Current Regulatory Considerations on Pharmaceutical Lyophilization

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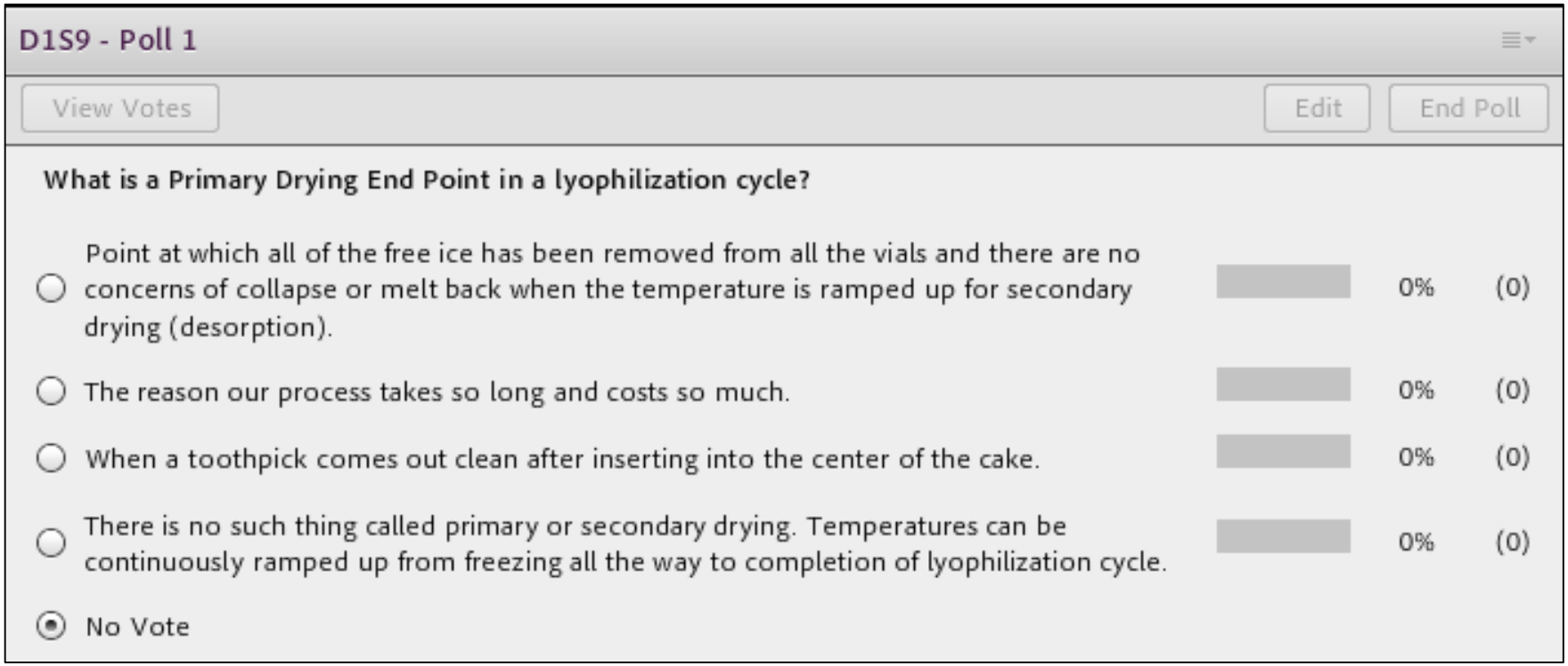
Poll Question



