Pharmaceutical Freeze-Drying: Barriers to Improving Process Efficiency

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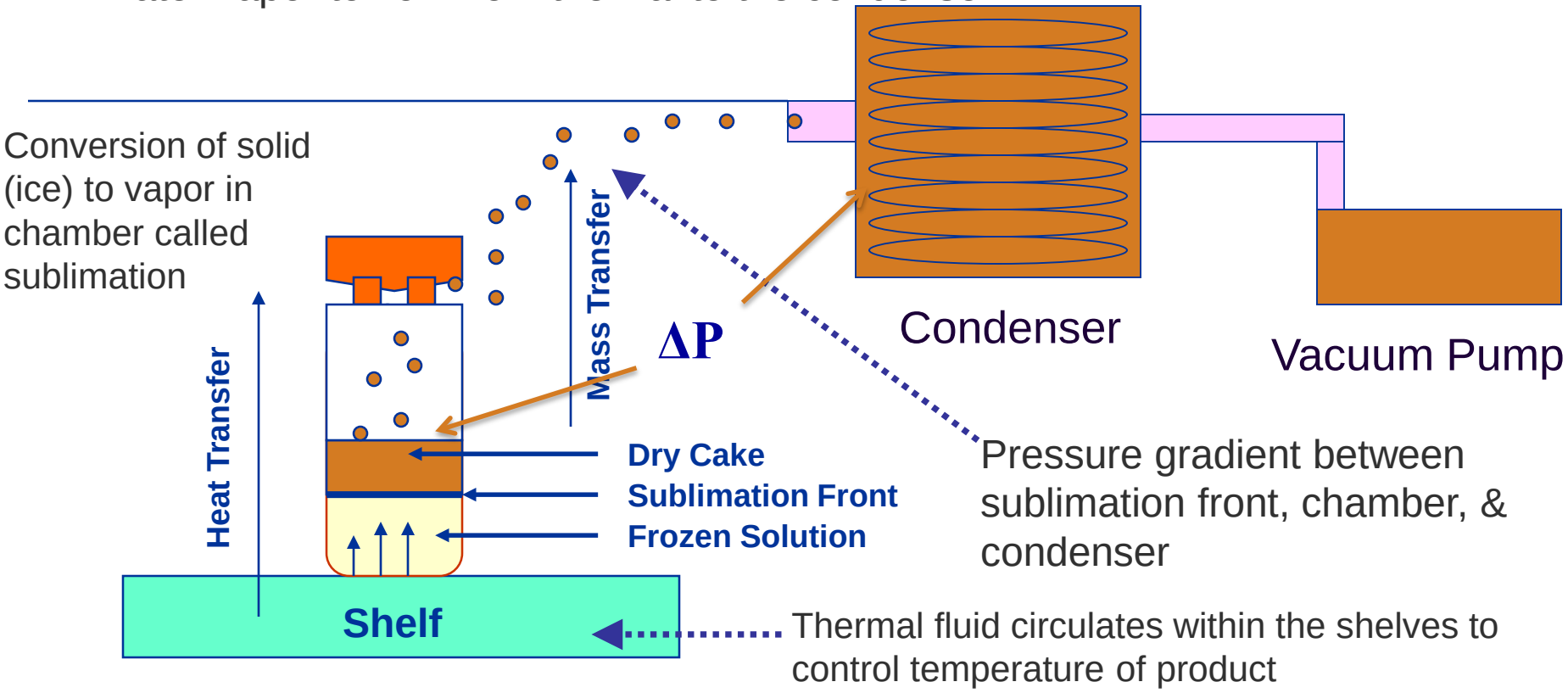
Schematic of Heat and Mass Transfer in the Freeze Dryer

The product is maintained at a temperature higher than the temperature of the condenser, creating a pressure differential between vapor pressure of ice at the sublimation front and vapor pressure of ice on the condenser, causing water vapor to flow from the vial to the condenser.



