U.S. FOOD & DRUG ADMINISTRATION

Advancing the formulation and manufacturing of lyophilized pharmaceuticals/biopharmaceuticals: Regulatory Perspectives

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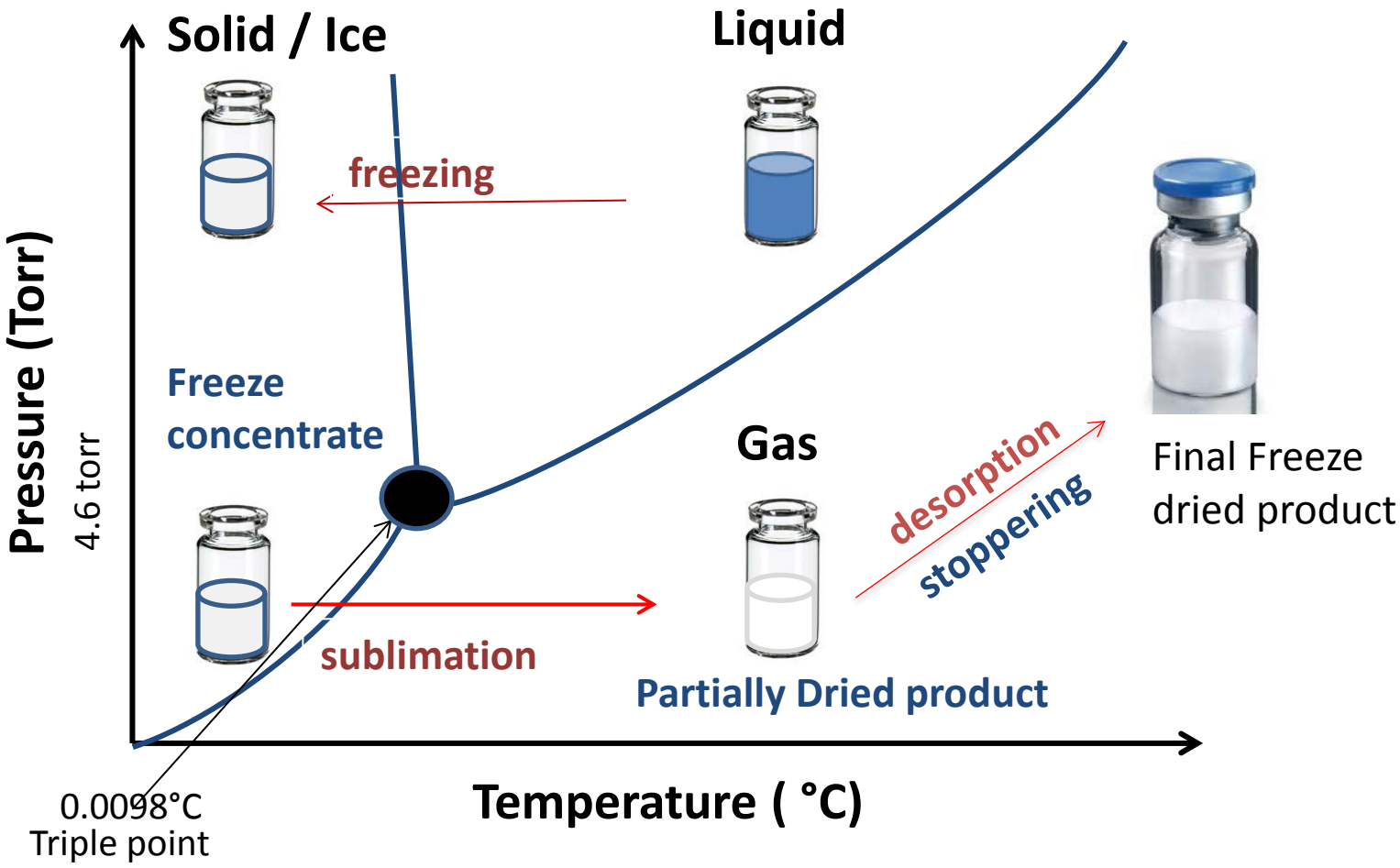
Disclaimer

“This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.”

