Freeze-dryer Characterization: Execution and Application from Lab to Commercial

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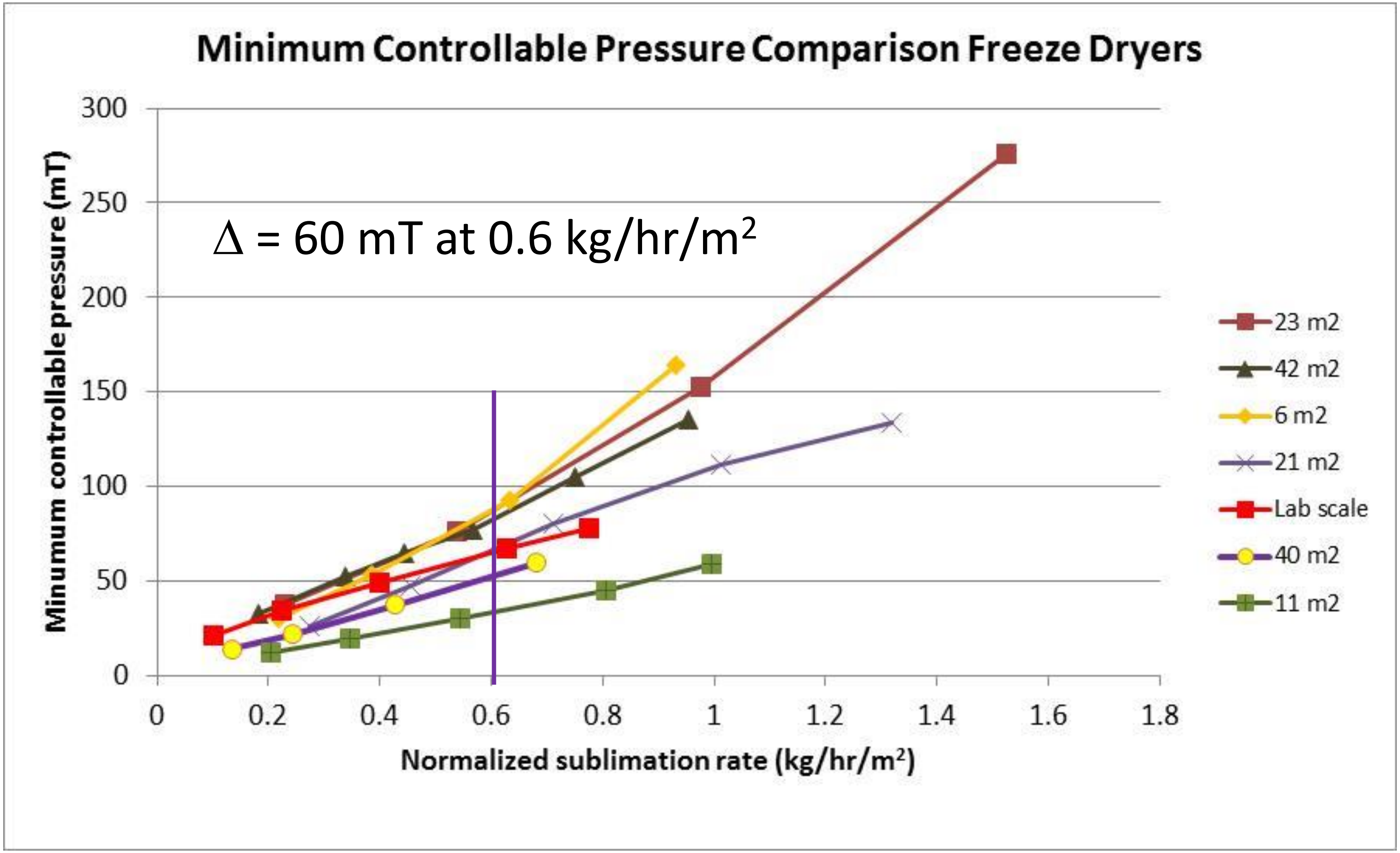
Outline

- Define the purpose of characterization
- Methodology
  - Minimum controllable pressure as a function of sublimation rate
  - Maximum sublimation rate
  - Vial heat transfer coefficient (K_v)
- Application of data: Primary drying model
  - How are the data used?
  - What value does it have?
- Examples of Challenges

