# Fundamentals of Freeze Drying:
## A Brief Review and Commentary

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TECHNOLOGY
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# Why Do We Care?

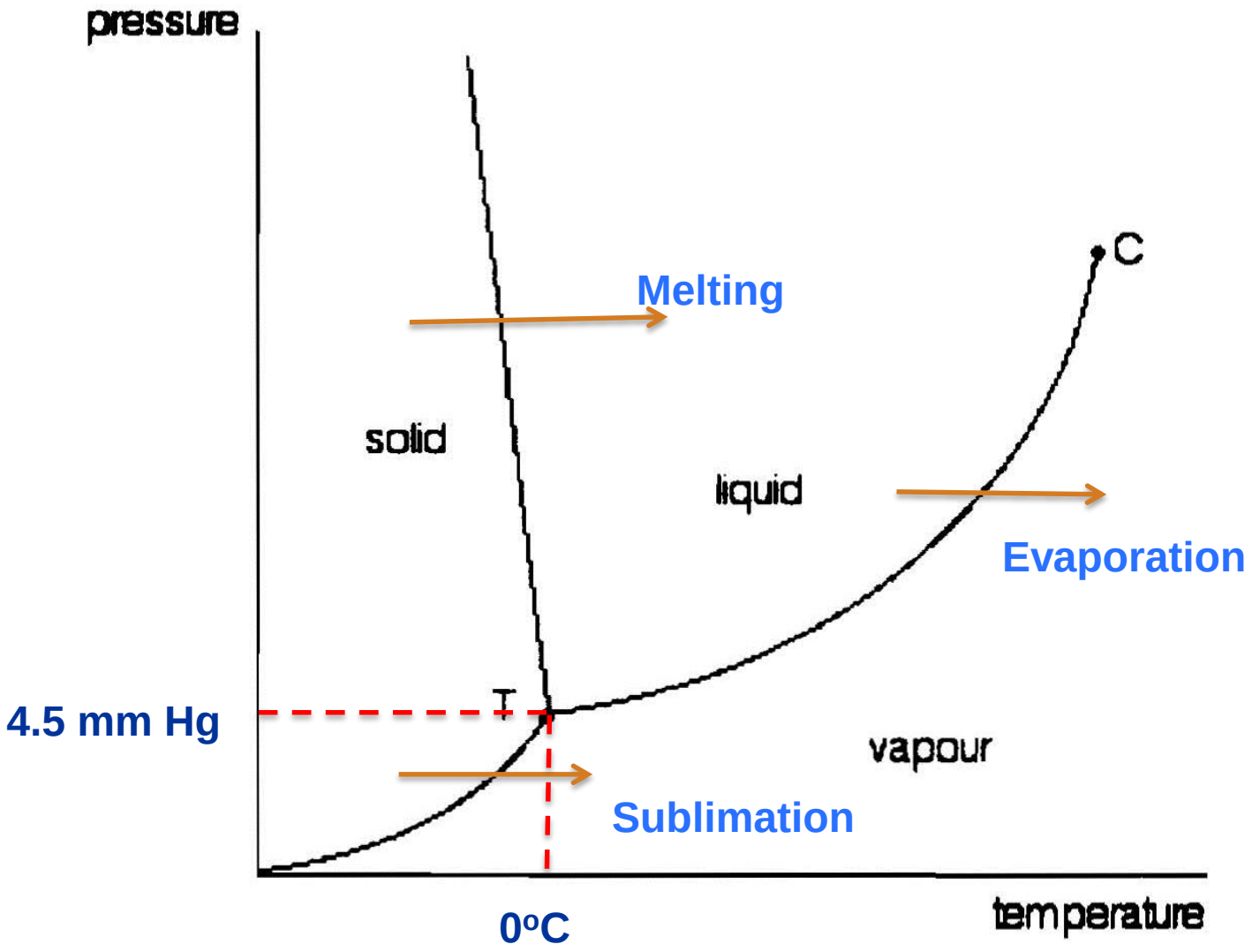
Large-molecule therapeutic agents, mostly proteins, represent a large, and growing, fraction of therapeutic agents under development. A significant percentage of these molecules (somewhere around half) are not stable enough in solution to allow a product presentation consisting of a ready-to-use solution.