Expectations

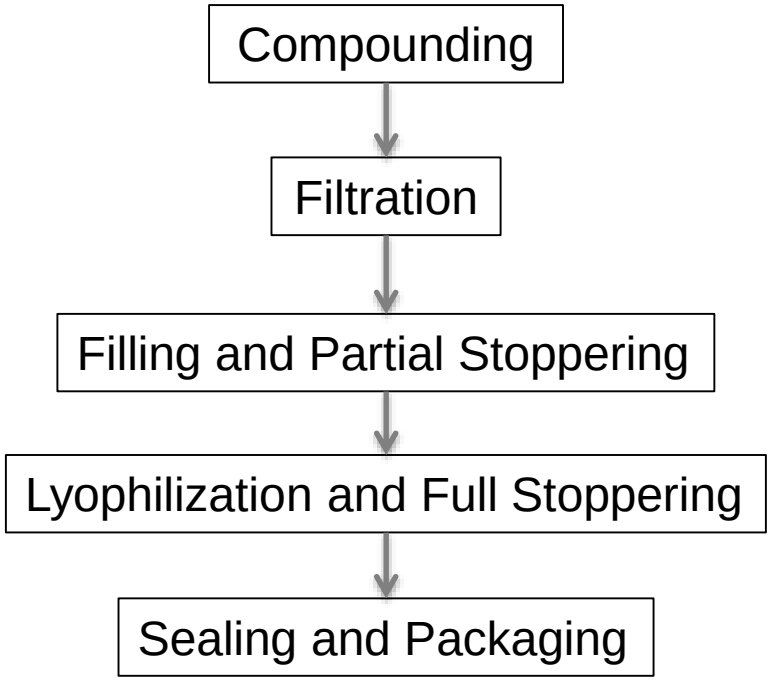
Fully Understand

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

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
Concentration of bulk solution	25 mg/mL	50 mg/mL
Fill Volume	Filling range: 3.90 – 4.10 mL target: 4.0 mL	1.90 – 2.10 mL target: 2.0 mL
Calculated Amount/vial	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 (Tg'), Eutectic (Teu), Collapse (Tc)
- Study Design (Ramp rates, Target Temperatures)
- Extrapolation of Information collected

Establishing the Critical Process Parameters

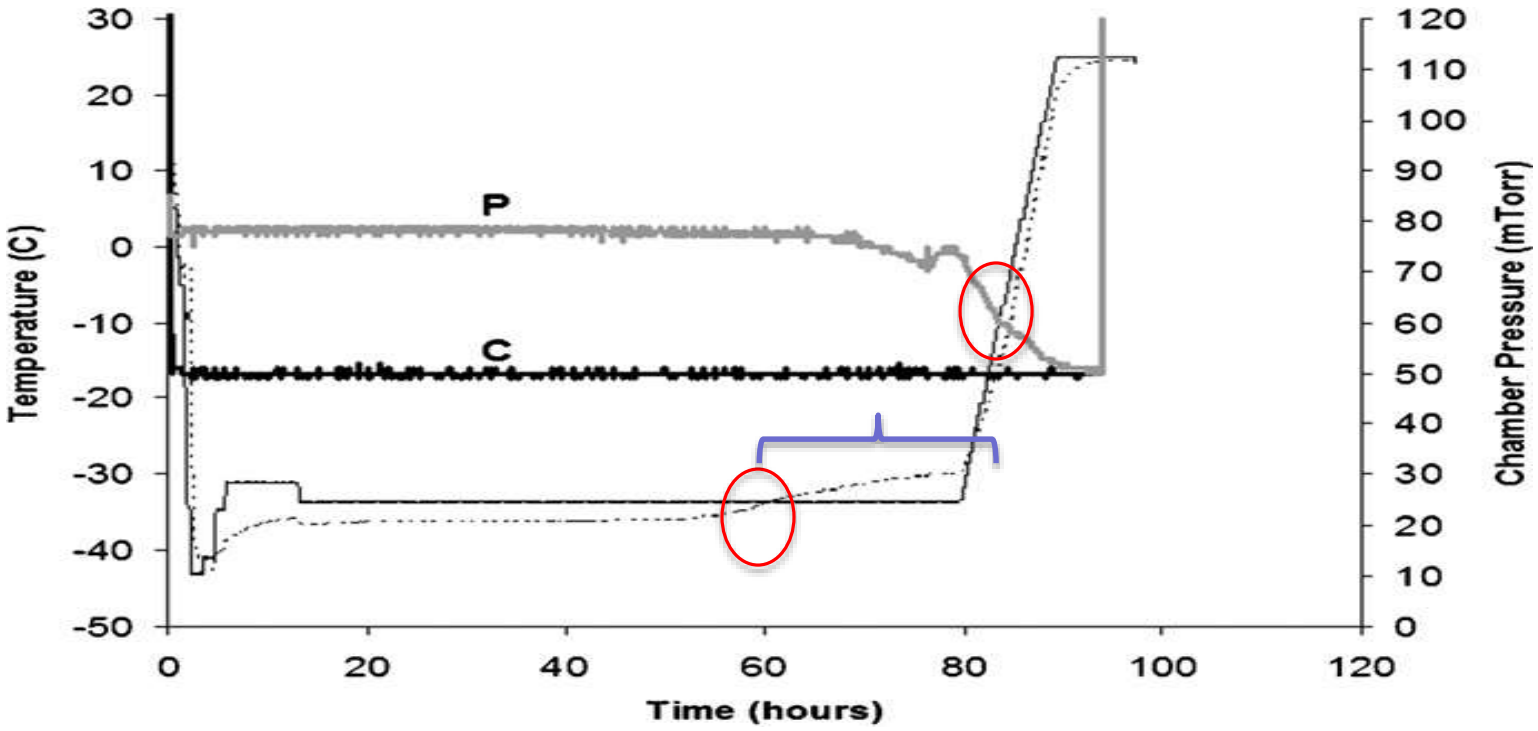
- Correlation of shelf temperature and chamber pressure and corresponding product temperature.
- Effect of critical process parameters on the powder properties.