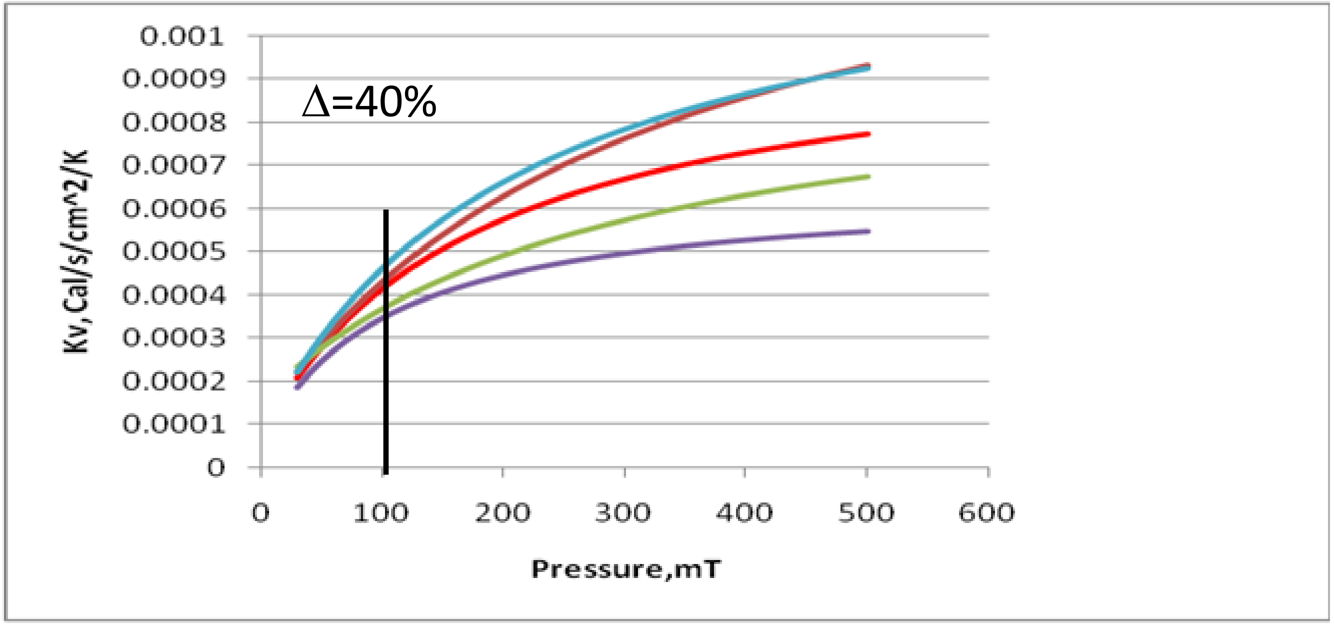
Purpose of Lyo Characterization

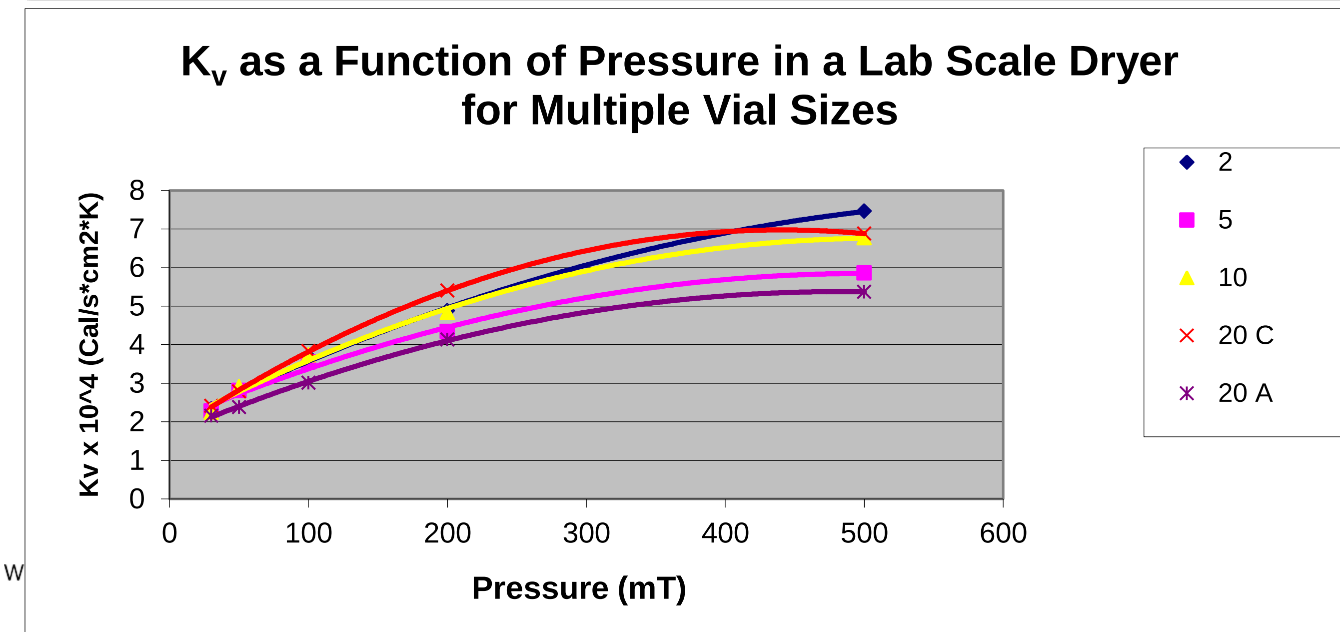
- Generate data for the Pfizer 1° drying model
  - Facilitate cycle design and scale up/transfer
- Mission to characterize all dryers in network
- Physical differences in lyophilizers
  - Shelf size/thickness
  - Utilities
  - Environment
- Functional differences
  - K_v
  - Cake resistance
- If a development cycle was transferred to a commercial dryer without modification, it ~~could~~ would fail

Differences: Minimum Controllable Pressure (MCP)



K_v Difference Between Laboratory, Pilot and Commercial Dryers (10-ml Schott vials)





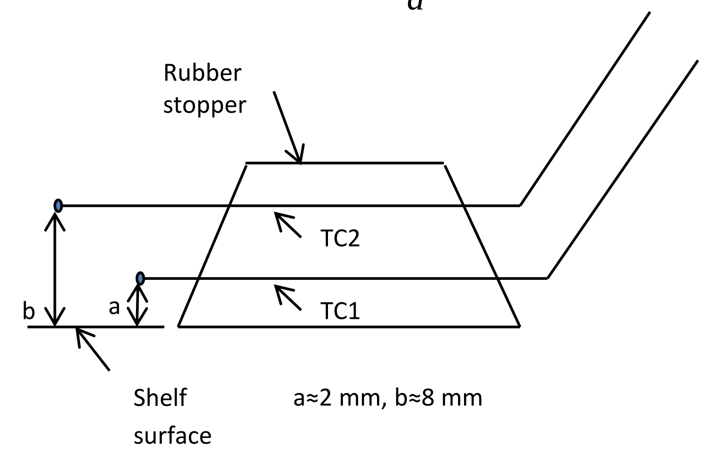
Minimum Controllable Pressure Test Execution

