Lyophilization Process Validation – Part 2

FDA Process Validation Guideline: Stage 3
FDA Validation Guideline
Continuous Process Verification: Stage 3

Current GMP Requirements
Overview of New FDA Guideline
Focus of Stage 3: Continuous Monitoring
Techniques in Trending: Control Charts
Control Charts for Product Data
Comprehensive Trending Program
Going Forward
211.192: Production record review as part of batch release.

Lyophilization Critical Process Parameters (CPP)
Product Critical Quality Attributes (CQA)
Routine Manufacturing: Annual Report
An ongoing program to collect and analyze product and process data that relate to product quality must be established. (§ 211.180(e))
CFR Requirements
Continuous Monitoring

211.180: Annual review of “representative” number of batches

*Evaluate need for changes in manufacturing and control procedures.*

*Assess need for changes in product specifications.*
FDA Validation Guideline
Life Cycle Approach

1987 – 2011: “…documented evidence…”
(Run 3 X’s in Manufacturing)

2011 – current: “…collection and evaluation…”
(Development – Scale-up – Routine Manufacturing)
FDA Validation Guideline

Life Cycle Approach

Collection and evaluation of data, from the process design through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.
FDA Validation Guideline

Objectives

Stage 1: Commercial manufacturing process is defined.

Stage 2: Capability to manufacture is evaluated.

Stage 3: Assurance that process is in control.
FDA Validation Guideline
“Life Cycle “ Validation

Stage 1: Development and Scale-up
  Product and Process
  Knowledge and Understanding

Stage 2: Integrate in Manufacturing
  Equipment Qualification
  Process Qualification

Stage 3: Continuous Monitoring
  Evaluate Process
  Assess Product
Stage 1: Development to Scale-up

The commercial manufacturing process is defined based on knowledge gained through development and scale-up activities.
FDA Validation Guideline
Development

- Process capability
  
  *Process knowledge, understanding process parameter relationships to quality attributes*

- Causes of variability
  
  *Sources*
  *Impact*
Established Process Parameters

CPP and PAR

Critical Process Parameters (CPP)
- Shelf (inlet) temperature
- Chamber pressure
- Time
Target Lyophilization Parameters

Chamber Pressure

Shelf Temperature
Established Process Parameters
CPP and PAR

Critical Process Parameters (CPP)
- Shelf (inlet) temperature
- Chamber pressure
- Time

Proven Acceptable Range (PAR)
- Acceptable parameters above and below ideal target conditions.
- Acceptable CQA and stability
Lyophilization Parameters PAR

-Shelf Temperature
-Chamber Pressure

TIME (Minutes)
FDA Validation Guideline

Scale-up
(Technology Transfer)

Stage 2: Qualification
Evaluate manufacturing operations and process design to establish capability for routine manufacturing.
FDA Validation Guideline
Technology Transfer

.gradient

Equipment Qualification

Installation Qualification
Operational Qualification
Performance Qualification (PQ)

Process Performance Qualification

Process Verification
Increased monitoring / sampling
FDA Validation Guideline
Continuous Process Verification

Stage 3: Routine Manufacturing
Operate within established PAR (boundaries)
Collect and analyze product and process data
Concurrent review and evaluation
State of control for process (reproducibility)
Consistent critical quality attributes
FDA Validation Guideline
Continuous Process Verification

Stage 3: Continued Process Verification
Ongoing assurance is gained during routine production that the process remains in a state of control.
FDA Validation Guideline
Continuous Process Verification

Stage 3: Continued Process Verification
Trending of process (CPP) and finished product quality (CQA) to monitor process variability and product consistency to verify commercial manufacturing is within a state of control.
FDA Validation Guideline
Continuous Process Verification

Stage 3: Continued Process Verification
“…measuring and evaluating process stability and process capability…”.
Stage 3: Continued Process Verification

“...guard against overreaction to individual events as well as against failure to detect unintended process variability.”
Stage 3: Continued Process Verification

“Homogeneity within a batch and consistency between batches are goals of process validation activities.”
Stage 3: Continued Process Verification

“Validation offers assurance that a process is reasonably protected against sources of variability that could affect production output, cause supply problems, and negatively affect public health.”
Stage 3: Continued Process Verification

“Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes.”
FDA Validation Guideline
Continuous Process Verification

Stage 3: Continued Process Verification

“Implementation of the recommendations in this guidance for legacy products and processes would likely begin with the activities described in Stage 3.”
FDA Validation Guideline

