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

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LYOPHILIZATION TECHNOLOGY, INC.
Integrating Science and Technology

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."

- (*FDA Guidance for Industry, Process Validation: General Principles and Practices*, 2011)

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

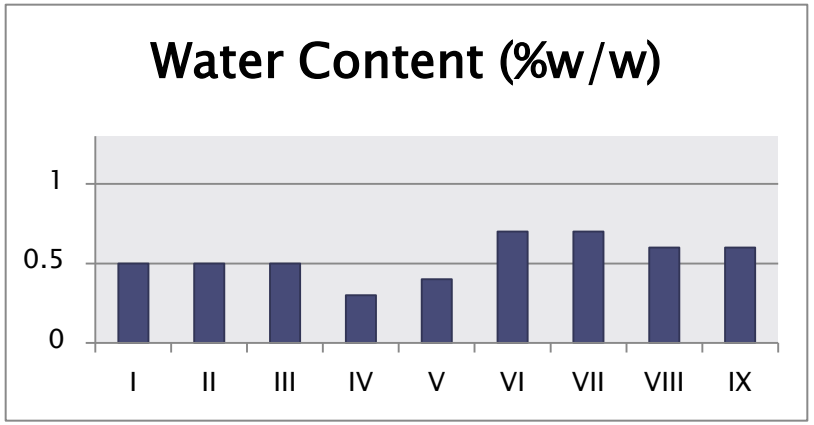
- **Stage 1 Process Design**
  - Commercial manufacturing process is defined.
- **Stage 2 Process Qualification**
  - Capability to manufacture is confirmed.
- **Stage 3 Continued Process Verification**
  - Provide assurance the process is within a state of control.

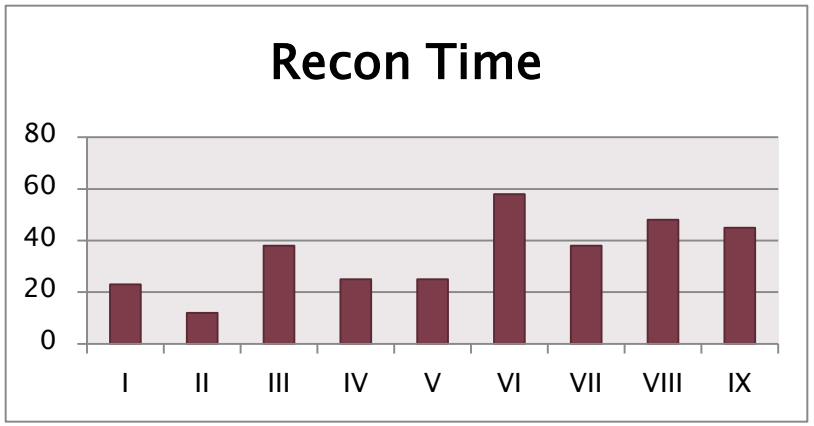
Lyophilization / CPPs

- 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.