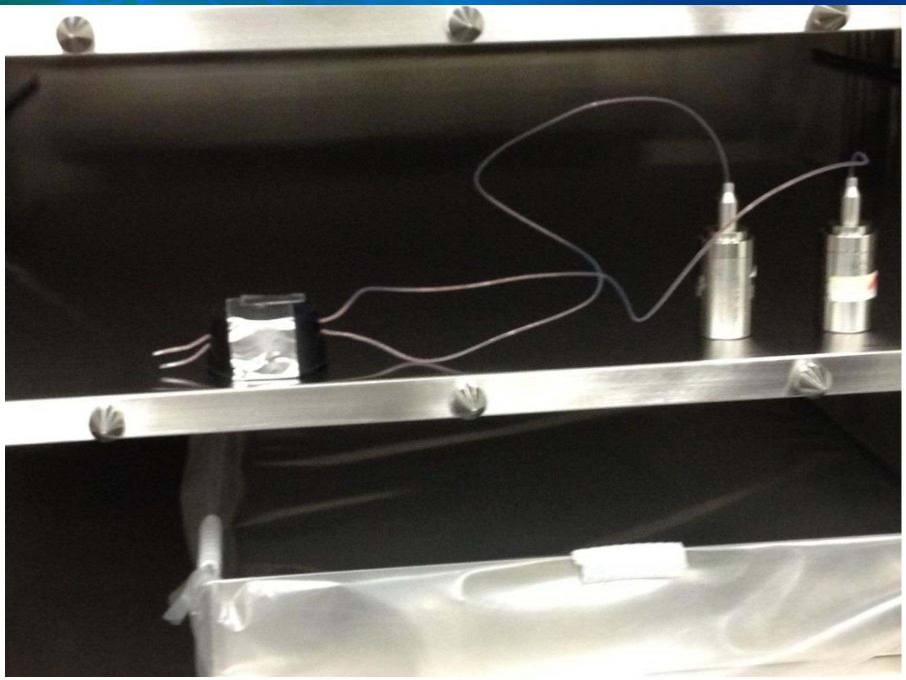
- Determine the lowest controllable chamber pressure as a function of sublimation rate
- Fully load the lyophilizer with water
  - Use vials
  - Bottomless trays with plastic
  - Trays with solid bottom
- Freeze water to -50 ºC
- Pull vacuum to a minimum level (low set-point: 1-3 mT)
- Sequentially raise shelf temperature and hold until the chamber pressure equilibrates, target 25% mass loss (total)
- Calculate the sublimation rate at each shelf temperature
- Plot minimum controllable pressure as a function of sublimation rate