According to 2016 sales data, of the five largest selling drug products in the world, four are therapeutic proteins and, of these four, two are available as a freeze-dried solid in a vial. This is a testament not only to the dominant role of proteins as therapeutic agents, but also to the critical nature of freeze drying in the manufacture of these drugs.

# Unit Operations in Manufacture of Injectable Drug Products

- Vial Washing/Sterilization
- Elastomeric Closure Processing (washing, siliconization, sterilization)
- Formulation
- Filtration
- Filling
- **Freeze Drying**
- Capping
- External Vial Wash?
- Inspection

# What is Freeze Drying?



# So. . .Why Do We Freeze-Dry ?

- **It allows removal of water at a low temperature, thereby avoiding the damage often caused by more conventional drying methods**
- It's compatible with aseptic operations
- Operationally, it's easier than, for example, filling a dry powder in a vial:
  - Fill weight uniformity
  - No dust control to deal with
    - Cross-contamination
    - Potential for operator exposure

# What's the Down Side of Freeze Drying?

- It's not as convenient to administer a freeze-dried injectable product as it is to administer a sterile, ready-to-use solution. Because of the additional transfer step, sterility assurance is probably not as high for a freeze-dried product.
- It takes a long time, it's very inefficient, and the equipment is expensive. This, of course adds to the cost of the product.
- The drug may not be stable as a freeze-dried solid.

**Comment: Alternatives to traditional freeze drying, such as aseptic spray freeze drying and continuous freeze drying, are well worth investigating. We (Baxter) choose to follow this type of technology development, but do not have an active development program.**

# Quality Attributes of Freeze Dried Injectable Products

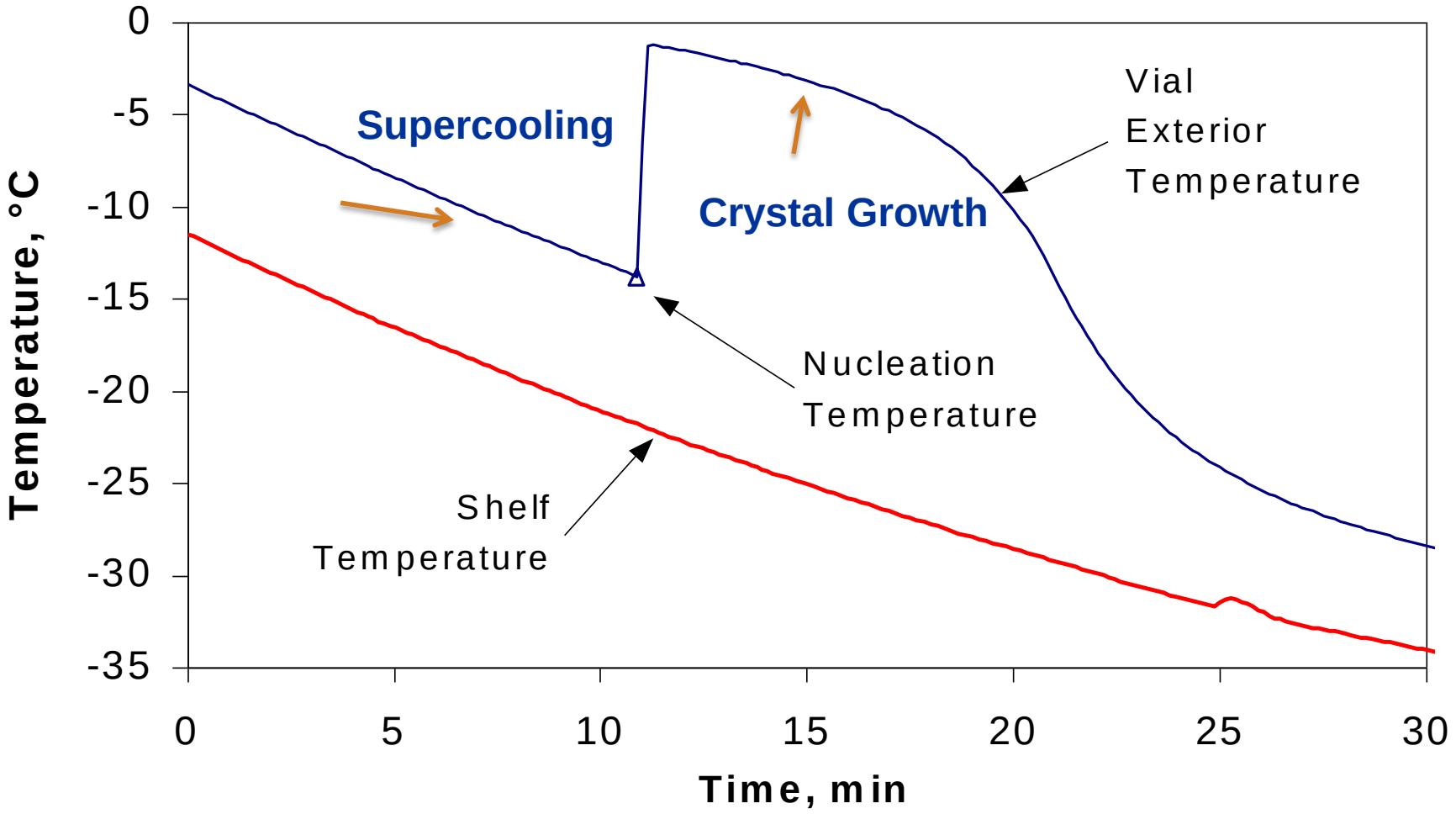
- Complete, or at least consistent, recovery of biological activity after reconstitution
- Sterile and with adequately low level of bacterial endotoxin
- Acceptable levels of subvisible particles
- Rapid, complete reconstitution
- Suitably stable at the anticipated storage conditions
- Adequately low level of residual moisture
- Appearance of the freeze dried solid – how much does it matter?

