

# Current Regulatory Considerations on Pharmaceutical Lyophilization

Kumar Janoria, Ph.D.

FDA/CDER/OPQ

Office of Process & Facilities/Division of Process Assessment III

# Quiz

What is a Primary Drying End Point in a lyophilization cycle?

Options:

1. Point at which all of the free ice has been removed from all the vials and there are no concerns of collapse or melt back when the temperature is ramped up for secondary drying (desorption).
2. The reason our process takes so long and costs so much.
3. When a toothpick comes out clean after inserting into the center of the cake.
4. There is no such thing called primary or secondary drying. Temperatures can be continuously ramped up from freezing all the way to completion of lyophilization cycle.

# Information Request

Deficiency

Supplements

# Disclaimer

- **This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies**
- Word 'should' only means suggestion or recommendation but is not required
- Opinions are based on small molecules review perspective

# OPF's Lyo Committee of Interest

- Lyophilization is considered high-impact manufacturing topic and therefore there is a need to develop common practices to ensure that appropriate and consistent evaluation will occur during manufacturing process assessment.
- **F**orum to gather information on freeze drying technology and manufacturing, establish applicable quality review standards, and **D**isseminate these findings to enhance submission quality and enable consistent review **prA**ctices.

# Expectations from Applicants

Demonstrate understanding of:

- Formulation
- Product
- Equipment
- Development of a lyo cycle specific to product
- Manufacturing process to achieve consistent batch to batch product

# Quality by Design (ICH Q8)

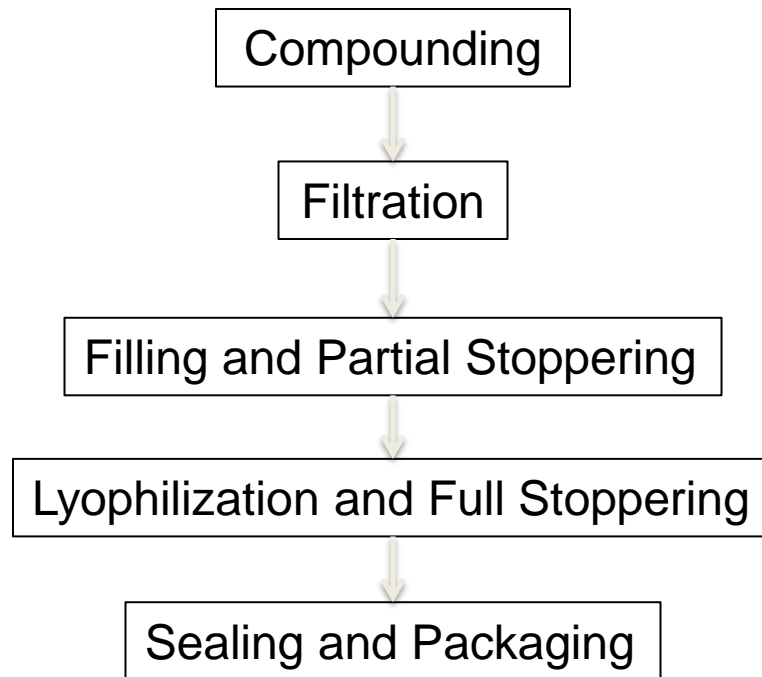
- Quality Target Product Profile
- Critical Quality Attributes
- Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAs Critical Process Parameters
- Design Space
- Control Strategy
- Product Lifecycle Management and Continual Improvement

# Regulatory Considerations

- Hold time and Equipment Compatibility
- Fill Volume/Fill Volume Tolerances
- Product Specific Characterization/Development Studies
- Establishing the Critical Process Parameters
- Establishing the end points for Primary and Secondary Drying
- Sampling Plan
- Critical Quality Attributes
- Scale-up
- Post Approval Lifecycle Perspective



# Manufacturing Flow Chart



# Hold time and

## Equipment Compatibility

- Product Stability after compounding (Bulk Hold)
  - Time
  - Temperature
  - Lighting
  - Inert Gas
- Compatibility with equipment train
  - Compounding Tank
  - Tubings
  - Pumps (Formulation contacting surfaces)
  - Filters

# Fill Volume

- Does USP <1151> Pharmaceutical Dosage Forms apply to lyophilized drug products?
- Example:
  - 50mg/vial labeled drug upon reconstitution with 5mL diluent results in 10mg/mL.
  - For a bulk concentration of 10mg/mL with recommended overfill per USP <1151> will result in 53mg/vial lyophilized product.
  - What is the concentration achieved upon reconstituting with 5mL vs. 5.3 ml?- Accurate description in PI?
  - Is this 6% overage or just acceptable overfill?