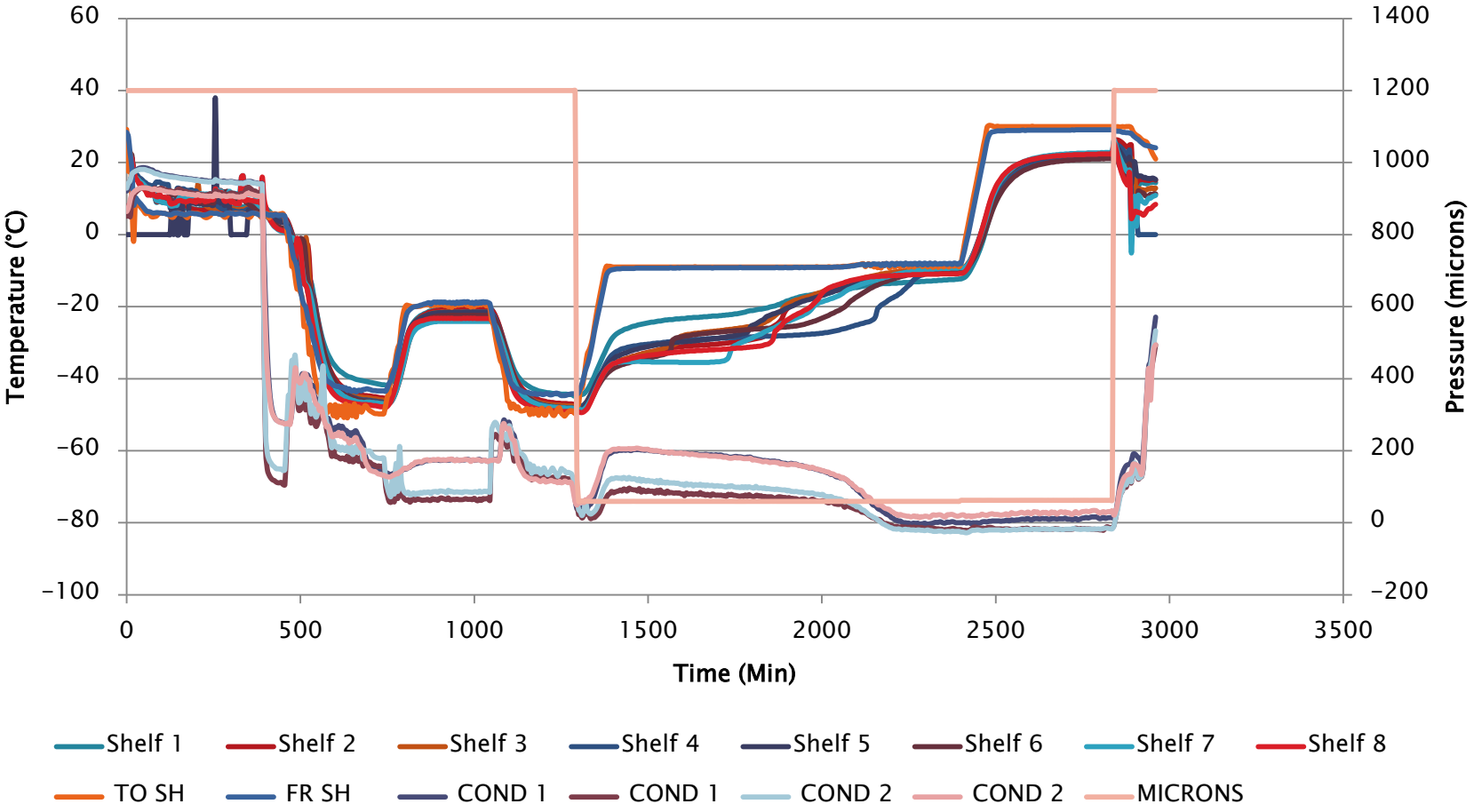
Case Study

- Nine lots, same product, same scale except for one lot manufactured at half-scale

