Process Validation for Lyophilized Drug Products: Developing a Program for Continued Process Verification

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Agenda

- Process Validation / Validation Life Cycle
- Lyophilization / CPPs

Methods for continued process monitoring
  - Individual Process Steps
  - Summarizing Data Across an Entire Batch
  - Multiple Batches, Multiple Steps

Summary
Process Validation

“...collection and evaluation of data, from the process design stage through commercial production, which established scientific evidence that a process is capable of consistently delivering quality product.”

Process Validation

- Understand the sources of variation.
- Detect the presence and degree of variation.
- Understand the impact of variation on the process and ultimately on product attributes.
- Control the variation in a manner commensurate with the risk it represents to the process and product.
Validation Life Cycle

- **Stage 1  Process Design**
  - Commercial manufacturing process is defined.

- **Stage 2  Process Qualification**
  - Capability to manufacture is confirmed.

- **Stage 3  Continued Process Verification**
  - Provide assurance the process is within a state of control.
Lyophilization / CPPs

- Critical Process Parameters for Lyophilization include:
  - Shelf (inlet) temperature
  - Chamber pressure (vacuum)
  - Time

- Processes for commercial products are described in these terms with the intent of consistent performance.
Case Study

- Nine lots, same product, same scale except for one lot manufactured at half-scale
Real Cycle Data
Focusing on One CPP

Target Lyophilization Cycle Temperature

Temperature (°C)

Elapsed Time (Minutes)

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Show variation for a single process step by plotting min, max and average for each lot during that step.

Allows comparison of ranges and averages batch to batch.

Data evaluation is for a single process step.
Typically, cycle data are graphed using temperature (CPP) data, but by plotting the data as variation from setpoint rather than temperature, may allow for a comparison of control.

- By keeping the data segregated by process step, there is an opportunity to assess machine function and look for consistency of operation at common setpoints, batch to batch (see last slide).
- Can graph data from multiple process steps and look at variation across the entire process for a batch (see next slide).
Variation Across Entire Process

Initial Freezing | Annealing | Final Freezing | Primary Drying | Secondary Drying

Temperature Variation (°C)
Variation Across Entire Process

- This approach assesses the relative control capability under the different processing conditions for each step across one batch, or across multiple batches.
- Differences in control can easily be seen.
- Operational or expected ranges for each segment could be established by pooling the data within each segment.
- This approach provides a comparison of control across the entire process and among multiple batches.
Variation Across Entire Process

- Previous example looked at min, max, and average values for each step.
- There can be value in looking at the same data for all batches, following the timeline for the process.
- Variation at specific process points becomes readily apparent as does atypical behavior for a given batch.
Variation Across Entire Batch

- Variation in Temperature (°C)
- Elapsed Time (Minutes)

- Initial Freezing
- Annealing
- Final Freezing
- Primary Drying
- Secondary Drying

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This method of data analysis is useful for comparing the profiles of multiple batches throughout the entire process.

However, there is a limit to the number of batches that can easily fit on a single plot!
All Steps, All Batches

- Pooling data from all batches and all process steps (setpoints) in the cycle, one graph can be constructed to depict variation.

- Individual differences can be difficult to detect, as can any (significant) deviations for a single batch, since the y-axis must be scaled to accommodate the entire range of setpoints (see next slide).
All Steps, All Batches

- Standard deviation calculations, along with averages, are commonly used to describe a data set.
- As in the previous example, this technique can be used to assess all batches and all process steps in one plot.
- Because the standard deviation is relative to a population distribution for a specific data set, the control capability can be difficult to accurately assess using this method.
All Steps, All Batches

Minimum and Maximum Standard Deviations from Average for Lyophilization Cycle (N=9)

- Initial Freezing
- Annealing
- Final Freezing
- Primary
- Secondary

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Using the min and max variation compared to the running average provides an effective means of evaluating variation in CPPs.

Ongoing trending of the range for the min and max reflects the variability in the control and can magnify events of individual excursions.
All Steps, All Batches

Variation from Setpoint Temperature (ºC)

Max  Min  Average
Methods can be used to evaluate individual cycle segments or the entire lyophilization process.

Evaluating lyophilization CPPs can focus on individual batches or batch to batch trending.

The methods illustrated in this presentation focused on shelf inlet temperature, but can be applied to other CPPs.

Selection of the most appropriate method should be based on need and value to the manufacturing operation.
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Thank You!!

Happy to field questions!

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