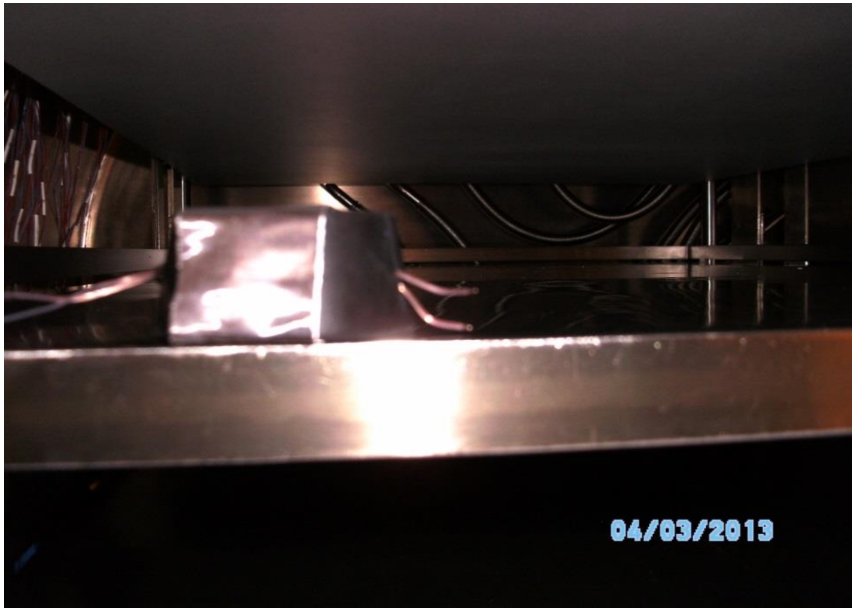
Experimental Set-up: Clinical Scale

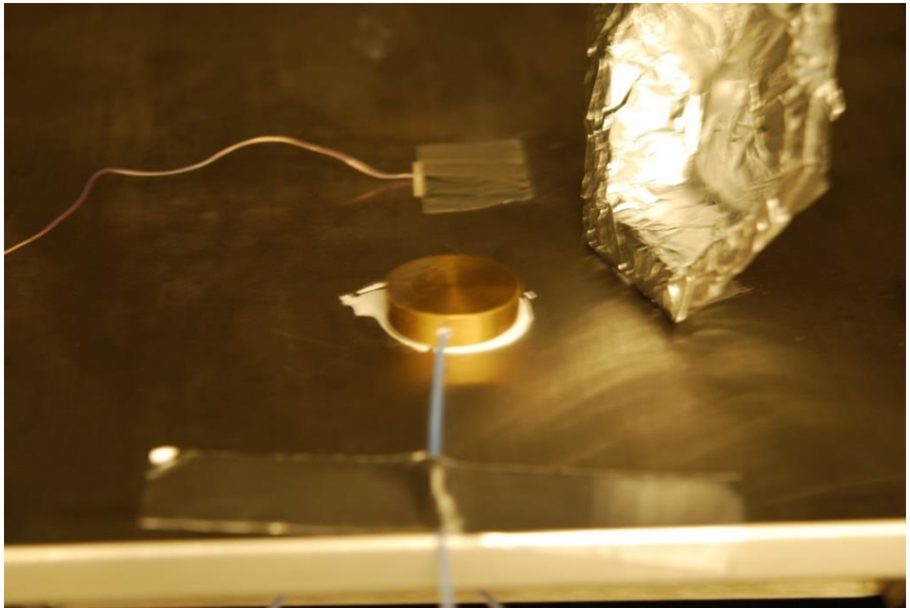
Measuring Temperature: Ice and Shelf Surface

$$T_{ice\_bottom} = \frac{K_{baq} T_{shelf\_surface} + \frac{K_{ice}}{a} T_{ice}(a)}{K_{bag} + \frac{K_{ice}}{a}}$$

