Lyophilization in Pharmaceutical Manufacturing: Deficiencies, Control Strategies, and Regulatory Expectations

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Learning Objectives

- Manufacturing unit operations - lyophilization
- Common deficiencies in drug applications
- Common control strategies used
- Inspectional findings

Poll Question

Which of the following is the definition of lyophilization found in the 1993 FDA guide to inspections of lyophilization of parenterals?

A. A process of transition where solid ice from a product turns into liquid water

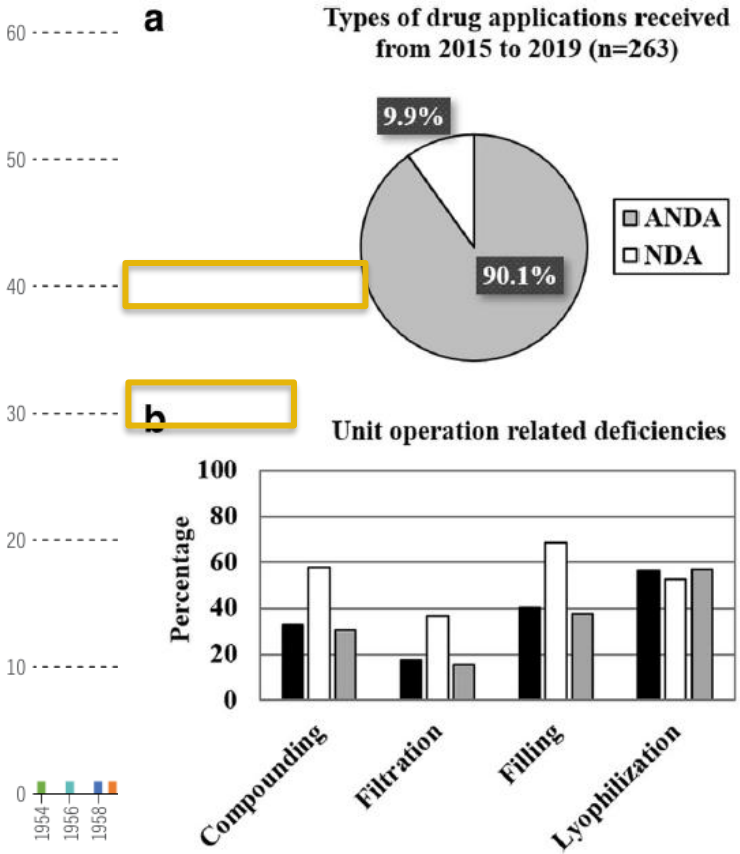
B. A process of transition where liquid water from a product turns into water vapor

C. A process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase

D. None of the above

Trends in lyophilization

- Lyo drugs approved per year*
- FDA lyo drug approvals by types of applications
- Accounting for 5% of *ca*. 800 generics reviewed annually
- Most frequent process-related deficiencies result from lyophilization**



*LyoHUB annual report 2025

**AAPS J. (2020) 22,100

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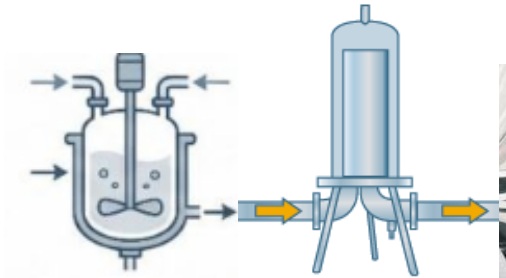
Manufacturing unit operations

- Compounding
- Filtration
- Aseptic filling
- Lyophilization (or freeze-drying)
- Crimping/packaging