Continuous Process Verification

Stage 3: Continued Process Verification

“Manufacturers should use ongoing programs to collect and analyze product and process data to evaluate the state of control of the process.”
Stage 3: Routine Manufacturing

Adherence to the CGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability.
FDA Validation Guideline
Continuous Process Verification

Stage 3: Routine Manufacturing

“...detecting unplanned departures from the process as designed is essential to accomplish this goal.”
FDA Validation Guideline
Continuous Process Verification

Stage 3: Routine Manufacturing
The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products.
FDA Validation Guideline
Continuous Process Verification

Stage 3: Routine Manufacturing
The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.
“...Quality, Safety, and Efficacy are designed or built into the product”.
- Quantifiable results
- Mean of multiple samples
- Individual OOS results are a special case

Data as reported results
- Quantifiable results
- Mean has no meaning
Quality Concepts
Quality Control Principles

Measure
- Identify what is important (CQA).
- Develop methods of measurements.

Assess
- Establish suitability for intended use.
- Compare product to expectations.

Adjust
- Know what impacts product quality.
- Modify inputs or process for desired outcome.
Quality Concepts
Quality Control Principles

Shewhart
- Defined assignable-cause and chance-cause.
- Developed control charts for assessing process output (product) and manufacturing success.

Juran
- Popularized Pareto Principle (80/20 rule).
- Formalized Quality Management.

Deming
- Refined quality management principles.
- Developed “Plan–do–check–act”.
Control Charts
Process Behavior Charts

Materials → Process → Process Output (Product)

Evaluate Control ← Compare to Trend ← Assess Output
Assessing Process Output
  ◦ Encompasses material input, process control and product analysis
  ◦ Influenced by number of test samples
  ◦ Indiscriminate of multi-variant factors

Evaluating results in trend
  ◦ Verifies relative level of control
  ◦ Compares average result
  ◦ Discerns single event vs shift in mean
Control Charts

Process Behavior Charts

Reflects process variation
- Variation from common process sources
- Highlights process events out of control

Provides assessment of control
- Shows state of statistical control
- Identifies parameter beyond normal control
- Reveals drift in trend
Control Charts
Data input for analysis

Classical: Process output (product) data
- Testing a sufficient number of samples
- Samples representative of batch

Progressive: Process parameters
- Evaluation of process data (CPP)
- Significant: Variations that impact CQA
Control Charts
Types of Control Charts

**Shewhart**
- Trends data and sets limits based on 3 Standard Deviations.
- Comparison of single data point relative to trend.
- Further refinements to data point and trend assessment (Less than 3 Standard Deviations).

**COSUM**
- Cumulative sum of data points.
- More complicated assessment of data trend.

**EWMA**
- Exponentially weighted moving average of data points.
- Most complicated assessment of data trend.
Creating a Control Chart
- Collection of at least 9 sets of data.
- For multiple tests, calculate average of each set of results.
- Calculate the mean of all the test results.

Setting Alert and Action Levels
- Calculate the standard deviation of all the data.
- Calculate 2 and 3 standard deviations.
Shewhart Control Charts

Trend Analysis

Plot y-axis scale
- Based on specifications.
- Scale so that the centerline is near the center of the y axis.

Alert Level
- Two Standard Deviations from the mean.

Action Level
- Three Standard Deviations from the mean.
Control Charts

Shewhart Trend Rules

Recognizing Special Cause Variation

Shift Rules
- Focuses on individual data points near or exceeding the control limit (Action Level).

Trend Rules
- Evaluates the group of multiple data points relative to the centerline of the trended data.
Control Charts

Shewhart Trend Rules
Recognizing Special Cause Variation

Shift Rules
- A data point above or below a control limit (Action Level).
- A series of data points near upper or lower control limit (Action Level).
Control Charts
Shewhart Trend Rules
Recognizing Special Cause Variation

Trend Rules
- Multiple data points that are close to the centerline and are not as large of a difference from the centerline as the majority of the trended data.
- Data that exhibits a consistent trend in a direction towards or away from the Centerline.
Control Charts
Shewhart Trend Rules

Rule 1: Single point above Action Level (control limits).

Rule 2: Shift of 8 or more consecutive points above or below Centerline.

Rule 3: At least 6 consecutive points with a continually increasing or decreasing trend.
Control Charts
Shewhart Trend Rules

Rule 4: A series of 2 or 3 consecutive points near an Action Level (control limits).