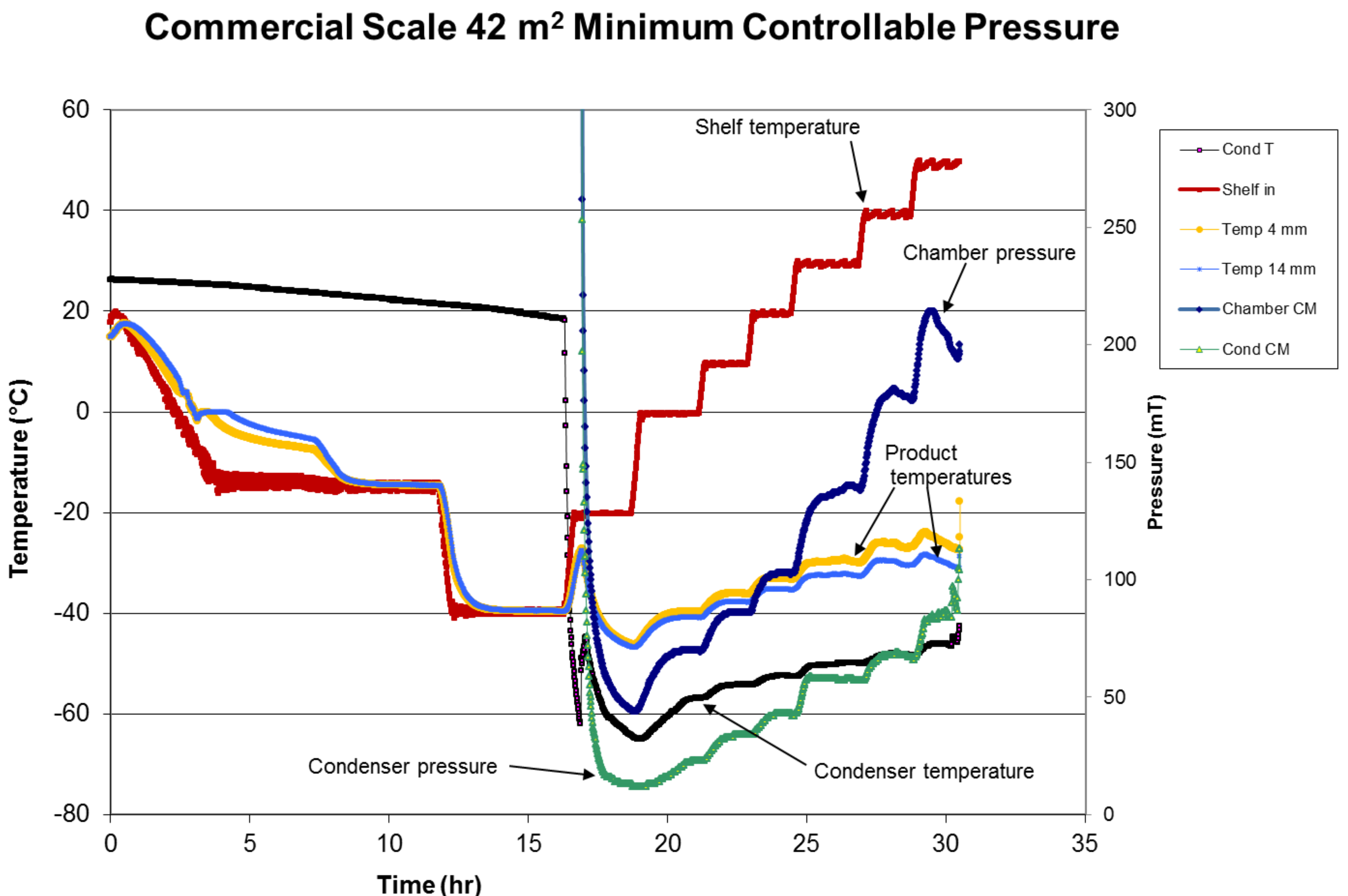








Minimum Controllable Pressure Cycle



Calculating Sublimation Rate