Common lyo deficiencies

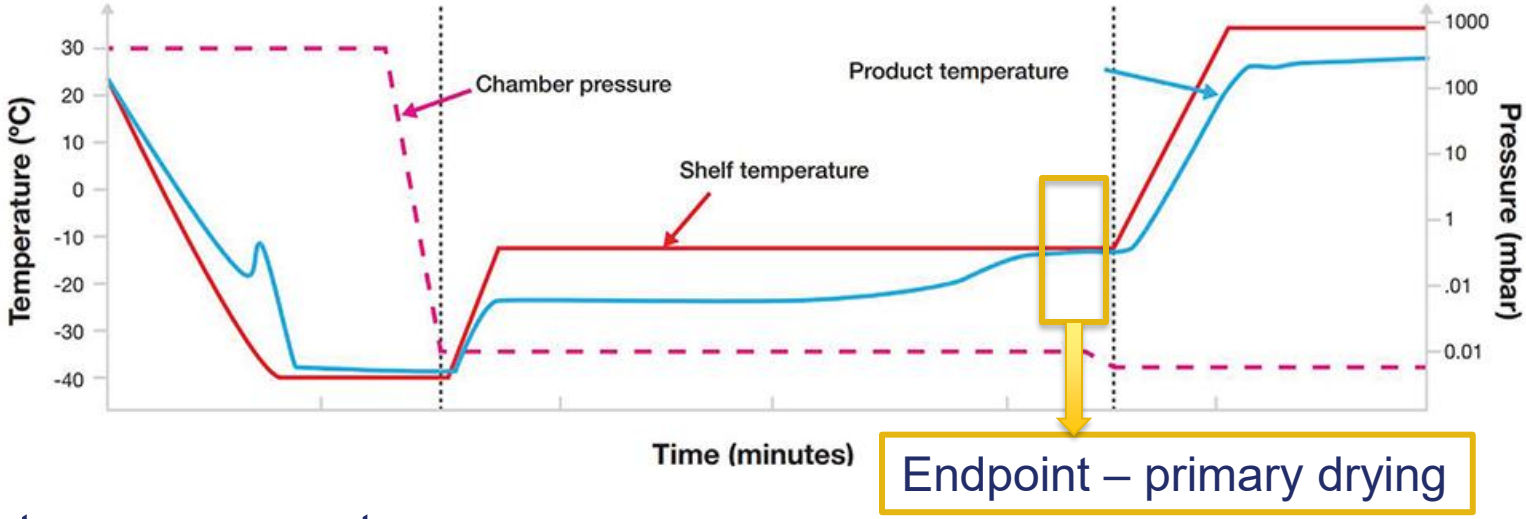
- Formulation specific issues
- Poor lyo cycle development
  - **Incorrectly identifying endpoint of drying**
  - **Cake collapse**
- No data/justification for scale-up

Regulatory expectations

- Reduce uncertainty in lyophilization
  - Endpoint determination
- Adoption of process analytical technology (PAT) tools
  - Increase detectability of failure modes
- Aligned with quality risk assessment (ICH Q9)

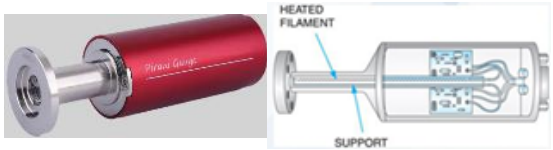
Common control strategies (PAT)

Thermocouple-based detection



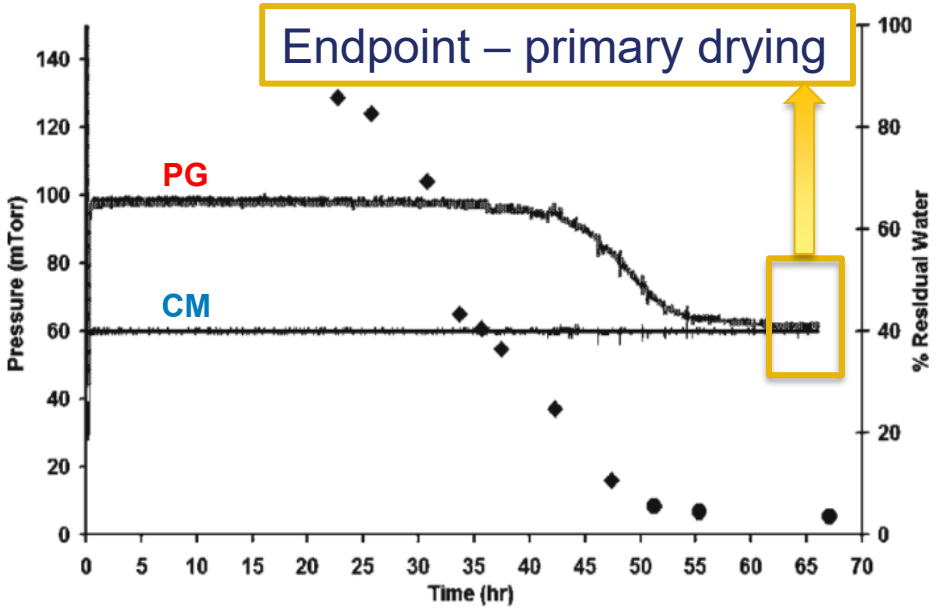
- Direct measurement
- Vials with thermocouple not representative of the entire batch
- Not suitable for commercial production