# Fill Volume Tolerances

Parameters	Reference Product [AMAZING®, 100 mg/vial]	Incredible HCl for Injection, 100 mg /vial
<i>Concentration of bulk solution</i>	25 mg/mL	50 mg/mL
<i>Fill Volume</i>	Filling range: 3.90 – 4.10 mL target: 4.0 mL	1.90 – 2.10 mL target: 2.0 mL
<i>Calculated Amount/vial</i>	100mg± 2.5mg	100 mg ± 5 mg

- What is bulk solution in-process assay specification? Can worst case combination of fill tolerance and in-process assay result out of specification at release?

# Product Specific Characterization

- Studies: Freeze Drying Microscopy and Differential Scanning Calorimetry
- Amorphous Vs. Crystalline Vs. Metastable
- Annealing Vs. Non- Annealing
- Critical Temperatures: Glass Transition ( $T_g'$ ), Eutectic ( $T_{eu}$ ), Collapse ( $T_c$ )
- Study Design (Ramp rates, Target Temperatures)
- Extrapolation of Information collected

# Establishing the Critical Process Parameters

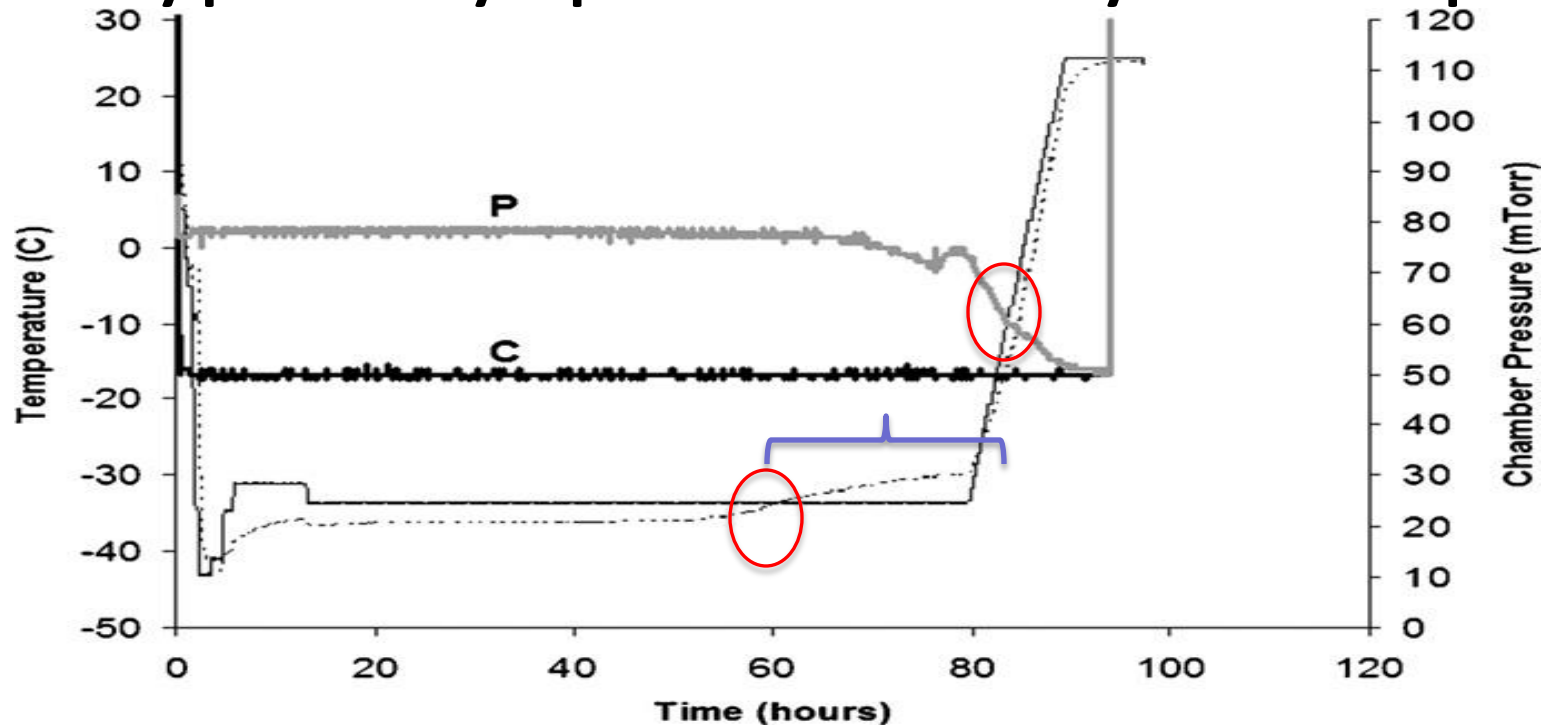
- Correlation of shelf temperature and chamber pressure and corresponding product temperature.
- Effect of critical process parameters on the powder properties.