Introduction

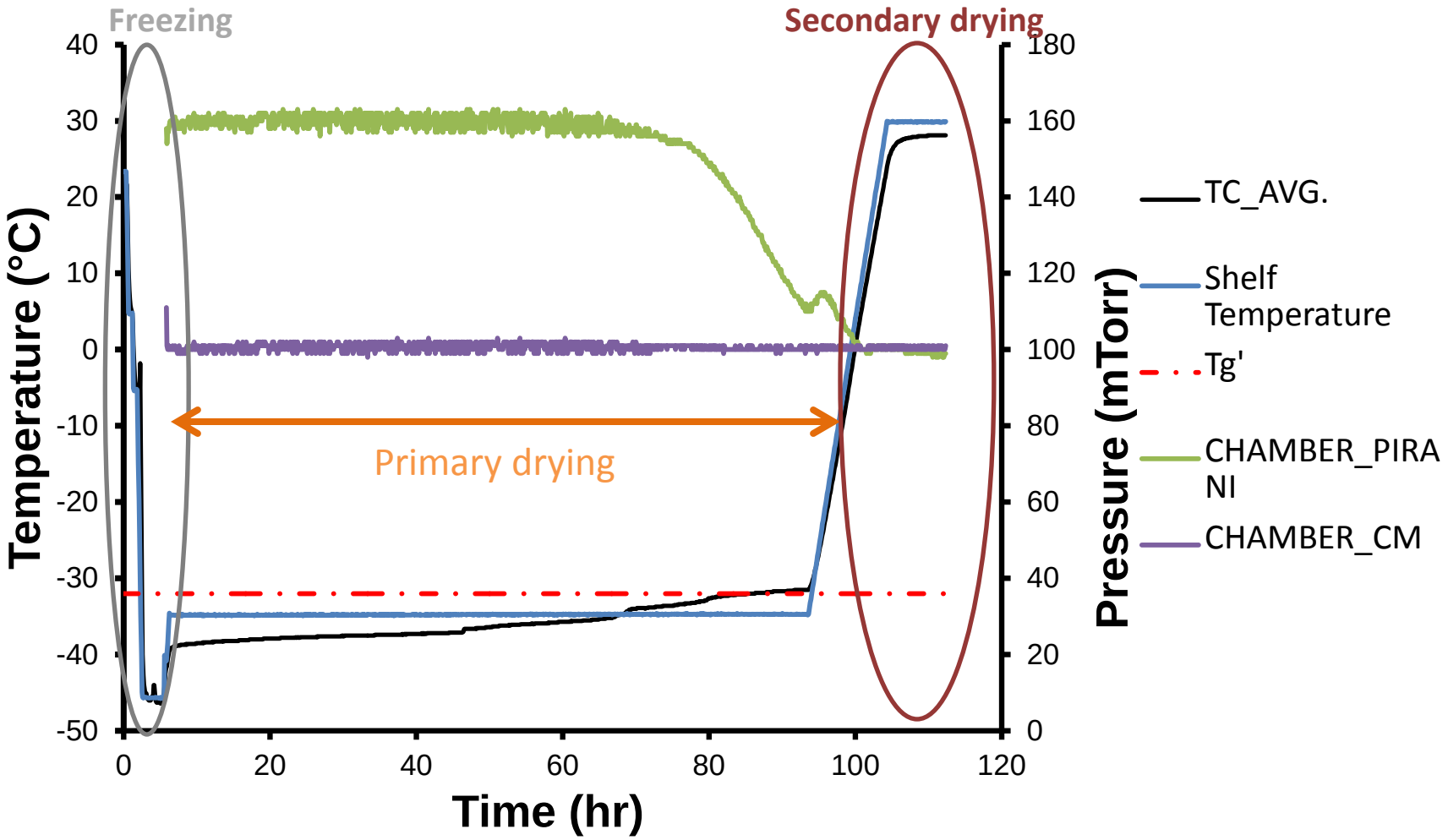
- Most commonly used process for improving the stability of moisture labile pharmaceuticals, especially biologics
- About 30% of parenteral products and ~40% of biopharmaceuticals are lyophilized
- Number of lyophilized products expected to increase with increase number of biologics
- Batch process- > 200 000 vials; Cost $1M - > $10 M per batch
- Process failure can lead to rejection of entire batch

Introduction



Lyophilization involves phase transitions and a coupling of heat and mass tranfer