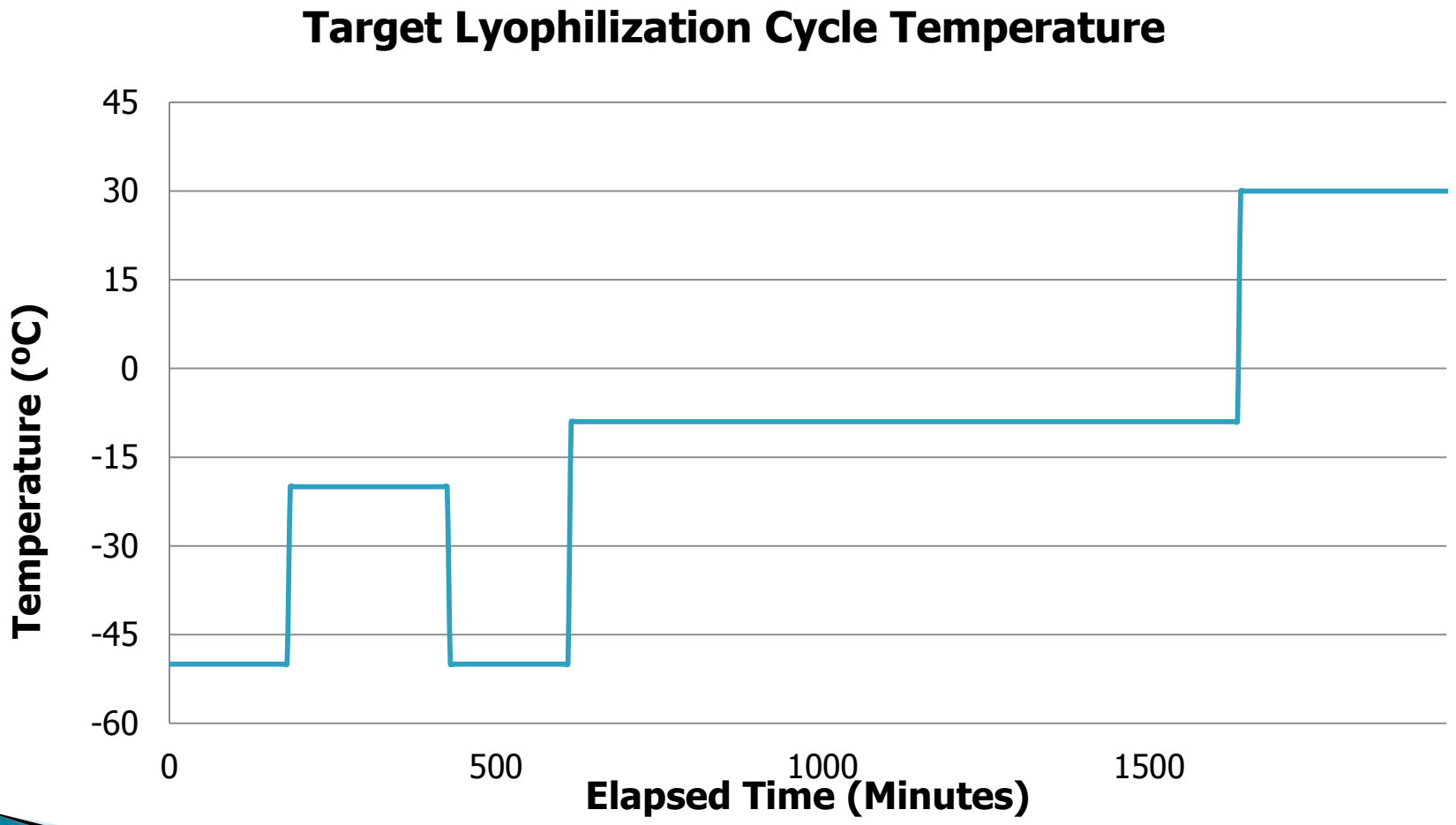




Real Cycle Data

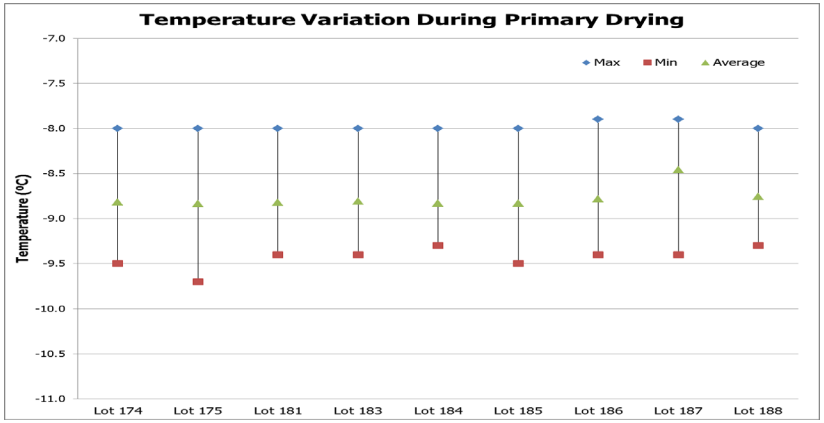


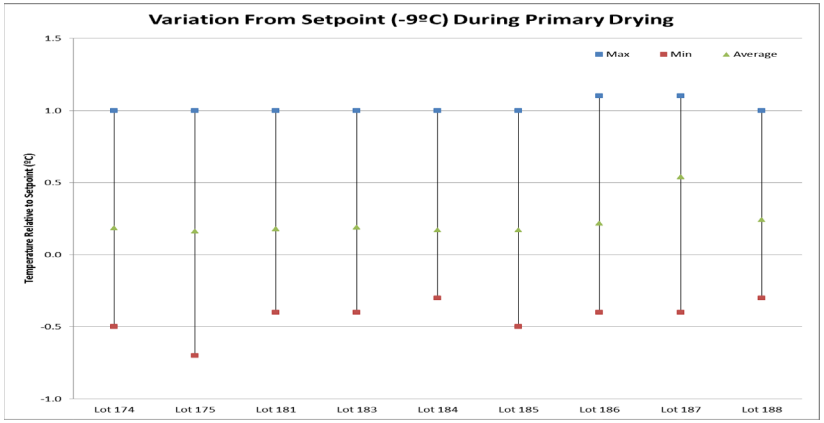
Focusing on One CPP



Variation from Setpoint

- 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.