Advantages and Limitations of Freeze Drying

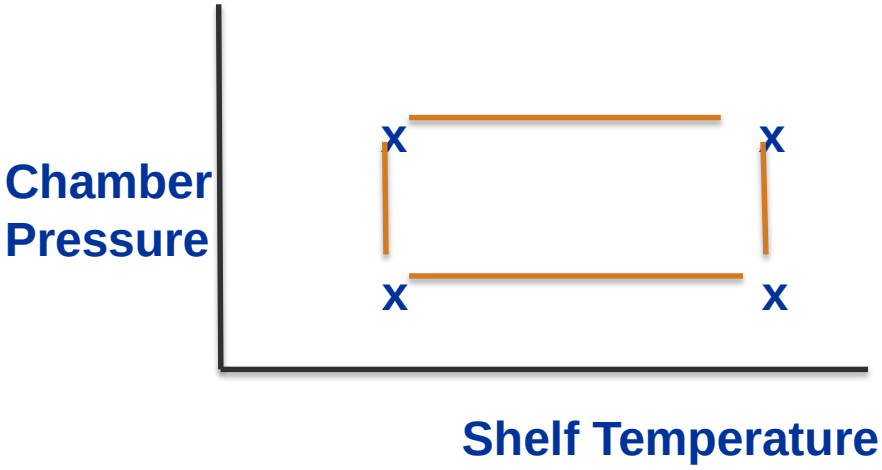
- Principal advantage:
  - It enables removal of water at low temperatures from thermally labile materials, thus avoiding the heat associated with more traditional drying methods
- Principal disadvantage:
  - The process is terribly inefficient. Cycle times are measured in days.

Approach to Process Development

- We want to develop process conditions that are as aggressive as possible without exceeding either the upper limit of product temperature or the maximum capability of the freeze drying equipment.

The Traditional Approach

- Characterize the formulation – determine the upper limit of product temperature during primary drying
- Carry out a series of trial cycles in a laboratory freeze dryer. Monitor product temperature, and arrive at a set of process conditions that consistently produce an acceptable product.
- Establish “proven acceptable ranges” of both shelf temperature and product temperature.



Uncertainties with Traditional Approach

- We have no idea of where we are with respect to the edges of failure:
  - Product related (usually collapse)
  - Equipment related (any freeze dryer has a limit as to the rate of sublimation that it will support)
- We have no idea of where we are with respect to the optimum processing conditions.
  - We define optimum as those conditions that result in a pharmaceutically acceptable product with the fastest sublimation rate.