Introduction



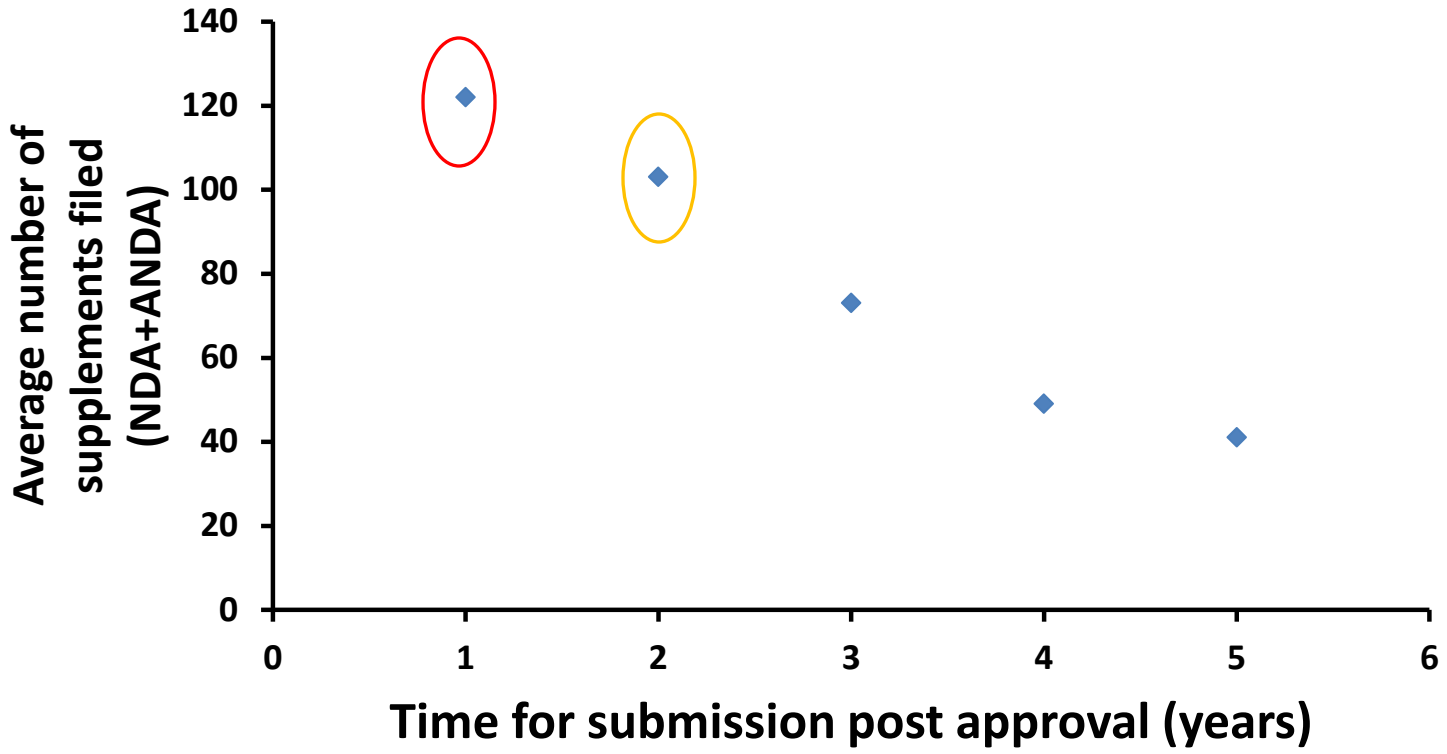
The three phases of a typical lyophilization cycle: Freezing, primary drying and secondary drying

Example of a Target Quality Product Profile of a Lyophilized product

Target Indication	Treatment of lyophilizemia
Dosage form	Sterile white to off white pharmaceutically elegant lyophilized cake for reconstitution with SWFI
Route of Administration	IV infusion (slow)
Infusion volume (deliverable)	4 mL in 100 mL of normal saline
Strength	42 mg/vial
Concentration after reconstitution	10 mg/mL
Reconstitution time	≤5 min
Target Reconstitution volume	4.2ml
Identity	Positive for protein assay
Isotonicity	280-350 mOsm
Aggregation	Within acceptable levels (<2%)
Shelf life	Not less than 2 years at 2-8°C. Reconstituted solution stable RT for 6hours
Container/closure	20 mL Type 1 tubing glass vial with 20 mm closure and crimp seal

Current state: Post Approval Submissions

Statistics on Lyophilized Products



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

Adapted from Kumar Janoria, "Current Regulatory Considerations on Pharmaceutical Lyophilization,"presentation at 2016 ISFLD East Coast Chapter meeting

The Desired State

“ a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive oversight”[1] – Dr. Woodcock

[1]Woodcock J, Pharmaceutical quality in the 21st Century- an integrated systems approach

The Desired State?