# Visual Attributes of Freeze Dried Products

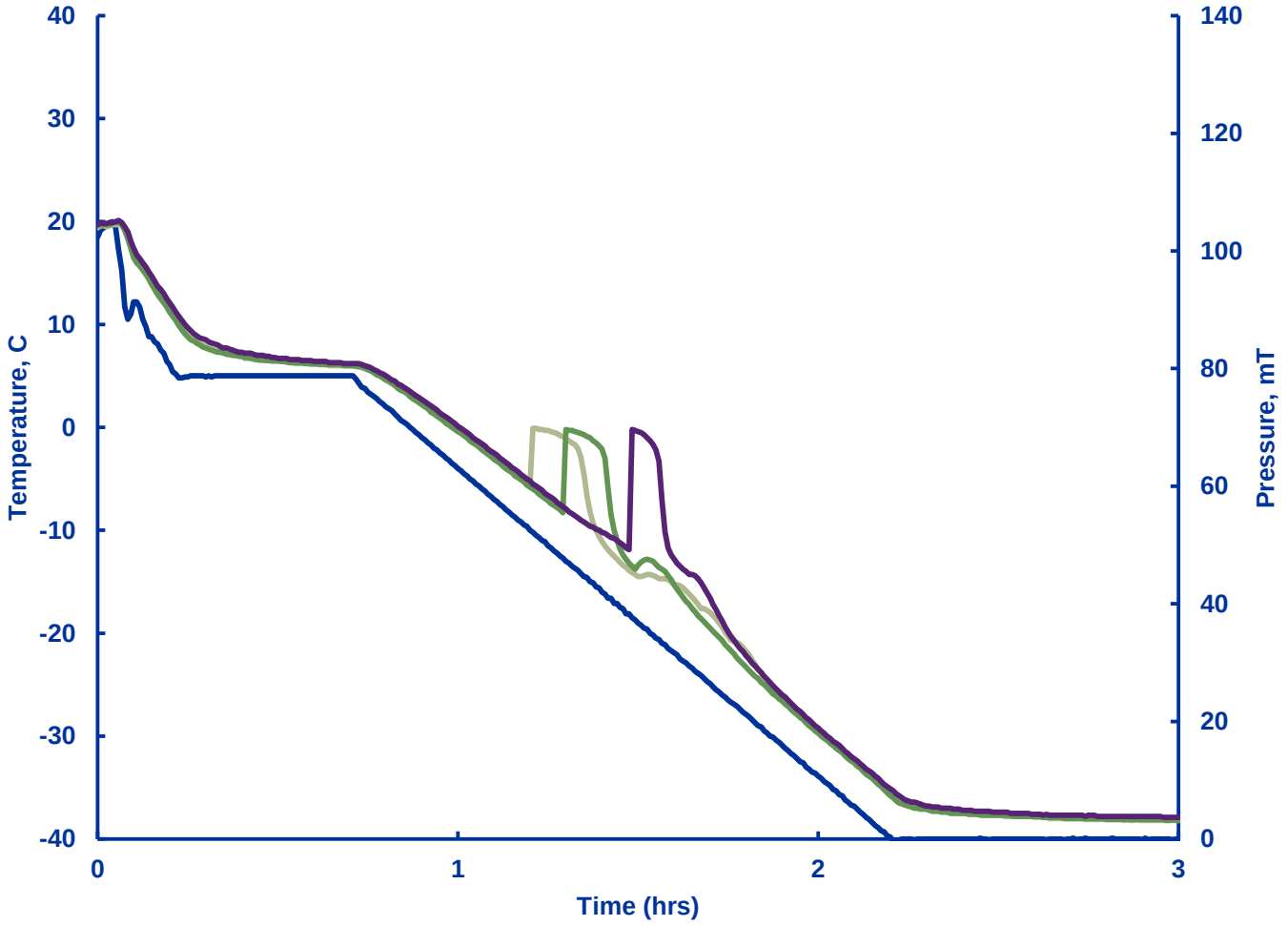
# A Closer Look at the Freeze-Dry Process

- Freezing
  - Solidify the contents of every vial
- Primary drying
  - Remove, by sublimation, the ice from the frozen matrix. This occurs by bulk flow from a region of higher pressure (the surface of the ice in the product vial) to a region of lower pressure (the chamber).
- Secondary drying
  - Remove the fraction of the water that didn't freeze. This occurs largely by diffusion – mass transfer by molecular motion from a region of higher concentration (the partly dried solid) to a region of lower concentration (the chamber).