Critical Process Parameters	Powder Properties
<ul style="list-style-type: none"> <li>❖ loading</li> <li>❖ cooling rate</li> <li>❖ primary and secondary drying conditions               <ul style="list-style-type: none"> <li>• temperatures</li> <li>• durations</li> <li>• pressure</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>❖ structure</li> <li>❖ cake appearance</li> <li>❖ water content</li> <li>❖ Assay</li> <li>❖ impurities</li> <li>❖ reconstitution time</li> </ul>

# Establishing the End Points for Primary and Secondary Drying

- Thermocouples
- Pirani Gauge vs. Capacitance Manometer
- Dew Point
- TDLAS
- Pressure rise test
- Sampling plan (moisture content)

# Typical Lyophilization Cycle Graph



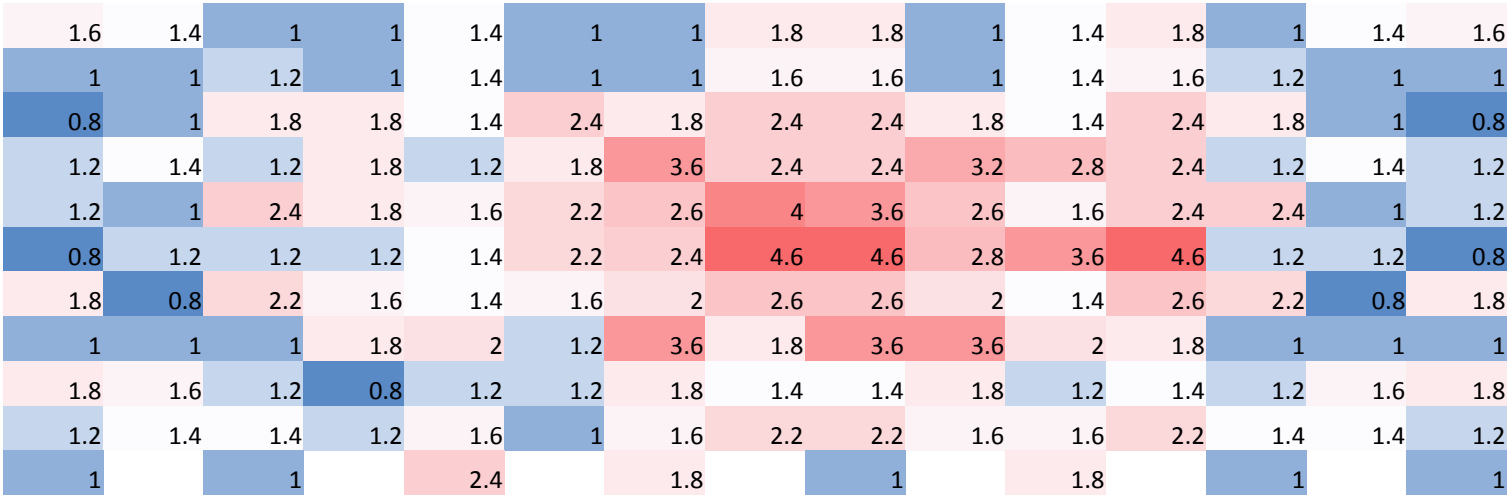
A typical graph shows the shelf temperature (—), average product temperature as measured by the thermocouples (...), capacitance manometer (C) and Pirani gauge (P) over the course of the run.