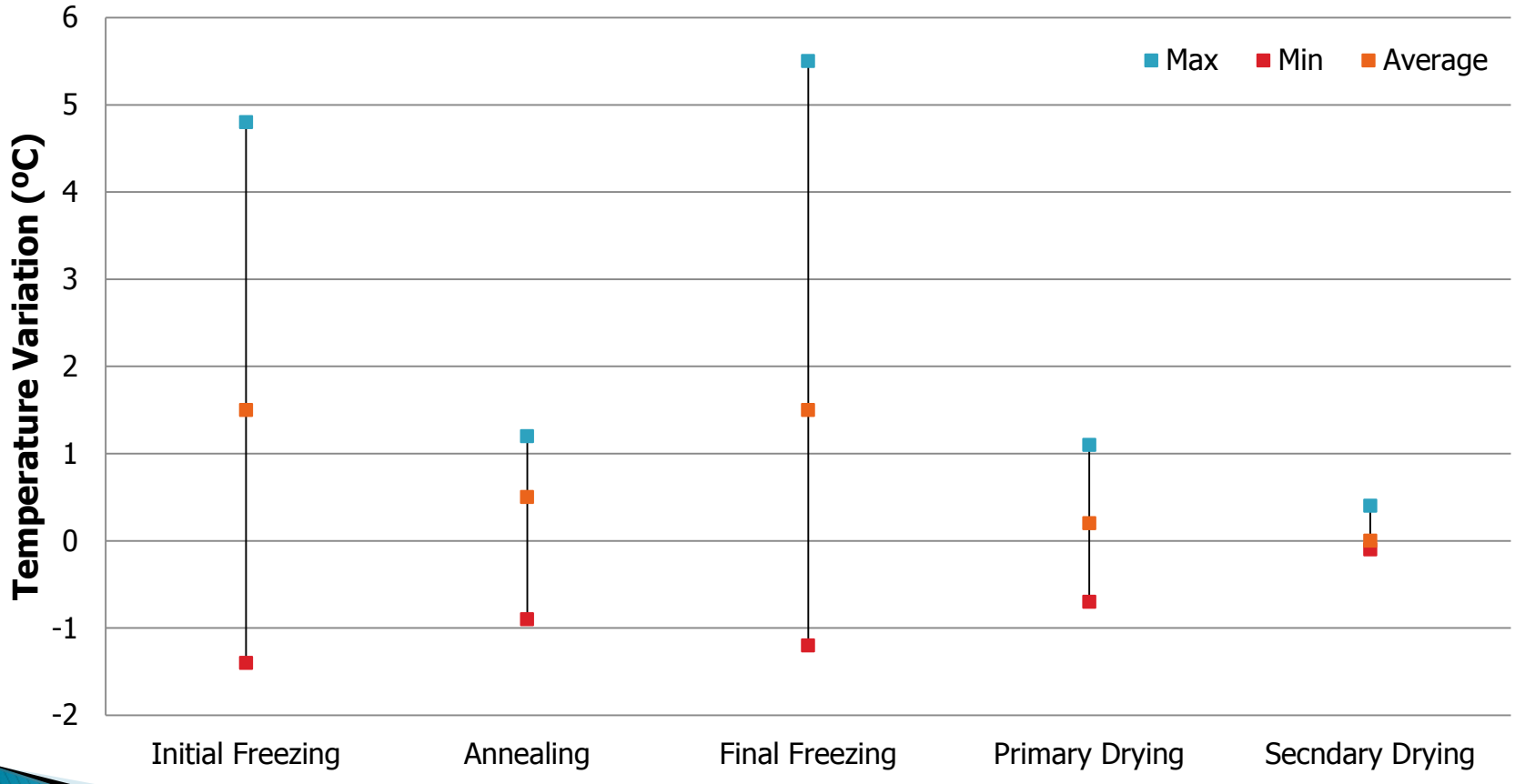




Variation from Setpoint

- 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



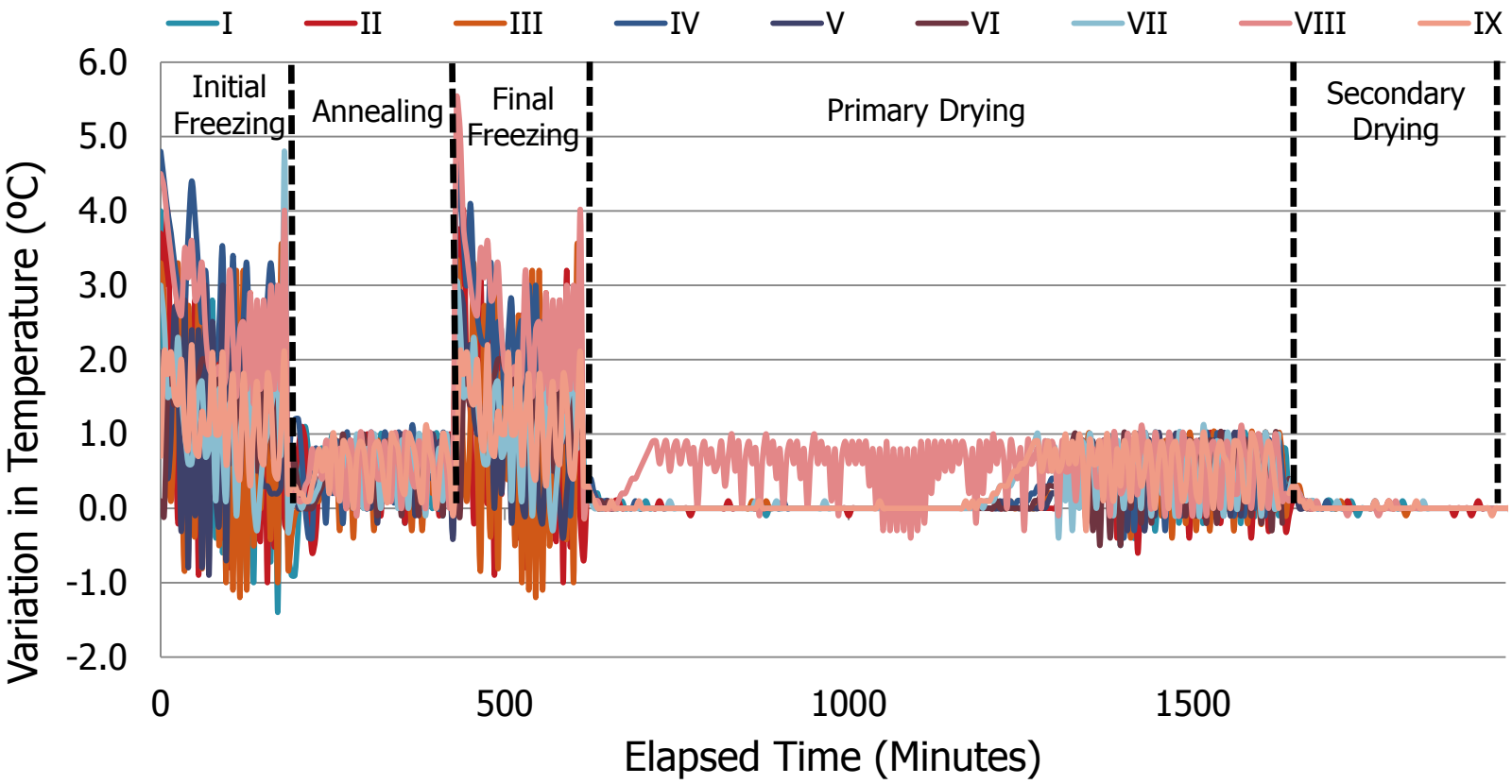