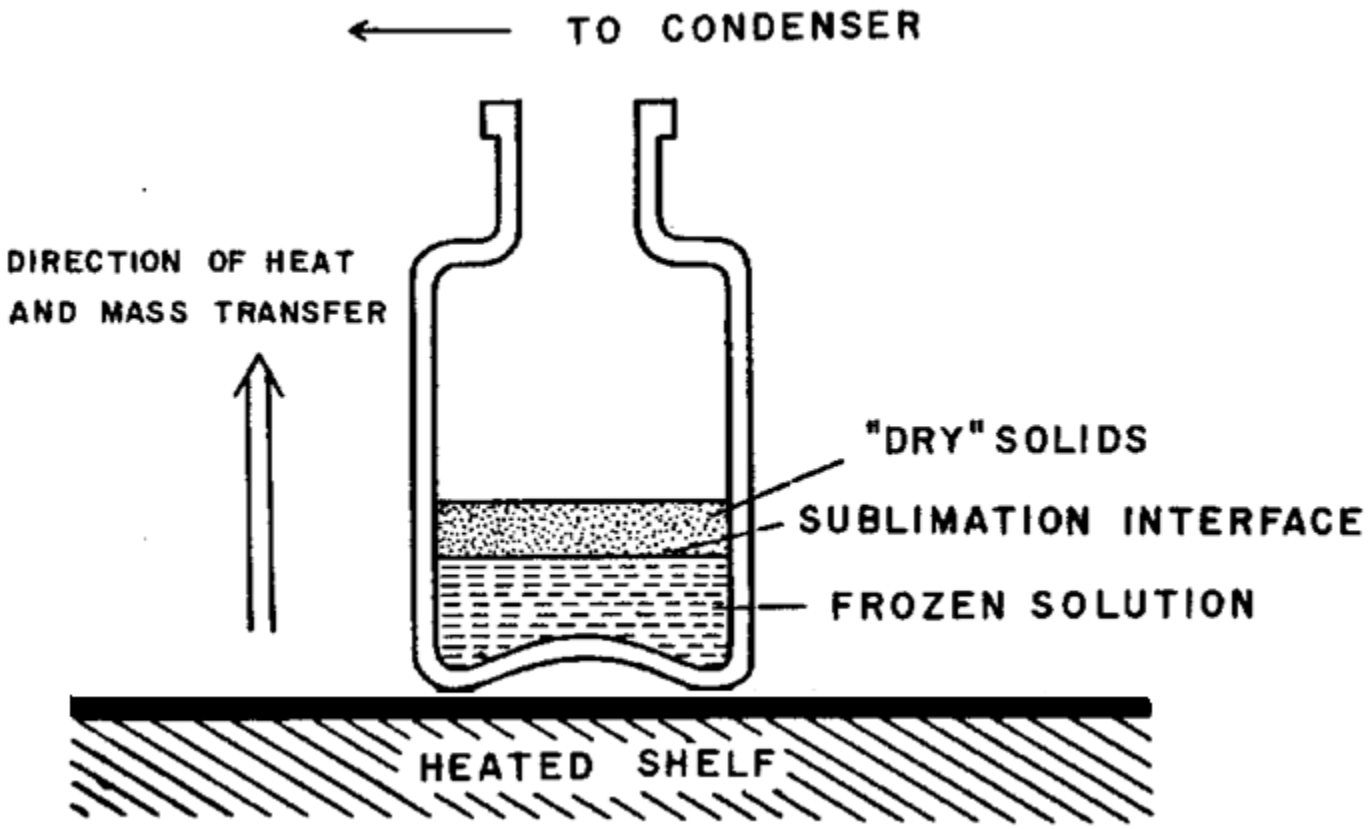
Barrier # 1: Failure to Think “Long Term”

- Early process development is almost always done in R&D groups. Priority is given to making sure that the product does not fail as a result of the process.
- Process efficiency is a secondary concern, and often cycle optimization is never done.
- Manufacturing groups are “stuck” with freeze dry cycles that require far more time than would be necessary under optimized conditions.

A Better Way: Construct a Design Space

- **Construct a map of all process conditions that produce an acceptable product, where this map includes the edges of failure.**
- **We do this by:**
  - **Characterizing the formulation – determine the maximum allowable product temperature during primary drying**
  - **Measuring the vial heat transfer coefficient**
  - **Measuring the resistance of the dried product to flow of water vapor**
  - **Constructing a graph showing the relationship between the variables that we control directly (shelf temperature and chamber pressure) and the critical variable that we don't control directly, the product temperature. This is based on a mechanistic understanding of the primary drying process via the use of heat- and mass balances [1,2].**
  - **Measure the freeze drying equipment capability.**

