PCMO\textsuperscript{SM} (Paradigm Change to Manufacturing Operations)

*Process Validation and Verification: A Life-cycle Approach*


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Process Validation and Verification: A Life-Cycle Approach

Presentation Contents

• Background and Technical Report Status
• Overview of Process Validation Lifecycle Concept
• Summary of PV Lifecycle Requirements by Stage
  ▪ Stage 1: Process Design
  ▪ Stage 2: Equipment and Process Qualification
  ▪ Stage 3: Continued Process Verification
• Team Members
Background

• Paradigm Change in Manufacturing Operations (PCMO)
  o PDA initiative; launched in 2008
  o Implementation of scientific application of ICH Q8, Q9, Q10
  o Emphasis on “Lifecycle” concept
  o Establishment of “best practice” documents and training
  o Teams currently addressing 16 different topics

• New FDA Guidance Document on Process Validation
  o Draft Guidance in Nov 2008; Final Guidance in Jan 2011
  o Emphasis on “Lifecycle”; “Scientific Justification”; “QRM”
Background

- Previous PDA Technical Reports Related to Process Validation
  - TR 14: Validation of Chromatographic Separations for Protein Purification (1992; updated in 2009)
  - TR 15: Validation of TFF for Biotechnology Applications (1992, updated in 2009)
Technical Report Status

• Team Established in Fall 2009
  • 35 Contributors
  • Representing 24 Companies
• Co-Leaders
  • Scott Bozzone – Pfizer
  • Hal Baseman – Val Source
• General Approach
  • Sub-Teams develop report chapters
  • Teleconferences and Face-to-Face Meetings
  • Review at PDA Meetings & Peer Review
• Status
  • Peer Review completed (40 reviewers; 1100 comments)
  • Final Draft being compiled
  • Publication Target: end Q2 2012
Process Validation Lifecycle Stages

Stage 1 - Process Design:
(Chapter 3)
Product Knowledge
Process Knowledge
Control Strategy

Stage 2 - Process Qualification:
(Chapter 4)
Confirm Process Design
Control Strategy

Stage 3 - Continued Process Verification:
(Chapter 5)
Monitoring Program
Continuous Improvement

INPUT/PARAMETERS

Evaluate for degree of criticality

OUTPUT/ATTRIBUTES

Facility & Equipment Qualification

Critical Process (Input) Parameters + critical quality attributes + additional Testing (i.e. clearance) = PPQ Protocols

Sub-set of PPQ Acceptance Criteria
Post PPQ monitoring and trending
CPV (continued process verification) plan
Quality Systems (ICH Q10) Evaluation

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Figure from draft Technical Report

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TR Organization

- Report organization reflects concepts introduced in FDA January 2011 Guidance
  - Introduction & Glossary
  - **Stage 1 – Process Design**
    - Building Product & Process Knowledge
    - Developing a Control Strategy
  - **Stage 2 – Process Qualification**
    - Equipment & Utilities Qualification
    - Process Performance Qualification
  - **Stage 3 – Continued Process Verification**
  - Tools (Risk Assessments, Statistics…)
  - Examples
Stage 1: Synopsis of Content

Deliverables at the end of Stage 1 listed and discussed

- Quality Target Product Profile (required at start of Stage 1)
- Critical Quality Attributes (with corresponding Risk Analyses)
- Process Descriptions; Flow Diagrams
- Analytical Methods
- Process Characterization Reports (Design Space; Parameter Ranges)
- Risk Assessments and Criticality Determination
- Control Strategy
- Characterization Test Plan
- Scale-up / Scale Down Approach (evaluation of lab models)
- Batch Records (Pilot, Clinical Manufacturing experience)
Stage 1: Development of a Control Strategy

• Elements of a Control Strategy
  ▪ In-Process and Release Specifications
  ▪ In-Process Controls
  ▪ Process Parameter Acceptable Ranges (or Design Space)
  ▪ Performance Parameter Acceptable Ranges
  ▪ Stability (Intermediates, DS, DP, Process Solutions)
  ▪ Raw Material Specifications and Impact of Variability
  ▪ Process Analytical Technology (PAT)
  ▪ Comprehensive Process Monitoring Plan
Stage 2 – Synopsis of Content

Activities included in Stage 2:

- Facilities / Utilities / Equipment Design and Qualification
- Equipment Capability Assessment
- Process Performance Qualification (PPQ)
  - Scale
  - Strategy & Approaches
  - Types of Studies
  - Setting Acceptance Criteria
  - Determining Number of PPQ Batches
  - Sampling, Testing, and Analysis
  - Documentation
Determining the Number of PPQ Batches

Three batches no longer the default number!!

Factors to consider include:

- Level of Risk for Process
  - Process Knowledge
  - Product Knowledge
  - Control Strategy
  - Novelty of Process / Unit Operations
  - Process Fit with Facility/Equipment
- Past experience / track record for organization
- What is being proven / demonstrated
- Statistical metrics being employed (intra-batch variability; inter-batch consistency)
Stage 3: Synopsis of Content

- Aspects of Continued Process Verification
  - Strategy
  - Developing the Process Monitoring Program
  - Data Analysis and Trending
  - Utilizing CPV Data
  - Documentation
  - Addressing Legacy Products
  - Change Control and CAPAs
Stage 1

Draft Initial Plan

Revise Plan Based on Control Strategy

Revise Plan Based on PPQ Data

Formalize or Update Plan

Periodic review to Assess state of control

Stage 2

- Statistical methods
- Data to be trended
- Lab Model Accuracy
- Reporting Frequency

Stage 3

- Update list of parameters / data to be trended

- Set # of batches to re-assess ranges
- Update statistical strategy based on PPQ
- Frequency of data review based on relevant statistical tools
Tools for the Process Validation Lifecycle

• Quality Risk Management
  ▪ Modeling Uncertainty
  ▪ Risk Tools that can be applied to:
    • Process Understanding
    • Control Strategy
    • Facility Design & Verification
    • Raw Materials
    • Commercial Manufacturing and Monitoring (CPV)

• Statistical Analysis Tools
  ▪ Design of Experiments (DOE)
  ▪ Statistical Process Control (SPC) and Process Capability
  ▪ Control Charts
  ▪ Statistical Acceptance Sampling
  ▪ Determining Number of Lots for Stage 2 PPQ
Tools for Analyzing Lot-to-Lot Variability

- Average run length to detect a lot failure
- Selecting range of inter-lot variation to be covered
- Normal tolerance intervals within and between lots
- Statistical Process Control Charts
- Process Capability Metrics
- Lot Conformance Rate at selected confidence level
- Wald sequential probability ratio
- Narrow limit gauging
- Comparison of between and within lot variation
- Demonstrating between lot std deviation at or below target
- Demonstrating lot-to-lot equivalence
Examples – Application of Concepts in the Guidance

- Biotechnology Product (monoclonal antibody)
- Radio-pharmaceutical
- Solid oral dosage form
## Team Members

<table>
<thead>
<tr>
<th>Name &amp; Role</th>
<th>Company</th>
<th>Name &amp; Role</th>
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<tr>
<td>Scott Bozzone</td>
<td>Pfizer</td>
<td>Igor Gorsky</td>
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<td>Hal Baseman</td>
<td>ValSource</td>
<td>Alpaslan Yaman</td>
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<td>Julie Spyrison</td>
<td>BioTechLogic, Inc.</td>
<td>Mark Varney</td>
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<td>Iris Rice</td>
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<td>David Reifsnyder</td>
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<td>Rebecca Devine</td>
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<td>Wendy Lambert</td>
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*ISPE Liaisons*
Thanks for your attention

Questions?

Comments?