# A Closer Look at the Freezing Process



# Freezing Process Data – A Stochastic Process

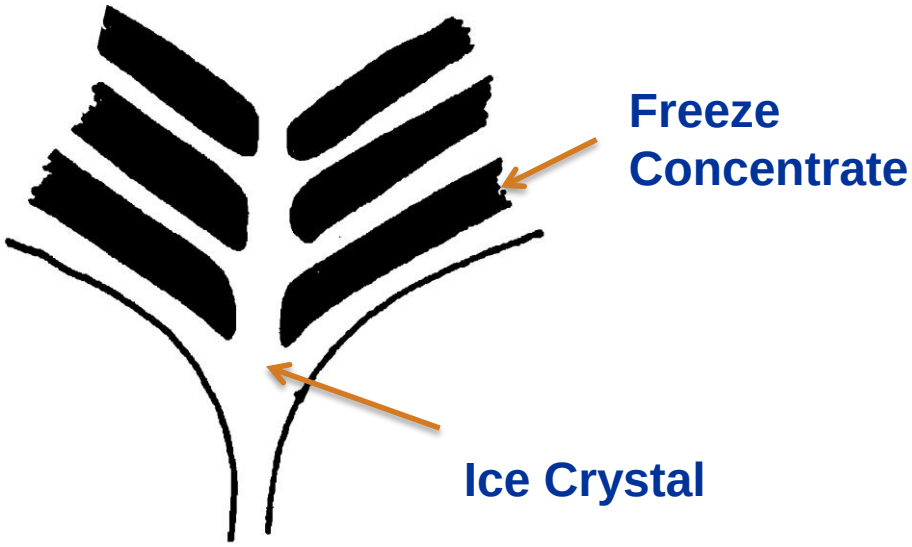


# Supercooling in Freeze-Drying

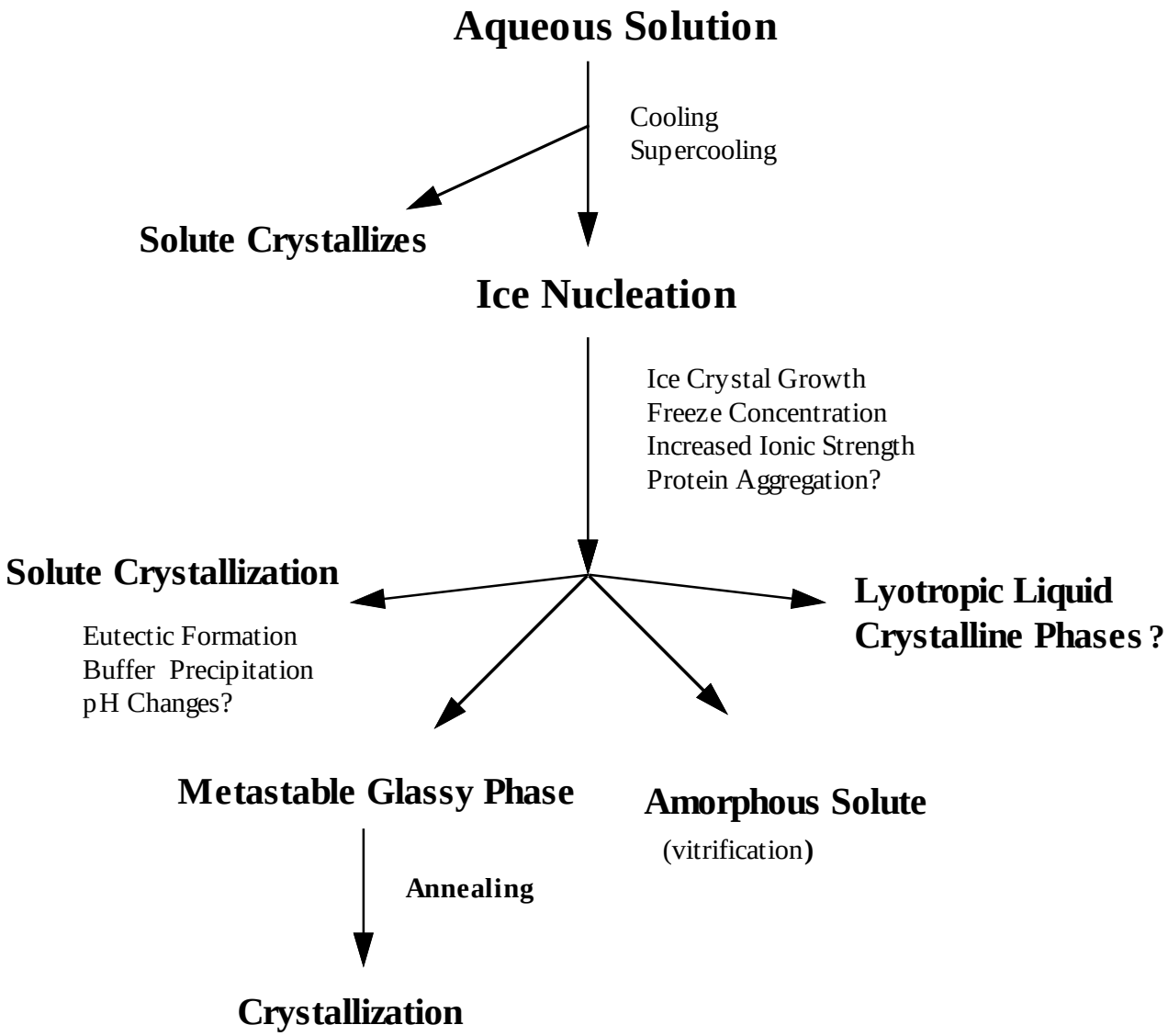
- Since we fill our product into clean, sterilized vials, and we sterile filter the formulation, there is relatively little “foreign” material to help nucleate the ice crystals, so we tend to get a **lot** of supercooling.
- Why do we care?
  - Because, the more the system supercools, the faster it freezes once we do get nucleation of ice crystals. Fast freezing generates small ice crystals, and slow freezing causes relatively large ice crystals. Small ice crystals leave behind small pores in the dried layer, and the small pores have a higher resistance to flow of water vapor than large pores. Thus variability in supercooling causes variability in the drying rate.
  - It’s a misperception that controlling the ramp rate of the shelf during freezing controls the freezing rate. Supercooling effects are more important