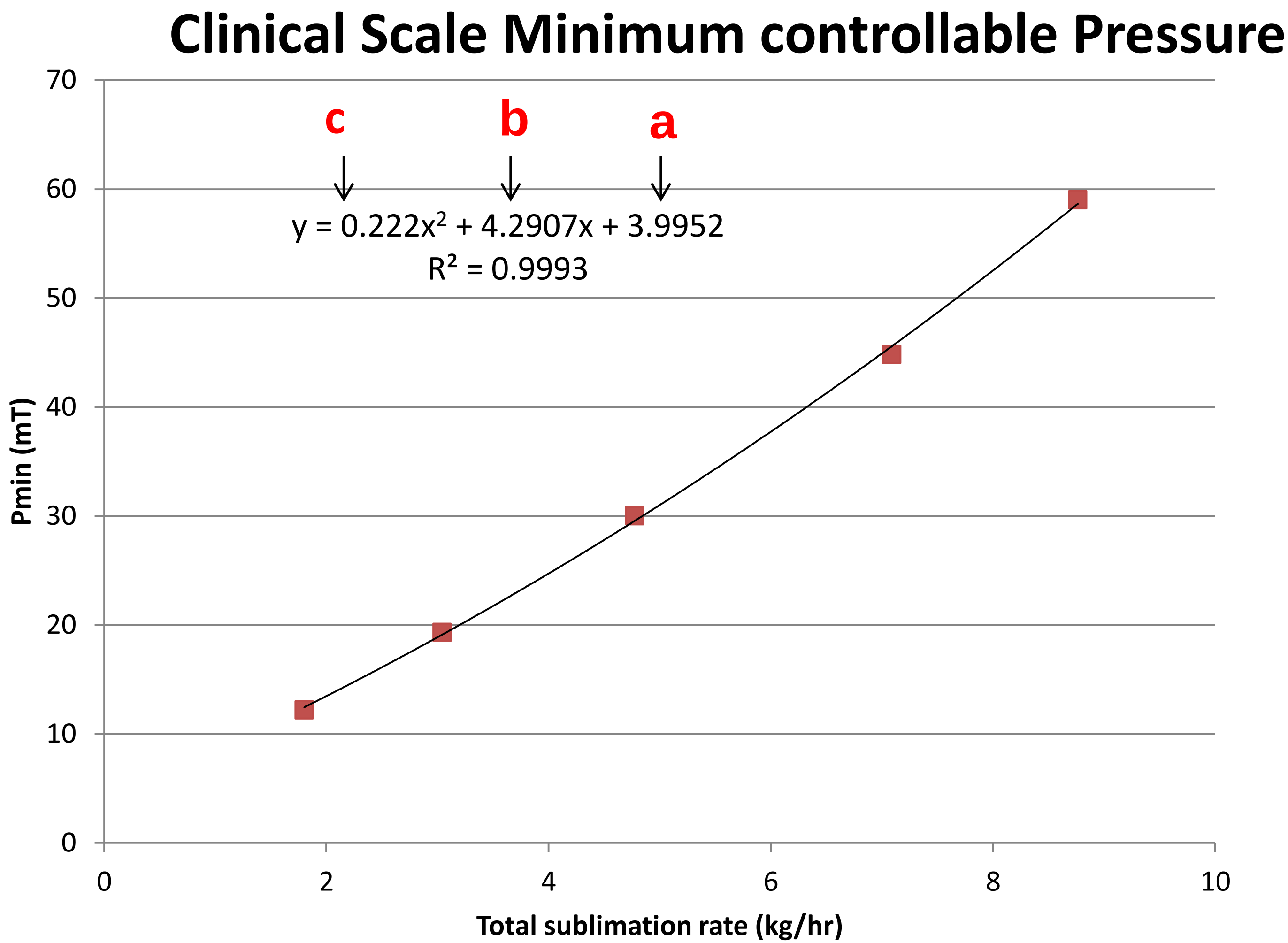
- Sublimation rate can be calculated over each time interval by:

$$\frac{dm}{dt}\left(\frac{kg}{hr * m^2}\right) = K_{cont} B (T_{shelf\_surface} - T_{ice\_bottom})$$

Where:

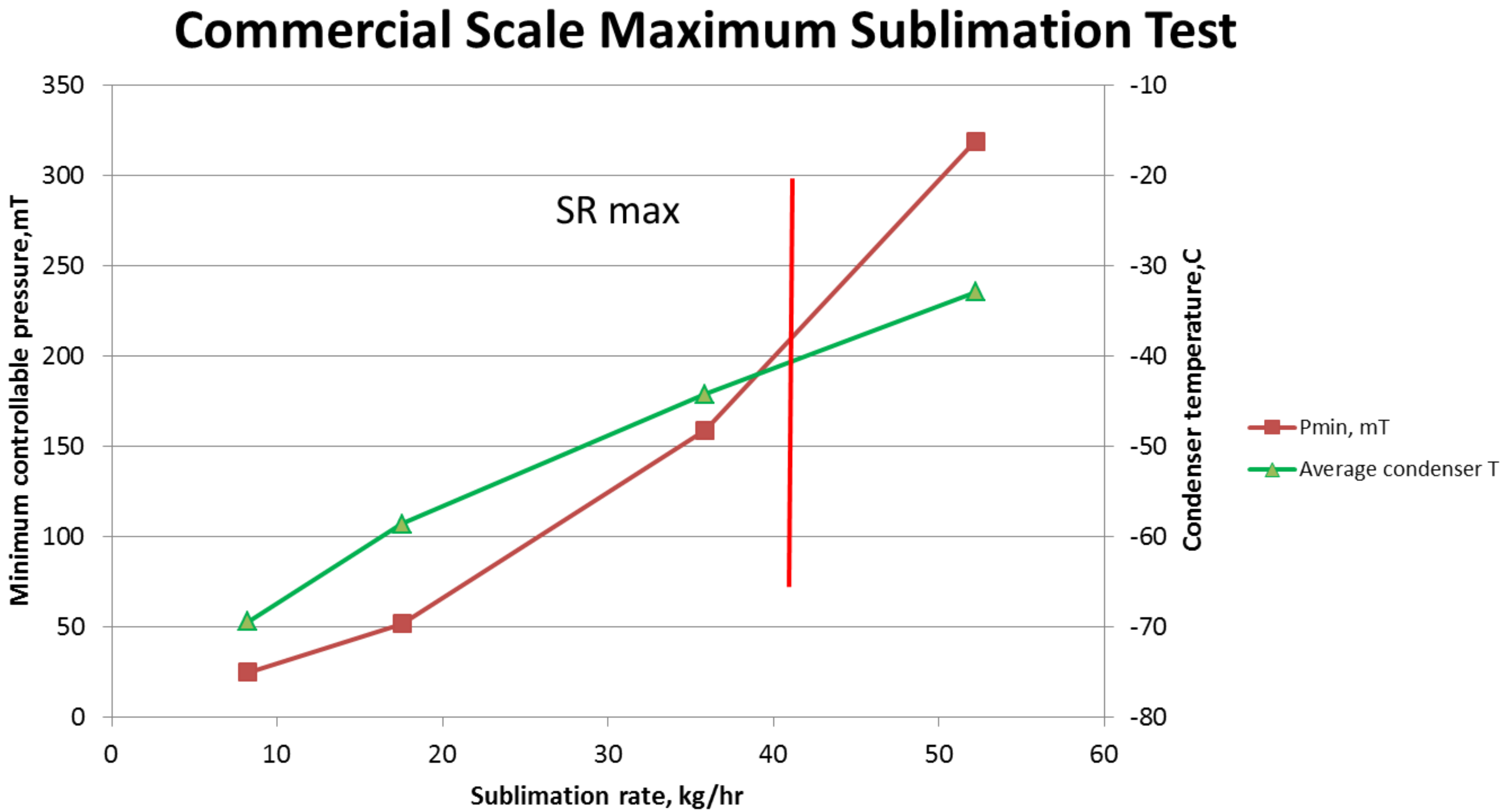
K_{cont} is the container heat transfer coefficient, Cal/s/cm^2/K;
B=53.25 is a unit conversion coefficient;
$T_{shelf\_surface}$ is the average temperature of the shelf surface, °C;
T_{ice_bottom} is the temperature of the ice at the bottom of tray, °C.