Reference: Quality by design: Impact of formulation variables and their interactions on quality attributes of a lyophilized monoclonal antibody. *International Journal of Pharmaceutics* 438 (2012) 167– 175



# Sampling plan

- To adequately capture the variation or uniformity
- Edge Effect
- Process development vs. Routine testing



Example of Edge effect: Variation in moisture content across the shelf due to edge effect.

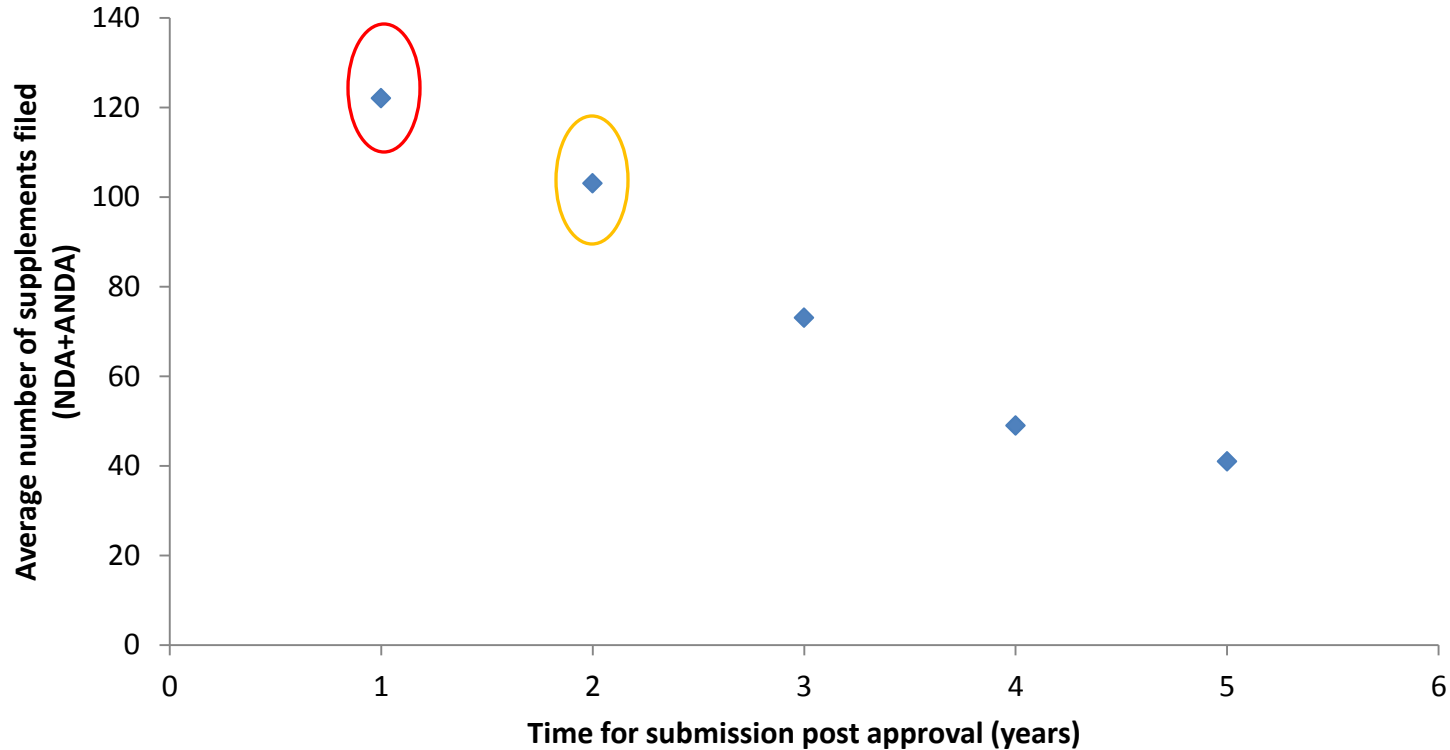
# Critical Quality Attributes

- Residual Moisture Content (using appropriate Moisture testing method)
- Appearance of Lyophilized Cake
- Assay (Loss due to sublimation)
- Reconstitution Time (Method consistency)