Heat and Mass Transfer in Freeze Drying



Equations Used for Construction of Design Space

$$dq/dt = K_v A_v (T_s - T_b)$$

$$dm/dt = A_p (P_i - P_c)/R_p$$

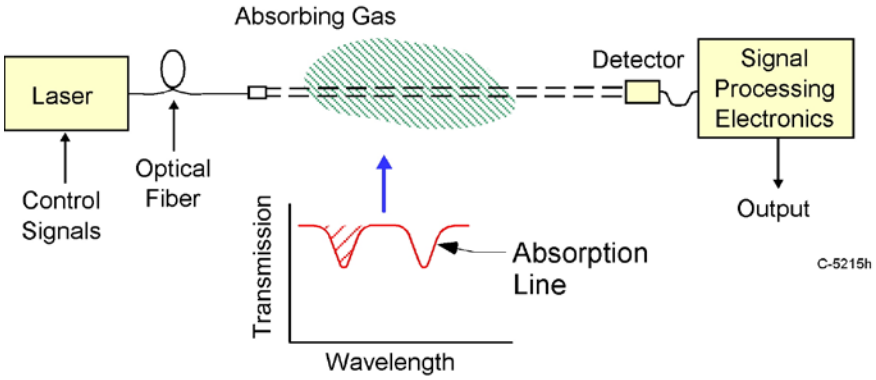
$$dq/dt = \Delta H_s \, dm/dt$$

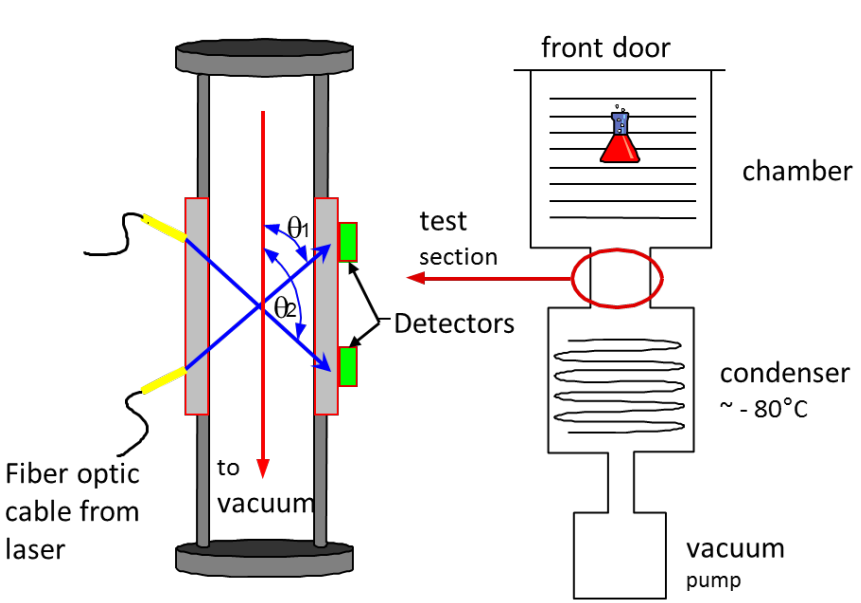
Where dq/dt is the rate of heat flow to the vials, k_v is the vial heat transfer coefficient, A_v is the area based on the outer wall of the vial, T_s is the shelf temperature, T_b is the product temperature, dm/dt is the mass flow rate of water vapor from the vial, A_p is the area based on the inner radius of the vial, P_i is the vapor pressure of ice at the sublimation front, P_c is the chamber pressure in Torr, R_p is the resistance of the dried product layer to flow of water vapor, and ΔH_s is the heat of sublimation of ice.

Tunable Diode Laser Absorption Spectroscopy (TDLAS) Mass Flux Measurements

- Optically measure water vapor concentration
- Optically measure gas velocity
- Use the concentration and velocity measurements to determine mass flow rate of water vapor