Common control strategies (PAT)



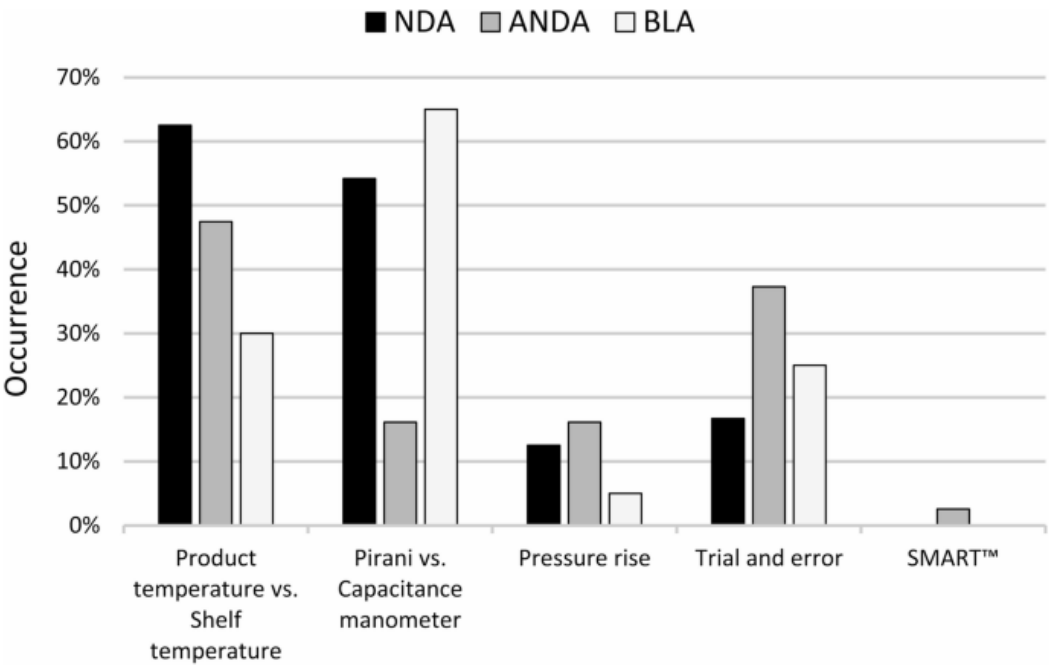
Pirani gauge (PG):
measure thermal gas conductivity (N_2 vs. H_2O)

Capacitance Manometer (CM):
measure absolute vacuum value (gas insensitive)



- Frequent calibration needed for PG and CM
- PG not robust enough to withstand repeated sterilization

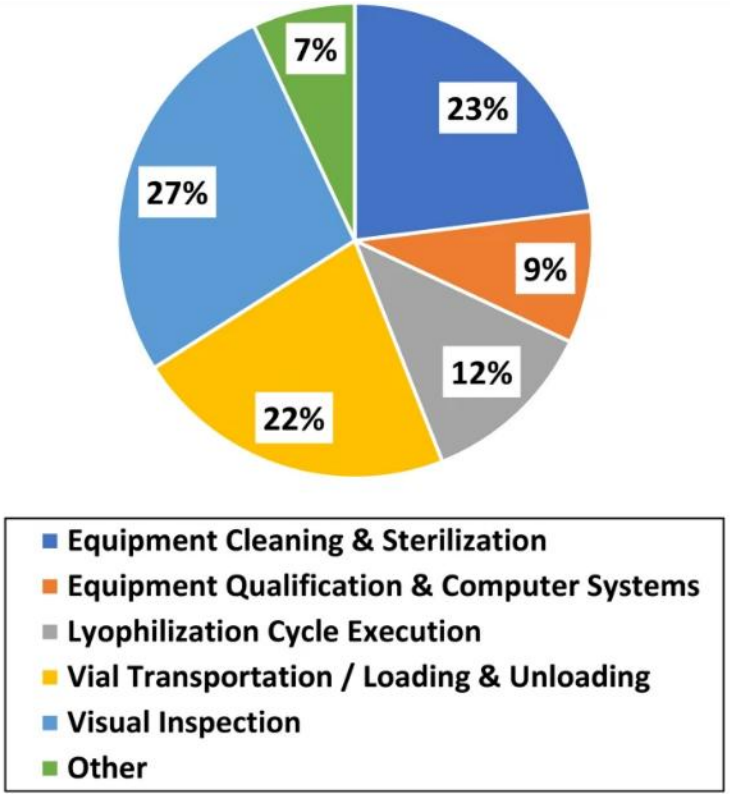
Common control strategies observed in drug applications*