Variation Across Entire Process

- 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 Across Entire Batch

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

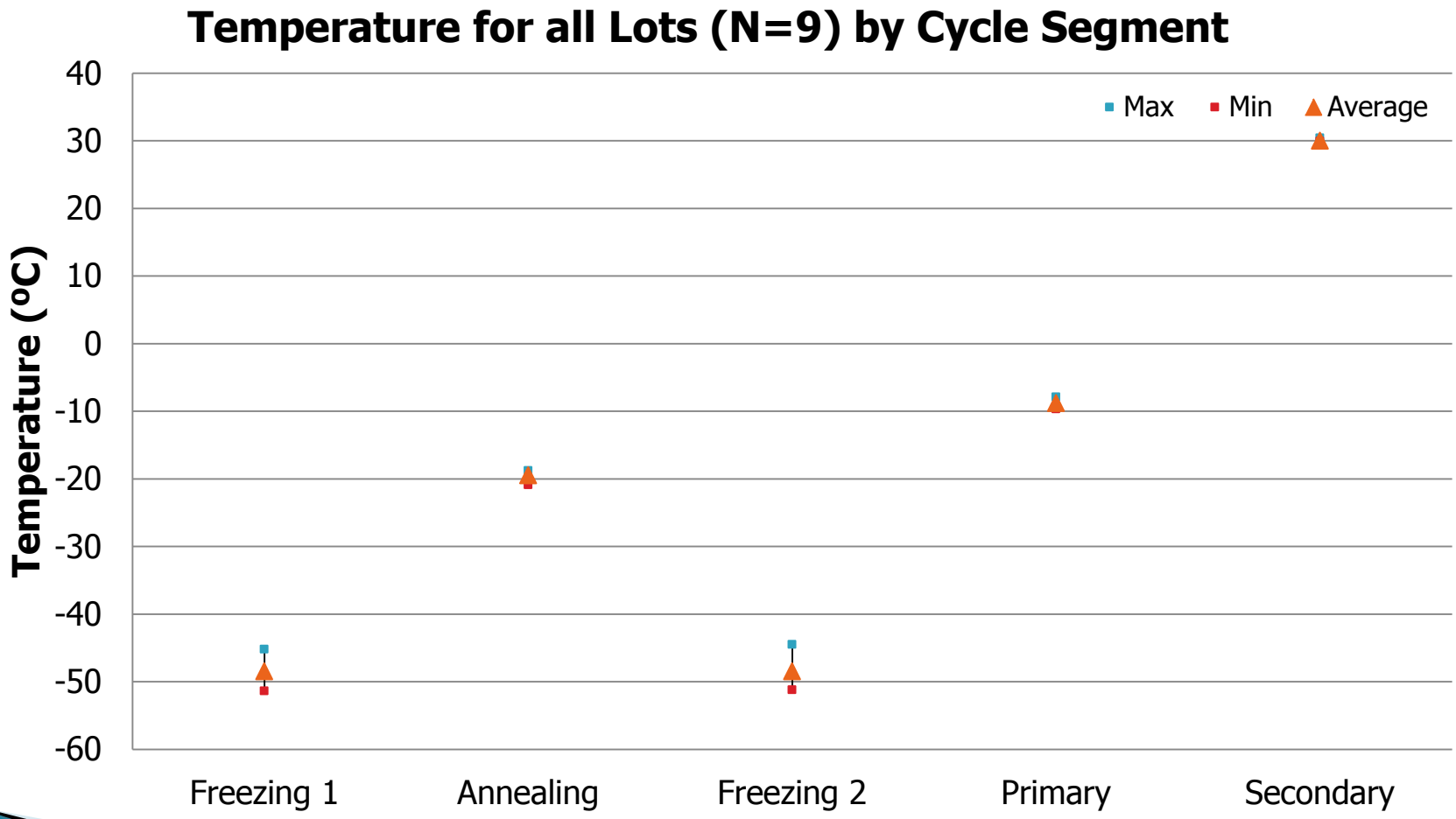
- However, there is a limit to the number of batches that can easily fit on a single plot!