# Freeze Drying Behavior is Largely Determined by What Happens to the Freeze Concentrated Solute(s)

The freeze concentrate is just that – a concentrated solution of formulation components and unfrozen water

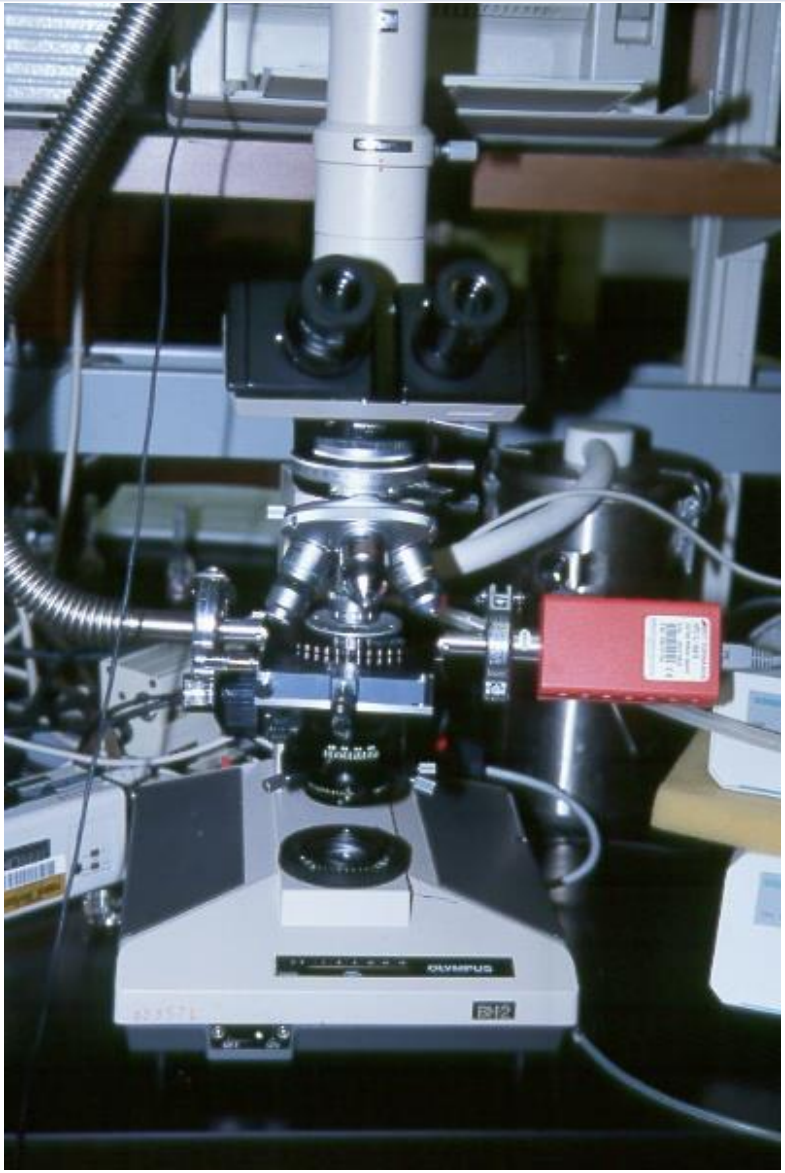


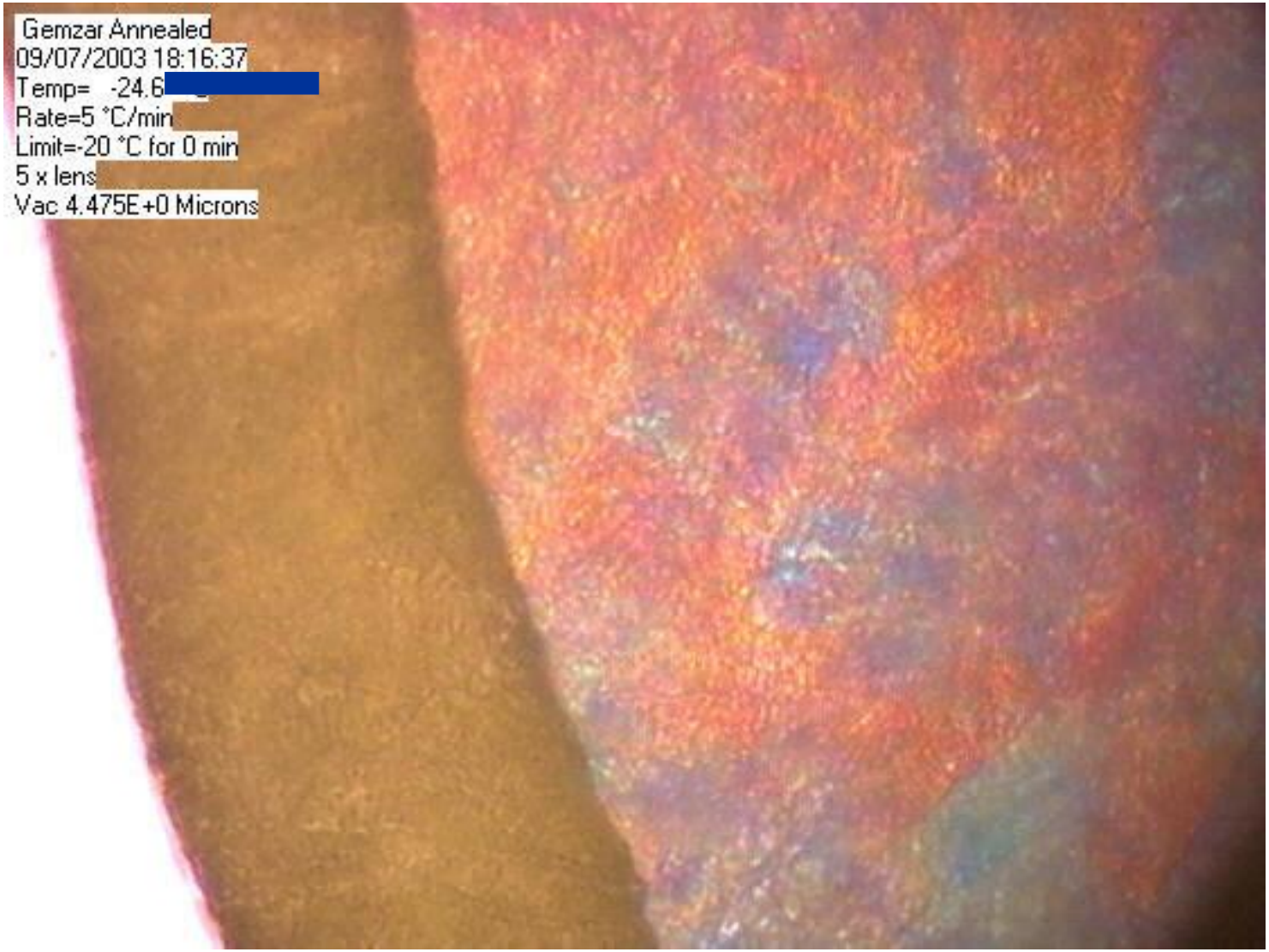
# What Happens to the Freeze Concentrate?