Methods used to determine the endpoint of drying observed from 24 New Drug Applications (NDAs), 118 Abbreviated New Drug Applications (ANDAs), and 20 Biologics License Applications (BLAs) examined

*AAPS One (2025) 11,27

Inspectional findings (2015–2019)*



- **Visual Inspection (27%)**
  - Inadequate defect libraries for training
  - Lack of training
  - Lack of SOP in place

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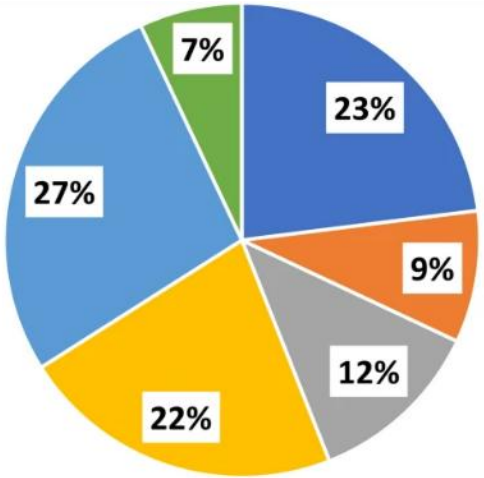
Inspectional findings (2015–2019)*



- **Cleaning/Sterilization (23%)**
  - Improper CIP/SIP for intricate components
  - Lack of integrity testing for filters
  - Lack of leak testing

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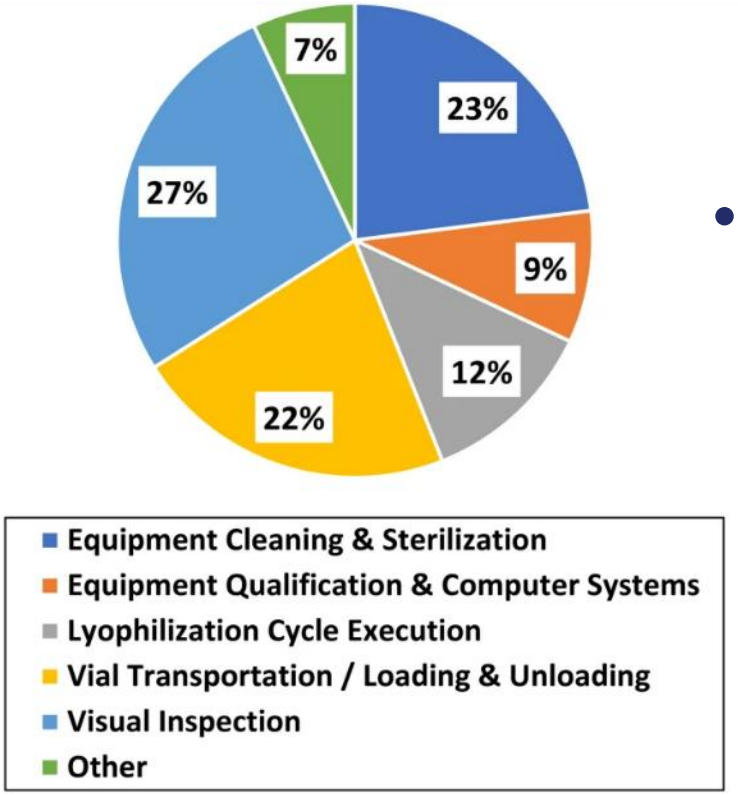
Inspectional findings (2015–2019)*



- **Loading/unloading (22%)**
  - Inadequate or absence of smoke studies
  - First air breached during vial transportation or while loading partially stoppered vials

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Key takeaways

- The necessity of identifying endpoint determination of drying
- Proper control strategies in place
- Manufacturing facilities should be ready for inspection and comply with cGMP requirements at the time of submission

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