# Scale-up

- Scale-up factor
- Same dryer vs. larger dryer
- Partial load vs. full load
- Equipment capabilities (Ramp rate, lowest chamber pressure, lowest shelf temperature)
- Sampling Plan

# Post Approval Lifecycle Perspective

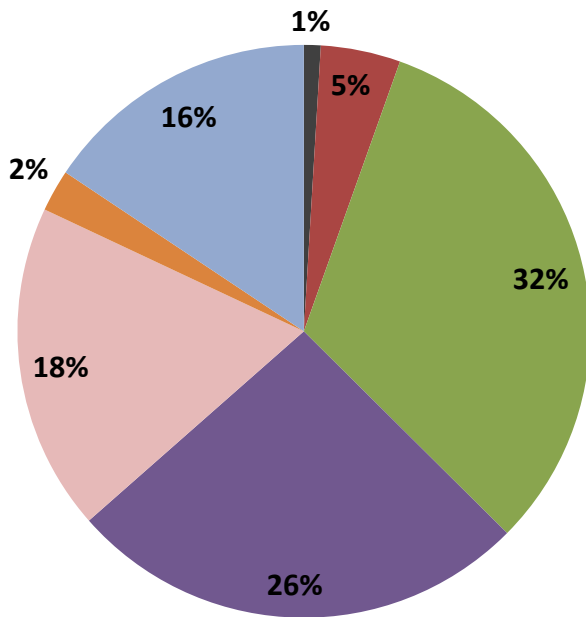


## Post approval of ANDA/NDA: Number of Supplements Vs. Filing Time

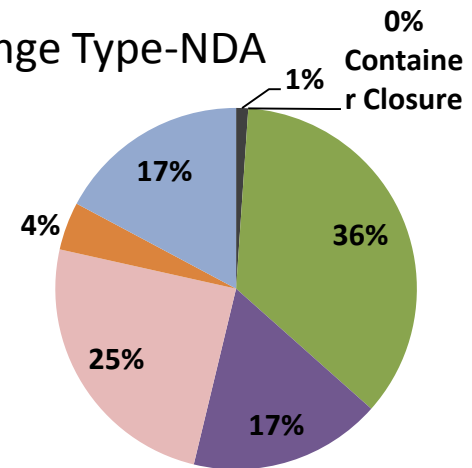
The information is based on total 125 applications with 103 ANDAs and 22 NDAs. There were total of 453 supplements filed of which 360 are ANDA supplements and 93 are NDA supplements. A descending trend of filed supplements was noted with the number of years post approval of the ANDA or the NDA.

# Post Approval Lifecycle Perspective

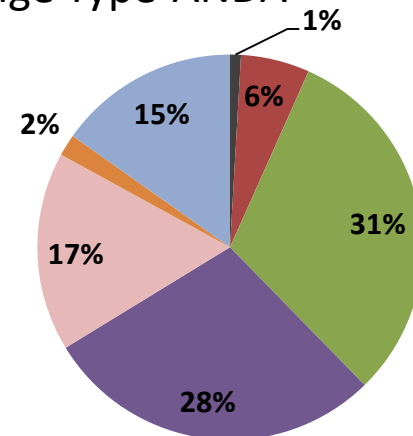
Change Type All



Change Type-NDA



Change Type-ANDA



- Component Composition
- Container Closure
- Labeling
- Manufacturing Process
- Manufacturing Site
- Miscellaneous
- Specifications

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# Commonly Used Terms

- Lyophilization
- Freeze Drying
- Lyophilizer
- Choked flow
- Freeze Drying Microscope
- DSC
- $T_g'$ / $T_c$ / $T_{eu}$ / $T_g$
- Freezing
- Ice Nucleation
- Annealing
- Vacuum
- Sublimation
- Condensation
- Condenser (Temperature)
- Ramp rate and Hold times
- Shelf vs. Product Temperature
- Thermocouple
- Vapor pressure
- Pressure Gauge
- Primary Drying
- Cake Resistance
- Secondary Drying
- Collapse
- Melt back
- Pressure rise Test
- Drying End Points
- Lyo recipe
- Cake/powder Appearance

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*Thank you!*

Questions, comments, concerns:

[CDER-OPQ-Inquiries@fda.hhs.gov](mailto:CDER-OPQ-Inquiries@fda.hhs.gov)