- Product and process **understanding** and process control based on **sound science** and quality **risk management**
- **Note QbD≠ DOE**
- DOE's may not always be the answer or feasible?
- However, leveraging QbD or the underlying principles of QbD even for parts of the process will go a long way in reducing the number/frequency of PAS

Lyophilization - Flow Chart

Compounding

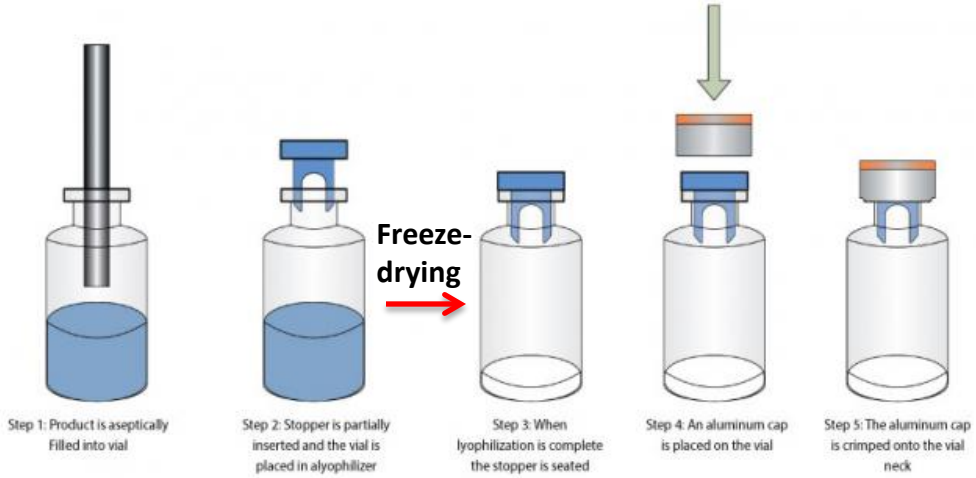
- Dispense
- Prepare solution/mixing

Holding through Loading

- Hold
- Filter
- Filling and partial stoppering
- Transfer/Loading

Freeze drying through packaging

- Freezing/Annealing
- Primary drying
- Secondary drying
- Vial stoppering
- Cap/Seal
- Secondary packaging



http://www.ivtnetwork.com/gallery/aseptic-core-images

DOE for Freeze Drying???

