but should not be considered acceptance criteria
• Used to alert of any process variability

You can set Control Limits during Stage 3a if you have good understanding of variability. There are two kinds of variability:
• Scale dependent
  • Some scale dependent variability is equipment-driven and known across products
• Scale independent
Which of the following parameters are scale dependent? Scale independent?

Pressure
Purity
pH
Conductivity
Hold Times
Impurity Profile
Chromatographic Profile
Step Yield
Case Study: CPV Approach for a New Product (Biotech)

Working Cell Bank Vial Thaw → Inoculum Expansion → Fed Batch Production Bioreactor → Continuous Flow Centrifugation & Depth → Column #1 Chromatography

Ultrafiltration / Diafiltration → Virus Filtration → Column #3 Chromatography → Column #2 Chromatography → Low pH Virus Inactivation

Formulation → 0.2 micron Bulk Filtration
### Corporate and site procedures in place

- Ensure compliance with regulatory expectations
- Provide minimum strategy
- Define roles and responsibilities of multiple functions

### Creation of a product-specific protocol

- Defined what parameters to monitor (all parameters from PPQ campaign)
- Will include data from PPQ campaign
- Defined minimum # of lots for Stage 3a
- Approach to statistical analysis
Case Study: CPV Approach for a New Product

Several Methods Employed for Data Collection:

- QC results
- PI Historian Trending
- Paper Batch Records
- SAP
- QMS for change controls and non-conformances

JMP used for statistical analysis
Case Study: CPV Approach for a New Product

Analysis of Data

- 170 parameters evaluated for 30 lots (12 unit ops, each batch takes ~ 45 days) during Stage 3a for process capability.
- Process Capability was calculated for all process inputs monitored during CPV if appropriate (ex: parameter had both a LSL and a USL).
- 35 additional parameters monitored for CPV but could not be evaluated statistically (non-normally distributed).
- Any Parameter with a Ppk < 1.33 would be evaluated.
- Each parameter that had a Ppk index value was ranked.
- A normal distribution was used to evaluate all attributes and parameters.
- Control charts were developed for each parameter monitored during CPV with statistical process run run applied.
Revised Approach to CPV for New Products: Lessons Learned

The Good:
• Process Capability (Ppk) calculated and control charts analysis indicated that process is in a state of control
• Determined which parameters to monitor for Stage 3b (and which to remove from the monitoring program)
• Determined frequency of Stage 3b monitoring based on Ppk values

The Bad:
• Use of minimum and maximum data does not allow for appropriate statistical analysis for all continuously measured parameters.
• Statistical analysis not suitable for non-normally distributed data
• For Stage 3b, analyze the average for all continuously collected data on a batch-to-batch basis
Revised Approach to CPV for New Products:

Risk Based Approach for Selection of Parameters

• Created a set of standards
  • Inclusion of all CPPs, IPCs, and CQAs
• Take a risk-based approach to determine which KPPs, and PAs should be included in Stage 3a
• Risk Assessment documents which parameters will be added/removed to Stage 3a monitoring plan.
• No application of trend rules during Stage 3a
• Statistical analysis will be performed according to corporate policy.
  • Control charts will be applied as appropriate
Revised Approach to CPV for New Products:

<table>
<thead>
<tr>
<th>Production Bioreactor</th>
<th>Risk Factors</th>
<th>KPP to be Included in CPV</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KPP</strong></td>
<td>Is the control capability of the KPP similar to its PAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is the Target of the KPP close to the edge of PAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is the KPP an indicator of the performance of the step or a previous step</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is the KPP in a step for which scales differences were found</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Dissolved Oxygen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 1st Nutrient Feed Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 1st Nutrient Feed Volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Duration Between 1st and 2nd Feed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 2nd Feed Volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Interactive Exercise

Participants will divide into Groups:

1. Each group will calculate process capability

   To Determine Cpk:
   1. Calculate the mean
   2. Calculate the Variance
   3. Calculate the Standard Deviation
   4. Determine Cpk

2. All groups will review control charts and determine if any Wester Electric rules have been violated.

\[
1. \quad \bar{X} = \frac{\sum X}{N}
\]

\[
2. \quad s^2 = \frac{\sum (x - \bar{x})^2}{n - 1}
\]

\[
3. \quad s = \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}}
\]

\[
4. \quad C_{pk} = \min \left( \frac{USL - \text{mean}}{3 \times \text{std.Dev}}, \frac{\text{mean} - LSL}{3 \times \text{std.Dev}} \right)
\]

USL: Upper Specification Limit
LSL: Lower Specification Limit
Summary

For Process Validation, Planning and Knowledge are EVERYTHING

By having a thorough understanding of the systems, equipment, processes and products, you are able to:

- Take a risk based approach to determine potential sources of variability, how they are controlled and what level of risk mitigation is required.

- Develop appropriate rationale in designing the qualification and validation study designs and the associated acceptance criteria in support of the product lifecycle approach.

- Provide a proper analysis of study data including adequate justification to address any unexpected results/departures from the protocol.
Summary – Thoughts on Transitioning to Stage 3b

When transitioning to Stage 3b, use scientific and statistical rationale to justify the following:

- Adjusted monitoring (add or remove parameters)
- Setting control limits
- Selection of trend rules
- Updating CPV protocol
- Re-baselining control charts
- Discuss frequency of reporting
- Response to signals
Questions?

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The Continued Process Validation Protocol

Protocols describe the validation study to be performed

The protocol includes the following elements:

• The manufacturing conditions, including operating parameters, processing limits, and component (raw material) inputs.

• The data to be collected and when and how the data will be evaluated.

• Tests to be performed (in-process, release, validation only) and acceptance criteria for each significant processing step.

• The sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute.
  
  • The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches.

  • Status of the validation of analytical methods used in measuring the process, in-process materials, and the product.

  • Criteria and process performance indicators that allow for a science- and risk-based decision about the ability of the process to consistently produce quality products.

• Review and approval of the protocol by appropriate departments including Validation and Quality Assurance. The criteria for approval should be in accordance with the company’s quality system.
The Continued Process Validation Report

Reports document how the validation study was performed

The report includes the following elements:

- Discuss and cross-reference all aspects of the CPV protocol.
- The results should be evaluated, analyzed and compared against the protocol documented pre-determined acceptance criteria.
- The results should meet the acceptance criteria. Deviations and out-of-limit results must be investigated:
  - Evaluate the impact of each deviation on the validation study, including appropriate justification.
  - Describe in sufficient detail any corrective actions or changes that should be made to existing procedures and controls and the associated impact to the validated state.
- The conclusion of the report should state whether or not the outcome of the validation was considered successful and include any corrective actions.
- In addition to Quality Assurance, the same departments that approved the protocol are to approve the report after the final review.
Example of a Parameter that is Not Normally Distributed

Bioreactor Cell Density
Raw Data:

Normal Quantile Plot:

Control Chart Sigma:
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