Minimum Controllable Pressure as a Function of Sublimation Rate



Coefficients a, b and c are inputs in the model for P_{min}

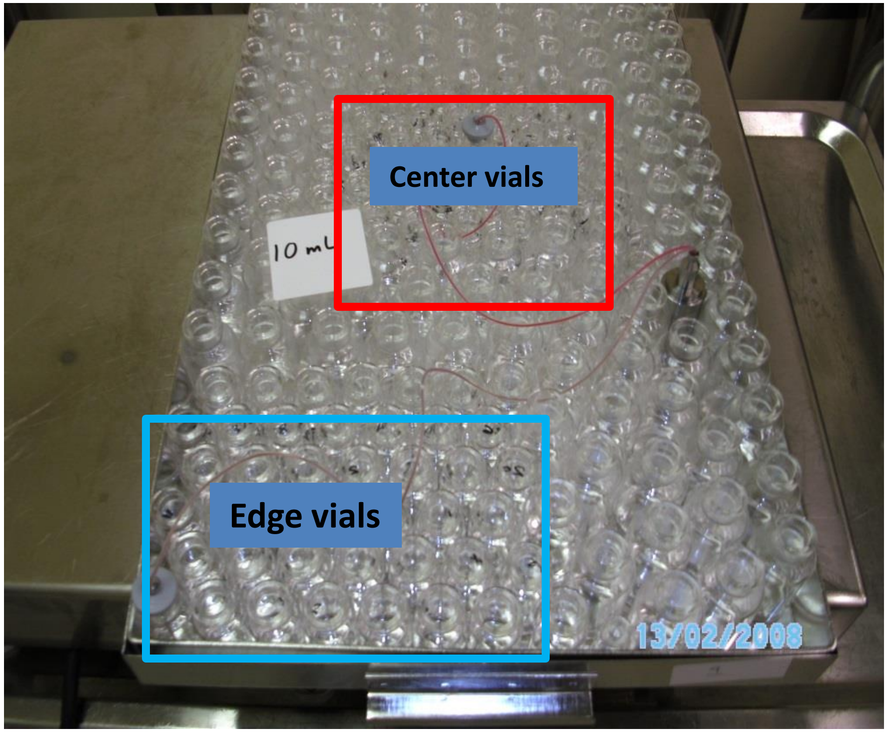
Maximum sublimation rate (Tcond>-40C)



Condenser temperature exceeded -40C at sublimation rate ~42 kg/hr
(number to enter as SR_{max} into model)

Vial Heat Transfer Coefficient Measurement

- Test calculates vial heat transfer coefficient at a single pressure
- Must perform multiple tests to determine heat transfer coefficient as a function of pressure
- Procedure:
  - Tare vials, add water to ~1 cm height, weigh
  - Set of vials at a front corner and a set of vials in the center
  - Use multiple vial sizes each run
  - Freeze, pull vacuum, ramp 1°C/min to 0ºC and desired pressure
  - Hold ~ 2 hr for 100 mT, adjust time for other pressures
  - Target 25% mass loss, end cycle
  - Weigh to determine mass loss
  - Calculate K_v ($dm/dt=K_vA\Delta T$)



Commercial Scale K_v: 680 Vials (x2)