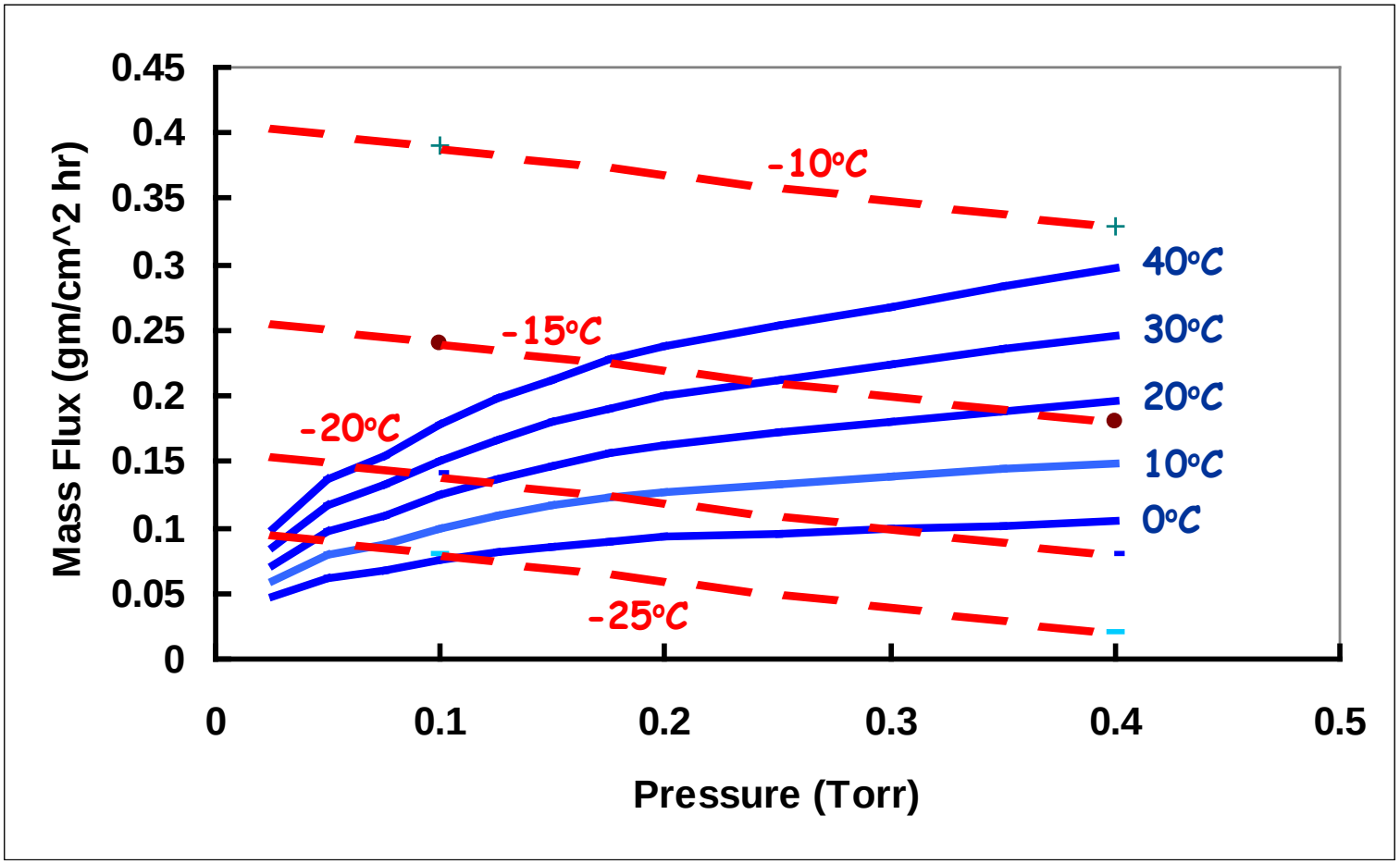
Slide courtesy of Bill Kessler, Physical Sciences, Inc., Andover, MA