Critical Process Parameters	Powder Properties
❖ loading ❖ cooling rate ❖ primary and secondary drying conditions • temperatures • durations • pressure	❖ structure ❖ cake appearance ❖ water content ❖ Assay ❖ impurities ❖ reconstitution time

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

1.6	1.4	1	1	1.4	1	1	1.8	1.8	1	1.4	1.8	1	1.4	1.6
1	1	1.2	1	1.4	1	1	1.6	1.6	1	1.4	1.6	1.2	1	1
0.8	1	1.8	1.8	1.4	2.4	1.8	2.4	2.4	1.8	1.4	2.4	1.8	1	0.8
1.2	1.4	1.2	1.8	1.2	1.8	3.6	2.4	2.4	3.2	2.8	2.4	1.2	1.4	1.2
1.2	1	2.4	1.8	1.6	2.2	2.6	4	3.6	2.6	1.6	2.4	2.4	1	1.2
0.8	1.2	1.2	1.2	1.4	2.2	2.4	4.6	4.6	2.8	3.6	4.6	1.2	1.2	0.8
1.8	0.8	2.2	1.6	1.4	1.6	2	2.6	2.6	2	1.4	2.6	2.2	0.8	1.8
1	1	1	1.8	2	1.2	3.6	1.8	3.6	3.6	2	1.8	1	1	1
1.8	1.6	1.2	0.8	1.2	1.2	1.8	1.4	1.4	1.8	1.2	1.4	1.2	1.6	1.8
1.2	1.4	1.4	1.2	1.6	1	1.6	2.2	2.2	1.6	1.6	2.2	1.4	1.4	1.2
1		1		2.4		1.8		1		1.8		1		1