Rule 5: At least 15 consecutive points trending near the Centerline.
Process Output Data

Product Quality Attributes

Assess Critical Quality Attributes (CQA)
Assay
Purity
Residual Moisture
Reconstitution
Appearance
Residual Moisture
Scaled to Specification

Mean % Residual Moisture

STD DEV = 0.116

Alarm Level: Mean + 2 STD DEV (0.232)

Action Level: Mean + 3 STD DEV (0.347)

Alarm Level (0.629)

Action Level (0.744)

Center Line Mean of All (0.397)

Alarm Level (0.165)

Action Level (0.05)

Batch Mean

Specification
Residual Moisture
Scaled to Trend

Mean % Residual Moisture

- Action Level (0.744)
- Alarm Level (0.629)
- Center Line (Mean of All: 0.397)

Batch Mean

Batch

Mean % Residual Moisture

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
0.7 0.6 0.5 0.4 0.3 0.2 0.1 0 1 2 3 4 5 6 7 8 9 10
Reconstitution Time
Scaled to Specifications

Reconstitution Time (Seconds)

STD DEV = 0.67

2 STD DEV = 1.34

3 STD DEV = 2

Specification

Center Line
Mean of All (5.2)
Reconstitution Time
Scaled to Trend

Reconstitution Time (Seconds)

STD DEV = 0.67

2 STD DEV = 1.34

3 STD DEV = 2

Action Level (7.2)

Alert Level (6.54)

Center Line
Mean of All (5.2)
Product Appearance
Scaled to Alert Level

Physical Appearance Rejects (%)

- STD DEV = 0.000622
- 2 STD DEV = 0.0012
- 3 STD DEV = 0.0019

Common Action Level

Center Line
Mean of All (0.00025)
**Product Appearance**

*Scaled to Trend*

Physical Appearance Rejects (%)

- STD DEV = 0.000622
- 2 STD DEV = 0.00124
- 3 STD DEV = 0.00186

- Action Level (0.00211)
- Alert Level (0.00149)
- Mean of All (0.00025)
FDA Validation Guideline
Continuous Process Verification

Stage 3: Routine Manufacturing
The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products.
Control Charts
Factors that influence CQA

❖ CPP variation
❖ Product/Process input materials
Control Charts
Factors that influence CQA

CPP variation
- Shelf Temperature
- Chamber Pressure
- Time
Control Charts
CPP Variation

- Parameter variation (Engineering Units)
- Deviation from target (Engineering Units)
- Greatest variation throughout process (Statistical Value)
Parameter variation (Engineering Units)

- Each step
- Expressed as temperature and pressure
- Complicated charting: each step
- Difficult for analysis
- Overly sensitive to variation
Deviation from target (Engineering Units)

- Each step
- Expressed as deviation from target
- Complicated charting: each step
- Difficult for analysis
- Extremely sensitive to variation

Control Charts
CPP Variation
Control Charts
CPP Variation

Greatest variation throughout process
- Conversion to statistical value: z-score or standard deviation
- Expressed as deviation from target
- Greatest variation throughout process
- Easier to trend
- Less sensitive to variation in each parameter
Product / Process input materials
  ◦ Formulation components
  ◦ Packaging components
Control Charts
Process input for analysis

Formulation Components
- Related substances
- Upstream substance carry-over
- Residual solvents
Control Charts

Process input for analysis

Packaging Components

- “Finished” (tooled) opening
- Bottom concavity (push-up)
- Bottom corner radius
- Stippling
Summary

Continuous Process Verification
Operate within CPP PAR (process boundaries)
Collect and analyze product and process data
Concurrent review and evaluation
Consistent critical quality attributes (CQA)
State of control for process
Stage 3: Routine Monitoring

Trending should include the process and quality of incoming materials, components, in-process material, and finished product attributes.
Summary
Factors that influence CQA

 CPP variation
  ◦ Shelf Temperature
  ◦ Chamber Pressure
  ◦ Time

 Product / Process input materials
  ◦ Formulation components
  ◦ Packaging components
**Summary**

- Assure trended variables are able to discern level of control.
- Include inputs to process as well as CPP.
- Utilize appropriate approach in trending.
Devise a plan for action when exceeding Action Levels.

Avoid overreacting to individual results or shifts in a trend.

Exceeding an Action Level does not mean failing to meet specifications.
Control (Shewhart) Charts

Process Behavior Charts

- Materials → Process
- Process → Output
- Output (Product) → Assess
- Evaluate Control → Compare to Trend
- Compare to Trend → Refine materials or adjust process
- Refine materials or adjust process → Control
Process Validation: Stage 3

Happy to answer questions!

Further contact:

Edward Trappler
President
etrappler@lyo-t.com
(215) 396-8373