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).

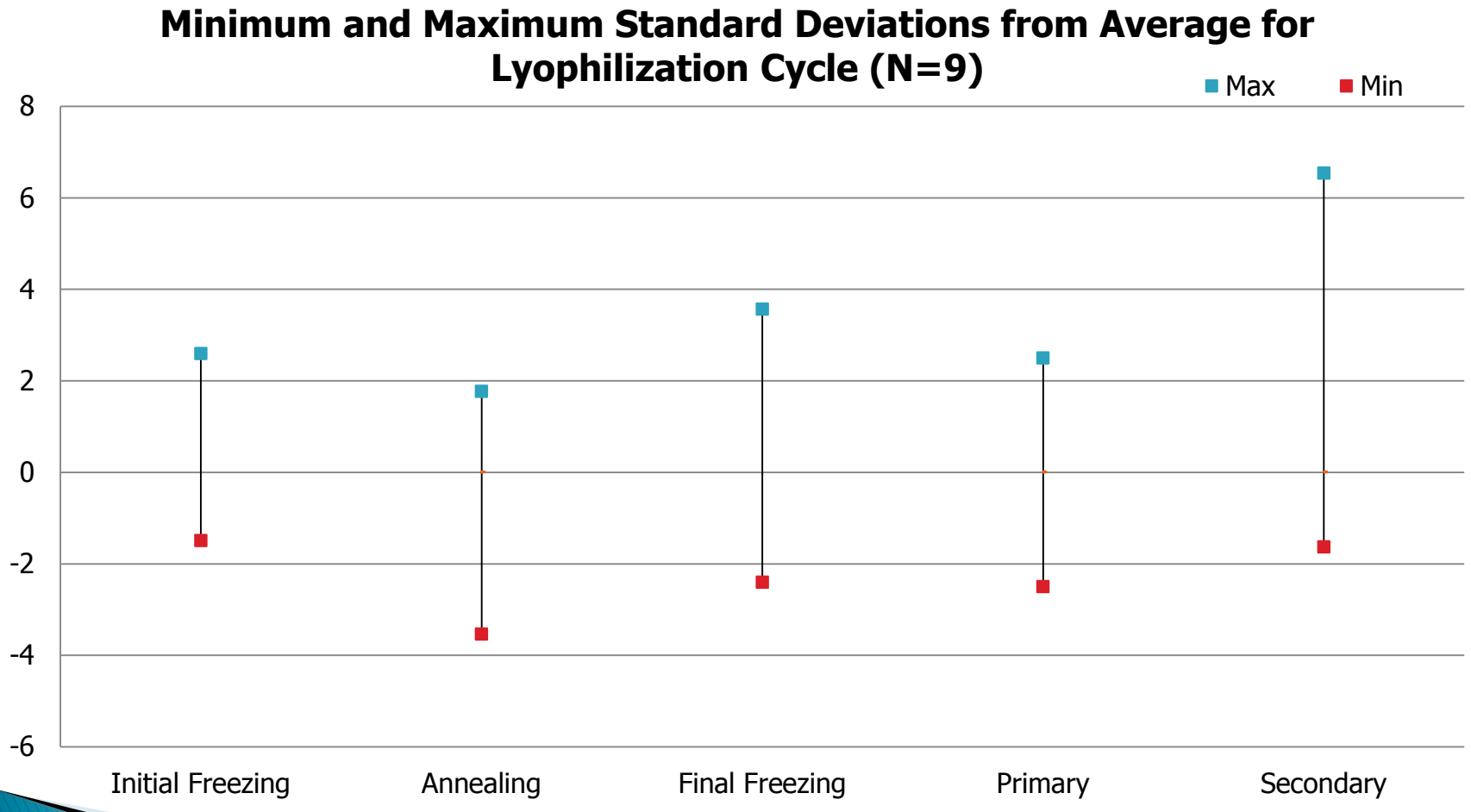
All Steps, All Batches



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.