Fishbone diagram for a lyophilized product

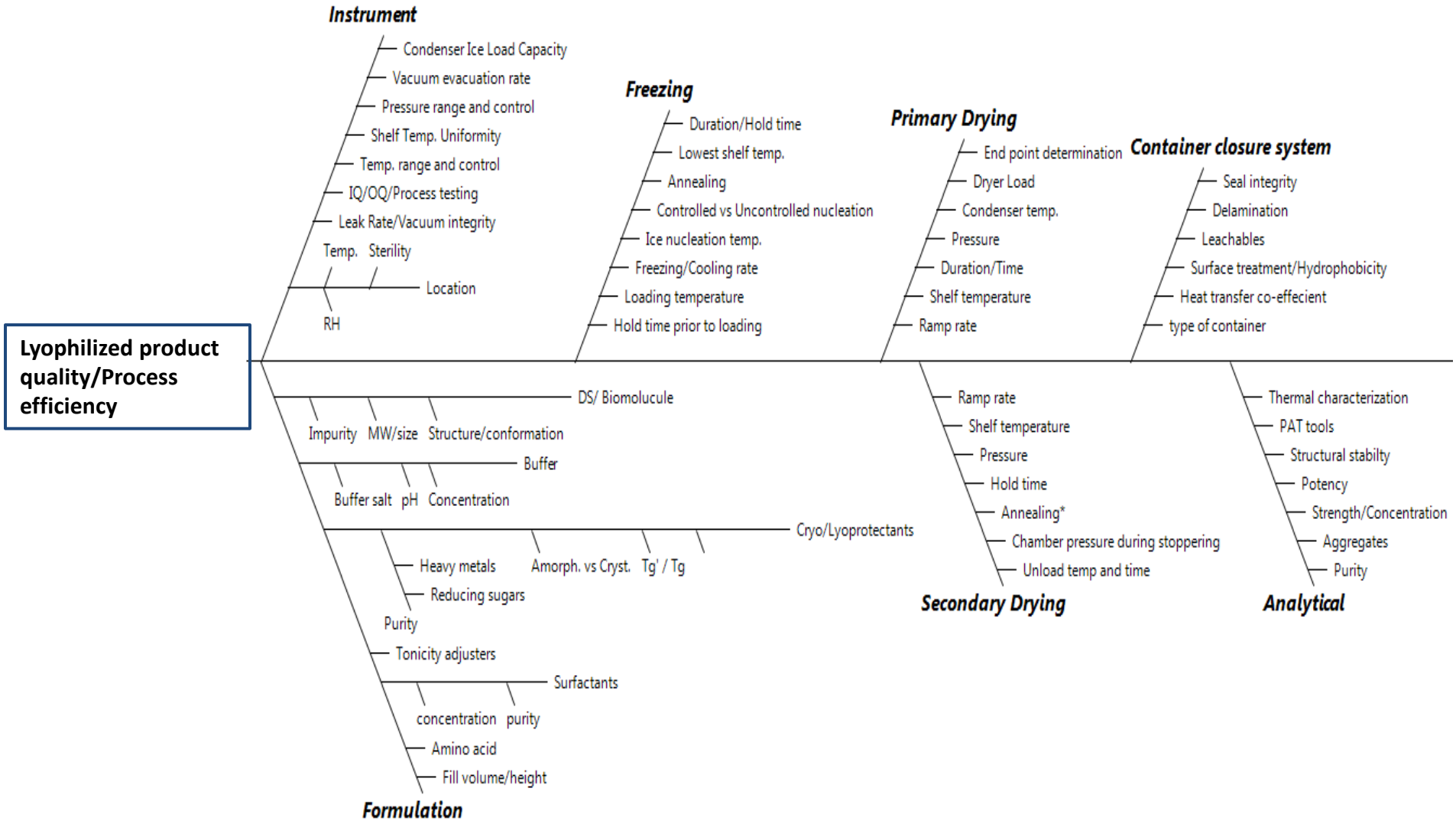


Diagram may not include all possible factors. Arrangement done arbitrary and not in any particular order.

Formulation and Hold Time studies

- Possible challenges to product quality
  - Product degradation
  - Container compatibility (leaching of metals, adsorption by transfer tubing)
  - Precipitation (order of addition/mixing)
  - Balance between optimum RPM and impact of shear stress on protein integrity
  - Bubbling and foaming concerns
  - **Sterility**

Formulation and Hold Time studies

- Considerations
  - Mixing rate (RPM) and mixing method
  - API dissolution time
  - Sequence of addition (salting out, precipitation)
  - Temperature
  - Light sensitivity
  - Hold time and temperature post filtration
  - Batch size/Scale down/scale up considerations
  - Manufacturing site transfer

Container Closure System (CCS)

- Rationale for Post Approval changes
  - Changes in manufacturer/supplier
  - Improvement in CCS design and technology
  - Particulates (visible and SVP)
  - Glass delamination
  - Vial breakage
  - Extractables and Leachables
  - Seal integrity
  - Stopper/vial incompatibility
  - Silicone oil contamination
  - Moisture transfer from stopper to product

Container Closure Systems

- Changes to primary packaging may be more common than anticipated
- For lyophilized products, the primary packaging role goes beyond storing and protecting the product
- CCS of lyophilized products are an integral part of the drying process
- What can be the approach to characterization of vial impact on lyophilization?

CCS : Impact on lyophilization process

– Heat flow $dQ/dt = A_V \cdot K_V \cdot (T_S - T_b)$ .....Eqn. 1

Mass and Heat Transfer in Vial Freeze-Drying of Pharmaceuticals: Role of the Vial

– Mass flow/sublimation rate

$$\frac{dm}{dt} = Po - Pc/Rs + Rs$$

M. J. PIKAL ˣ, M. L. ROY, and SAROJ SHAH

Received April 25, 1983, from the *Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285.* r publication June 8, 1983.

– Rearranging Eqn. 2 *dm/dt (mass flow)* can also be expressed as

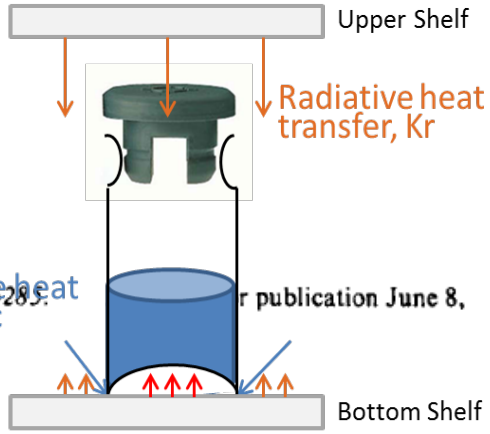
$$\frac{dm}{dt} = Av.Kv.(Ts - Tb)/\Delta Hs$$