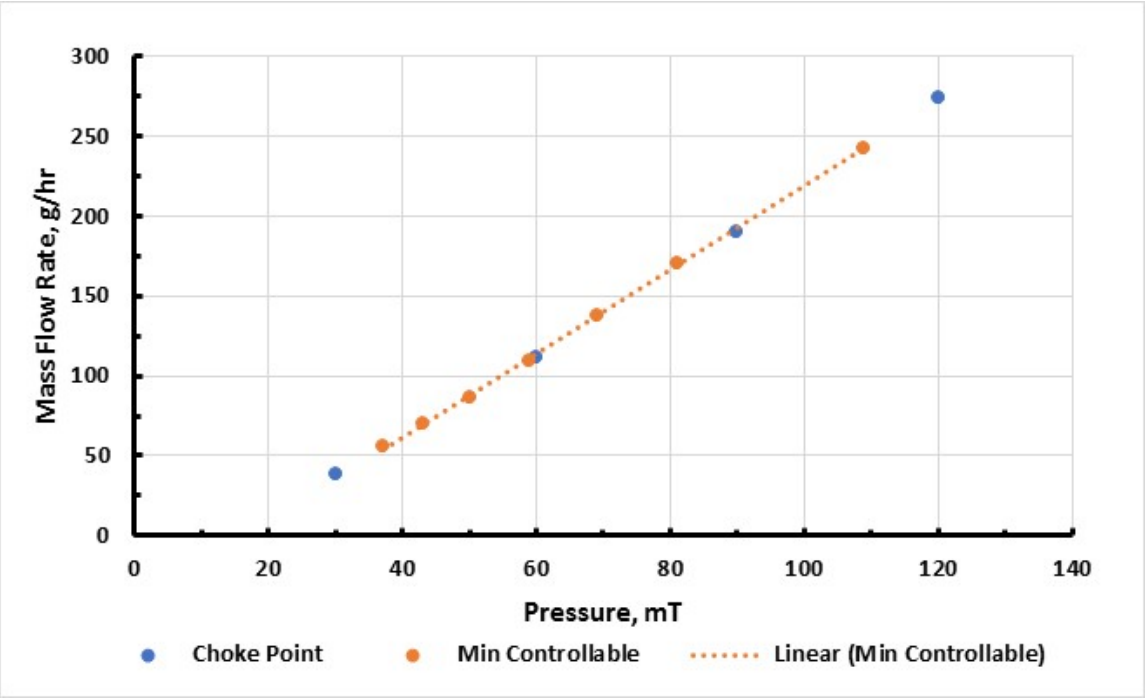


LyoFlux 200 Optical Spool
Installed in a Lyostar III lyophilizer

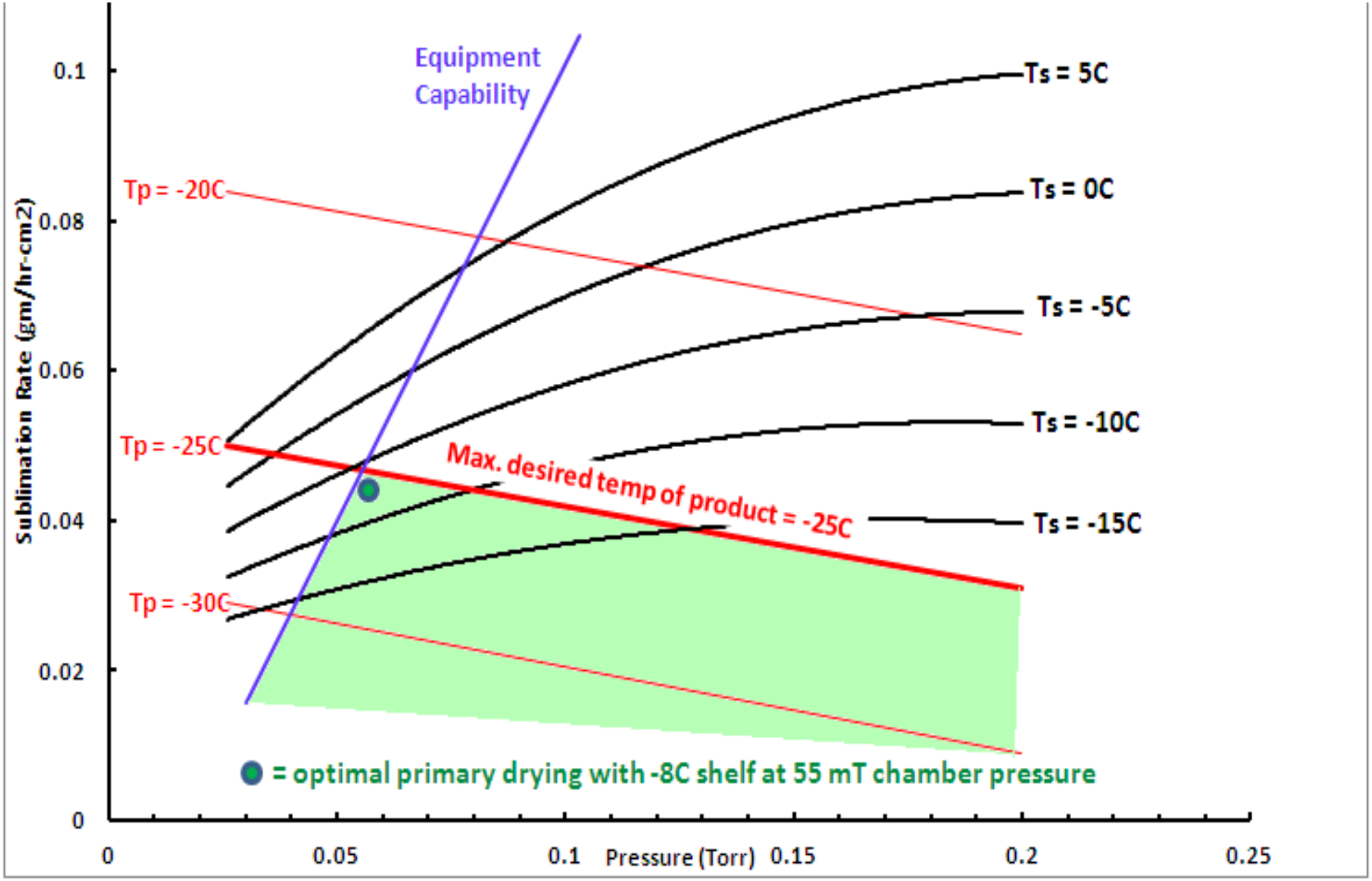
Product Temperature Isotherms



Both Methods Give the Same Result



The Graphical Design Space

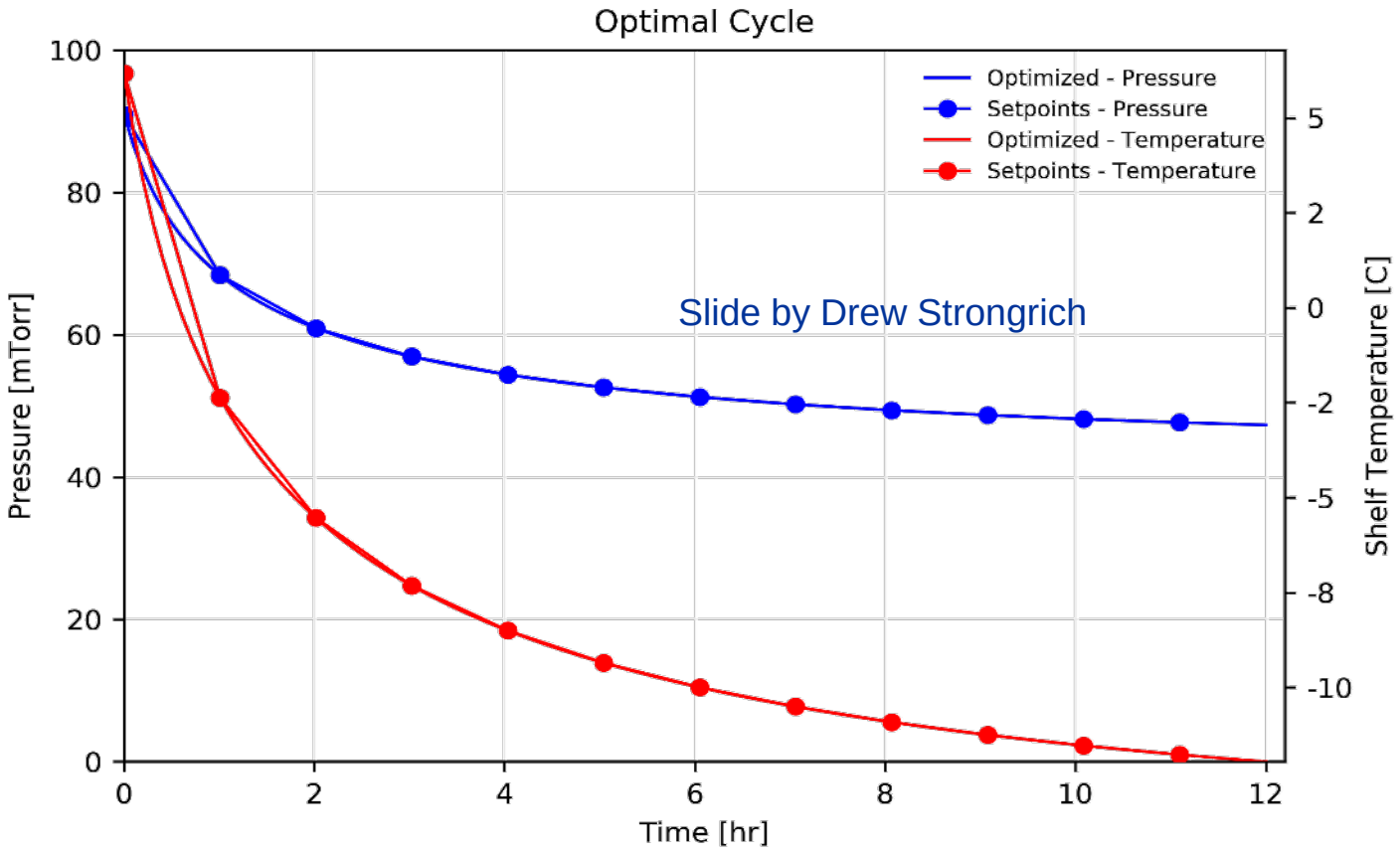


Barrier # 2 – Perhaps Overemphasis of DOE?

- A significant number of regulatory authorities have come to expect a Design of Experiments approach to establishment of process conditions.
- Any trial-and-error approach should be focused near the optimum point on the design space.