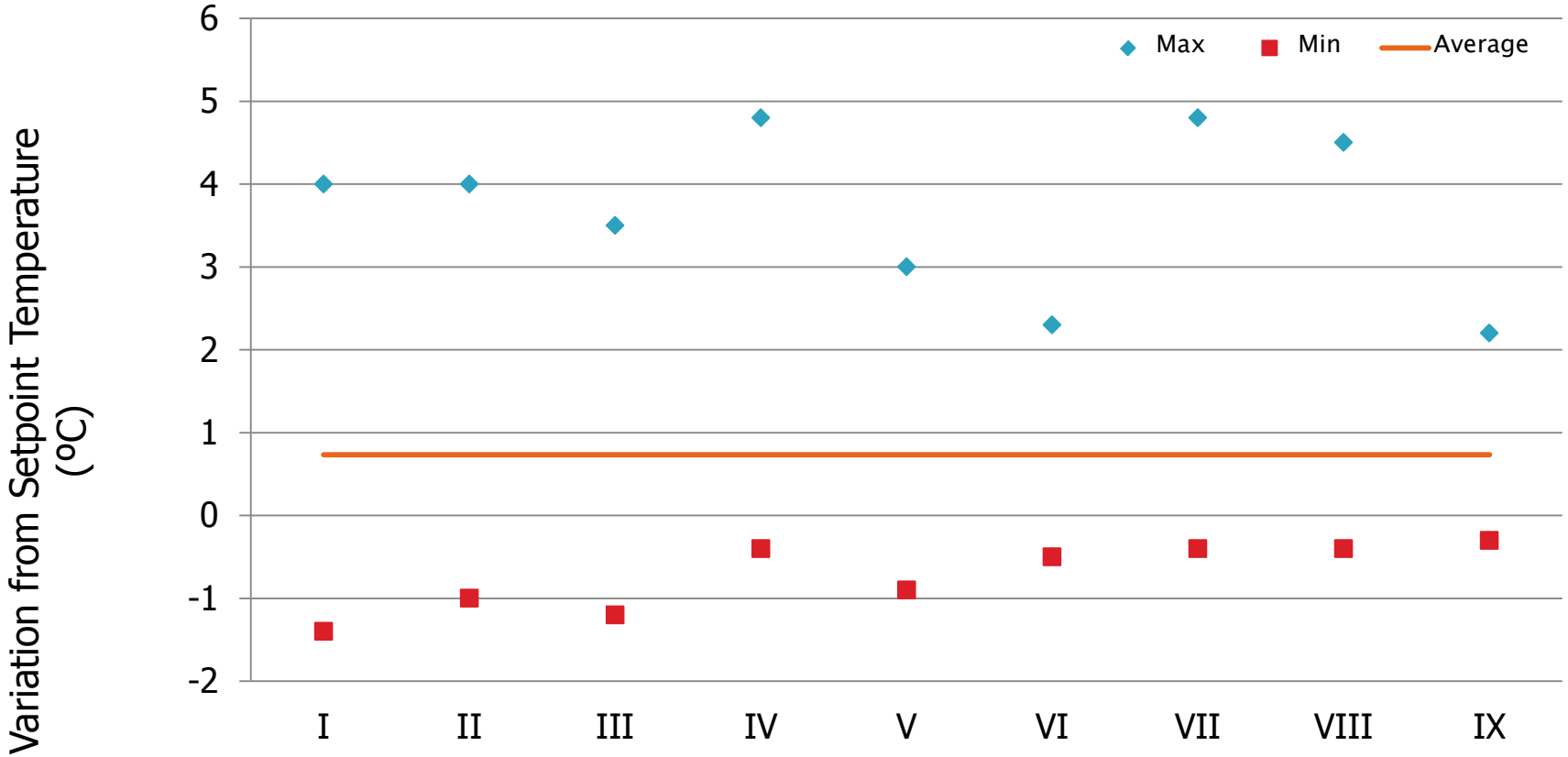
All Steps, All Batches



All Steps, All Batches

- 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



Summary

- 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.

Acknowledgements

- Edward Trappler
- Amit Sitapara

Thank You!!

Happy to field questions!

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