Where Kv is the vial heat transfer coefficient, Av vial outer surface area, Ts the shelf temperature, Tb the temperature at the vial bottom and ΔHs

$$Kv = Kc + Kr + Kg$$

Kv can be further expressed as

$$Kv = C_1 Ac + Kr + \frac{C_2 Pc}{1 + {}^{l}/_{\lambda} C_2 Pc}$$



1. Heat and mass flow during freeze-drying is influenced by the vial [heat transfer coefficient (Kv), stopper resistance]

2. The heat transfer coefficient is dependent on vial dimension(area of contact with the shelf Ac, bottom curvature *l*) and process conditions(chamber pressure Pc)

Does changes in Kv without parallel change to process pose a risk to product quality?

- The product temperature which is the most important product parameter during freeze drying is dependent on the Kv
- Level of risk may vary with product and drying conditions
  - Increase in Kv due to changes in primary packaging
    - Macroscopic collapse as product temperature increases beyond Tc
    - "Bone" or "over dried" products**??** – stripping the water level below monolayer covering may promote product instability*(Town JK. J Chromatogr A 1995)(Few reports, stronger evidence may be needed)*
  - Changes in primary packaging that results in lower Kv may lead to
    - Higher residual moisture content as products may not dry (increase risk of physical and chemical instability)
    - Macroscopic collapse during ramp to secondary drying(Tp exceeds Tg' during ramp)

Container Closure Systems

- How do we assess the risk of CCS changes to product quality and process efficiency (machinability and lyophilization)?- Real risk vs perceived
- What should be the approach for qualifying the heat transfer characteristics of the CCS?
- What variation in Kv, bottom curvature and area of vial in contact with the shelf can significantly impact product quality and drying efficiency?
- What is the extent of change in stopper dimension that poses **real** risk to mass flow?

Container Closure Systems

- Considerations for comparability assessment
  - Scale: lab vs. man. scale
  - Which physical parameter? Kv only, Kv and Rp (product resistance) or dm/dt(sublimation rate profile) or all
  - Sample: Placebo vs Buffer/DI H2O vs. product
  - Length of run: 25% of primary drying or complete run (primary and secondary drying)
  - Order of vial arrangement: individual runs or a mixed run
  - Number of vials/batches to be considered
  - Machinability assessment

Risk based approach for assessing comparability of heat transfer characteristics of primary package may be beneficial

Emerging Concepts/trends of Interest

- Hybrid stability/storage

REMICADE

REMICADE should be stored at 2°C to 8°C (Refrigerate.) Do not use beyond the expiry date. **REMICADE may be stored at temperatures up to a maximum of 30°C for a single period of up to 12 months; but not exceeding the original expiration date.** The new expiration date should be written on the carton. Upon removal from refrigerated storage, REMICADE cannot be returned to refrigerated storage. REMICADE vials are for single use only. Any unused portion should be discarded

http://www.janssen.com/australia/sites/www_janssen_com_australia/files/prod_files/live/remicade_cmi.pdf

REBINYN® (Coagulation Factor IX (Recombinant) lyophilized powder for iv inj.

Store REBINYN under refrigeration at a temperature of 36°F-46°F (2°C – 8°C) for up to 24 months from the date of manufacture until the expiration date stated on the label. • **REBINYN may be stored at room temperature not to exceed 86°F (30°C) for up to 6 months within the 24-month time period.** Record the date when the product was removed from the refrigerator in the space provided on the outer carton. The total time of storage at room temperature should not exceed 6 months. Do not return the product to the refrigerator. • Do not use REBINYN after the end of the 6-month period at room temperature storage, or after the expiration date stated on the vial, whichever occurs earlier. • Do not freeze REBINYN. • Use REBINYN within 4 hours after reconstitution when stored at room temperature. Store the reconstituted product in the vial. • Discard any unused reconstituted product stored at room temperature for more than 4 hours.

https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM561316.pdf

Emerging concepts/trends of Interest

- Controlled Ice-nucleation- from lab to manufacturing scale (from ETT, proprietary)
  - What criteria determines a successful CIN process?
  - How sensitive are traditional product characterization techniques in distinguishing between a failed and successful CIN process?
  - **What control strategies needs to be in place?**
- In-line PAT for primary end-point determination
  - moving away from the fixed cycle time concept
  - Challenges in method validation

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THANK YOU

Questions, comments, concerns:

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