In the Near Future. . .

- Optimized Primary Drying

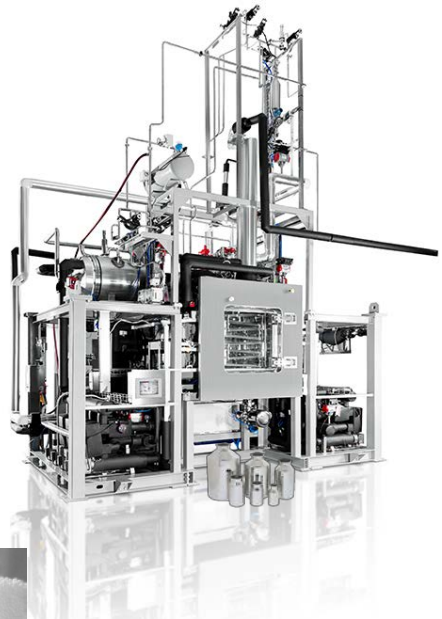


Barrier # 3: Physics

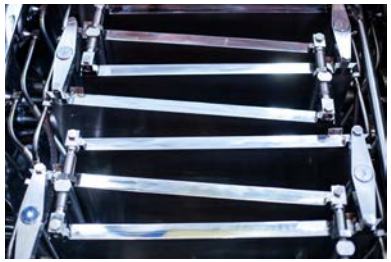
- In order to really make freeze drying efficient, we need to redesign the process; in particular, look for alternatives to traditional freeze drying in a vial.
- There are two alternative approaches worthy of our attention:
  - Spray freeze drying
  - Continuous freeze drying

Continuous Lyophilization with Spray Freeze Drying

- Most freeze drying in aseptic conditions is designed for vials, or bulk product in trays placed on shelves
- The process has traditionally been a batch process making it both time consuming and energy intensive
- Continuous spray freeze drying technology is designed for:
  - Complete containment starting with bulk liquid product and ending with discharging dried particles aseptically
  - Enabling continuous lyophilization



Droplet delivery



Cascading shelves for transport

Product transport

Final dried product in vials

LYnfinity

Continuous Freeze Drying