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

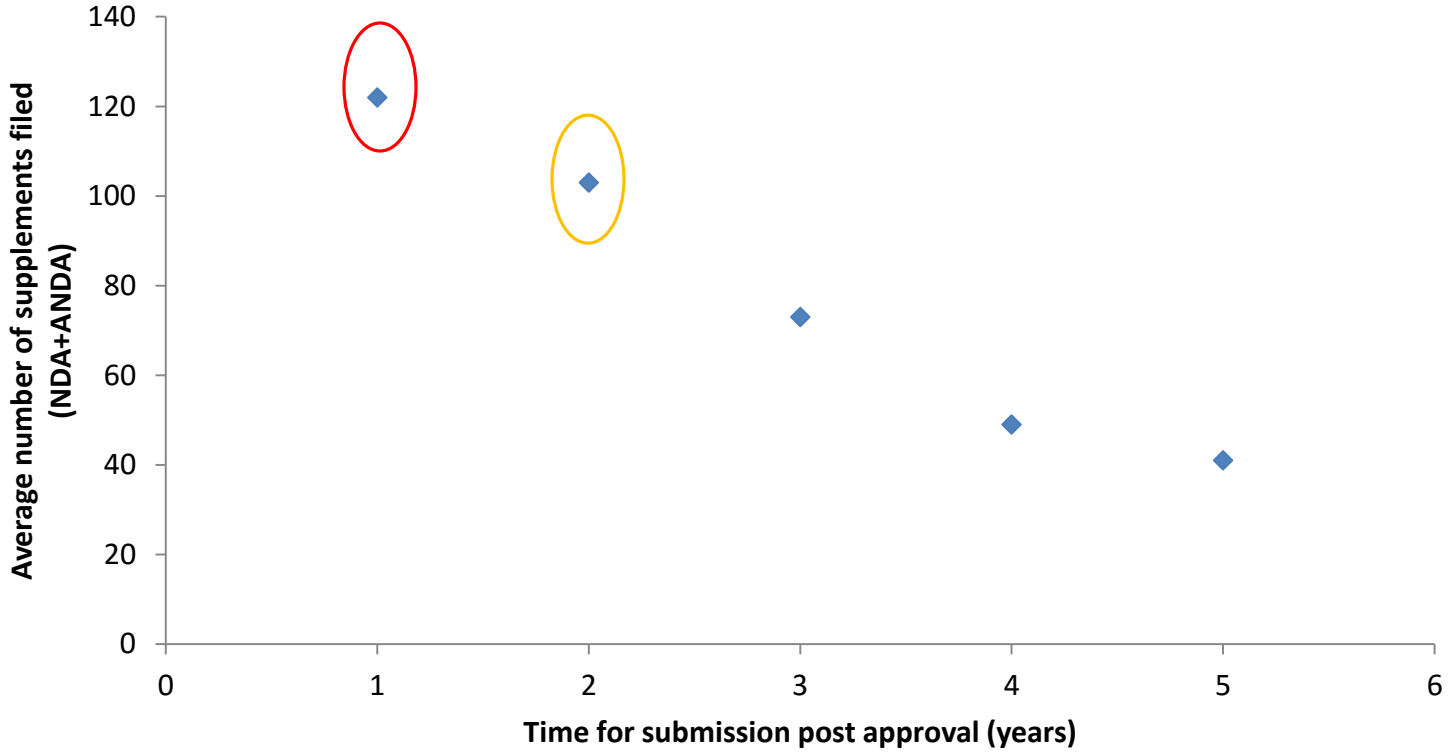
Critical Quality Attributes

- 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

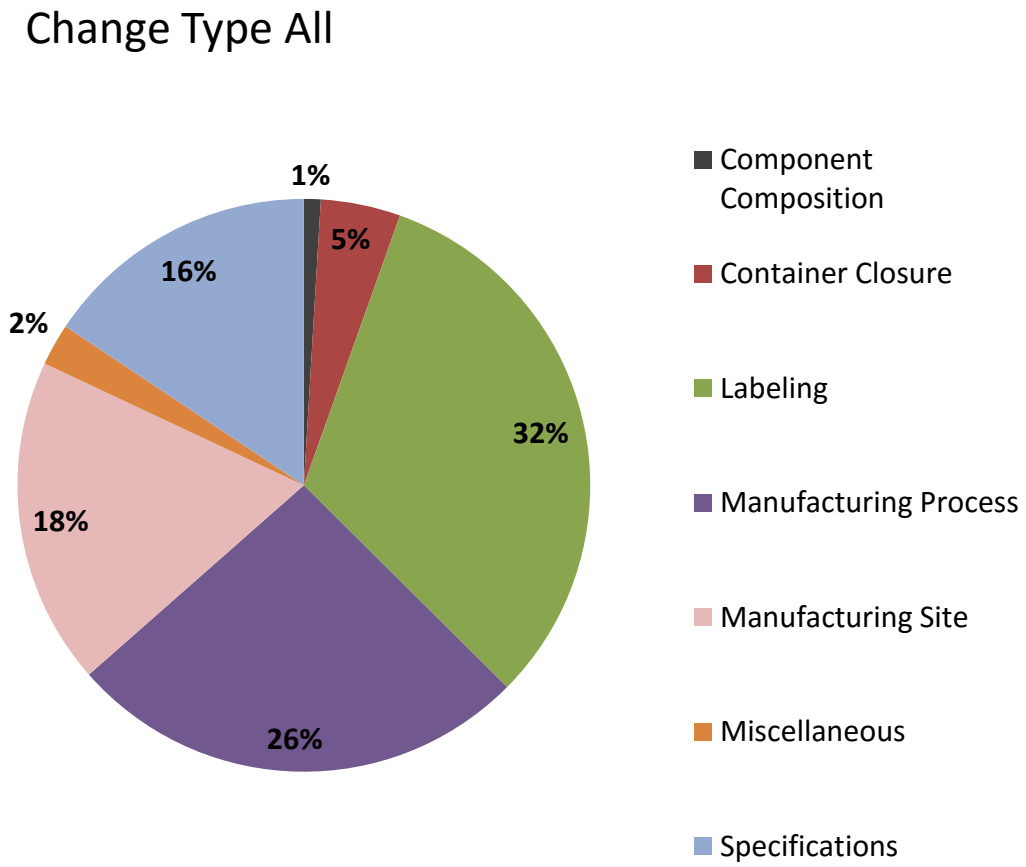
Post Approval Lifecycle Perspective

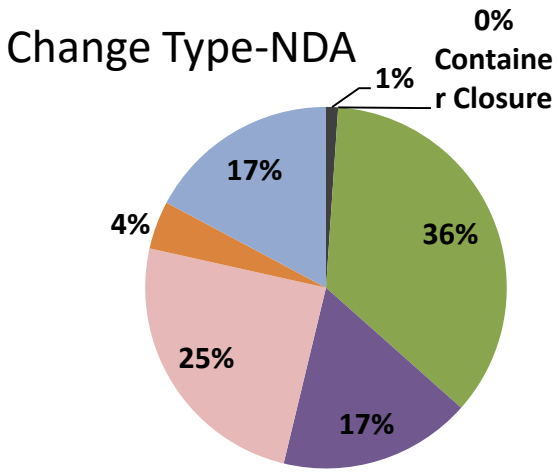


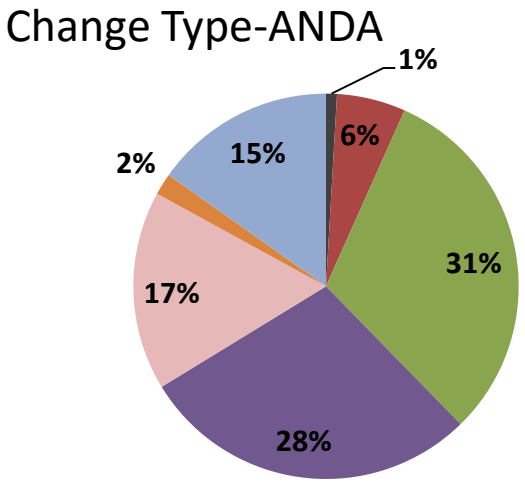
Post approval of ANDA/NDA: Number of Supplements Vs. Filing Time

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







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. The supplements were divided into 7 categories based on the proposed change type. The categories were created based on the “Guidance for Industry: Changes to an approved NDA or ANDA”.

Commonly Used Terms

- Lyophilization
- Freeze Drying
- Lyophilizer
- Choked flow
- Freeze Drying Microscope
- DSC
- Tg'/Tc/Teu/Tg
- 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:

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