# Collapse in Freeze Drying

# Characterization of Freeze Drying Behavior – Freeze Dry Microscopy

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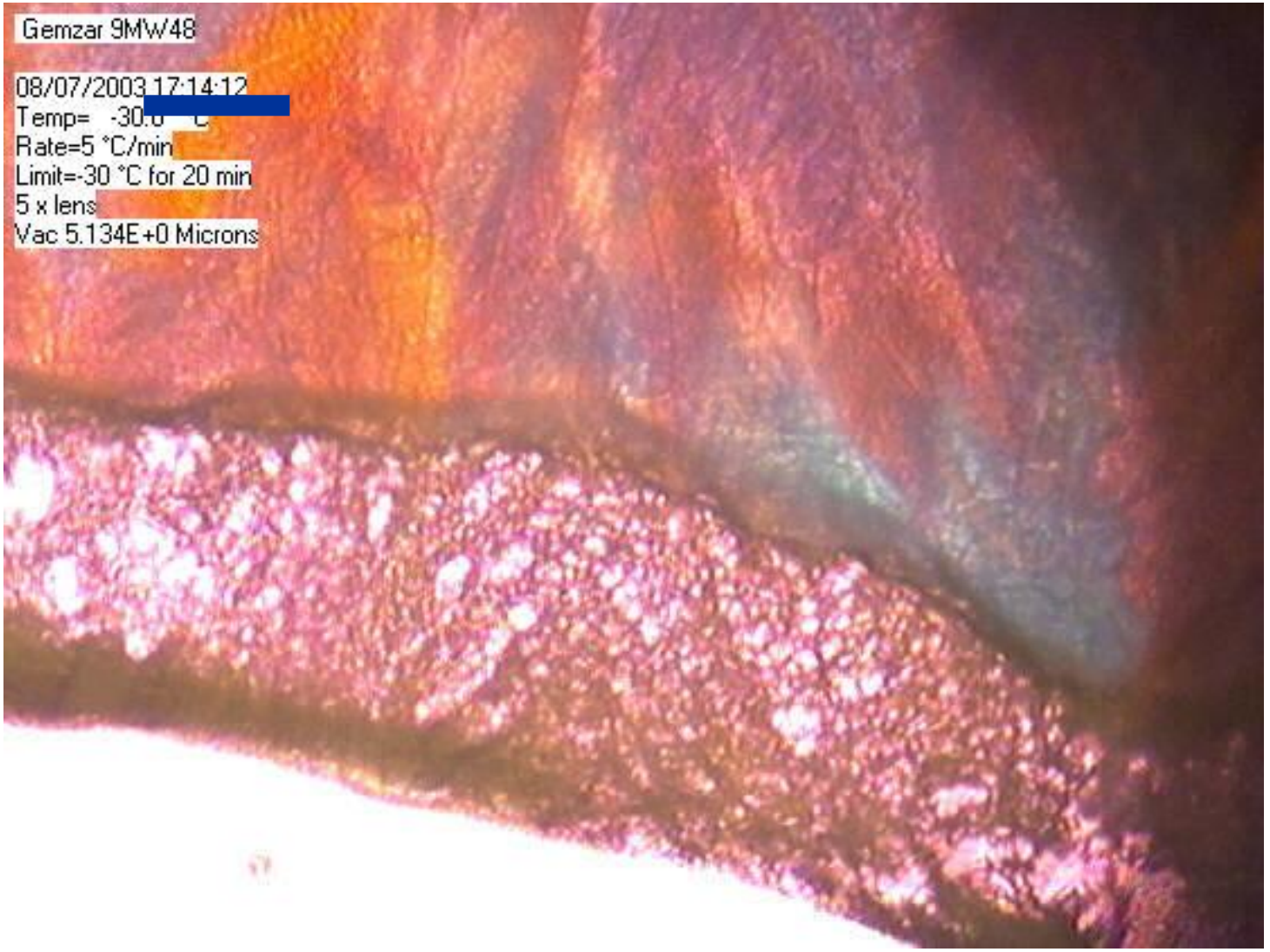
Vac 4.475E+0 Microns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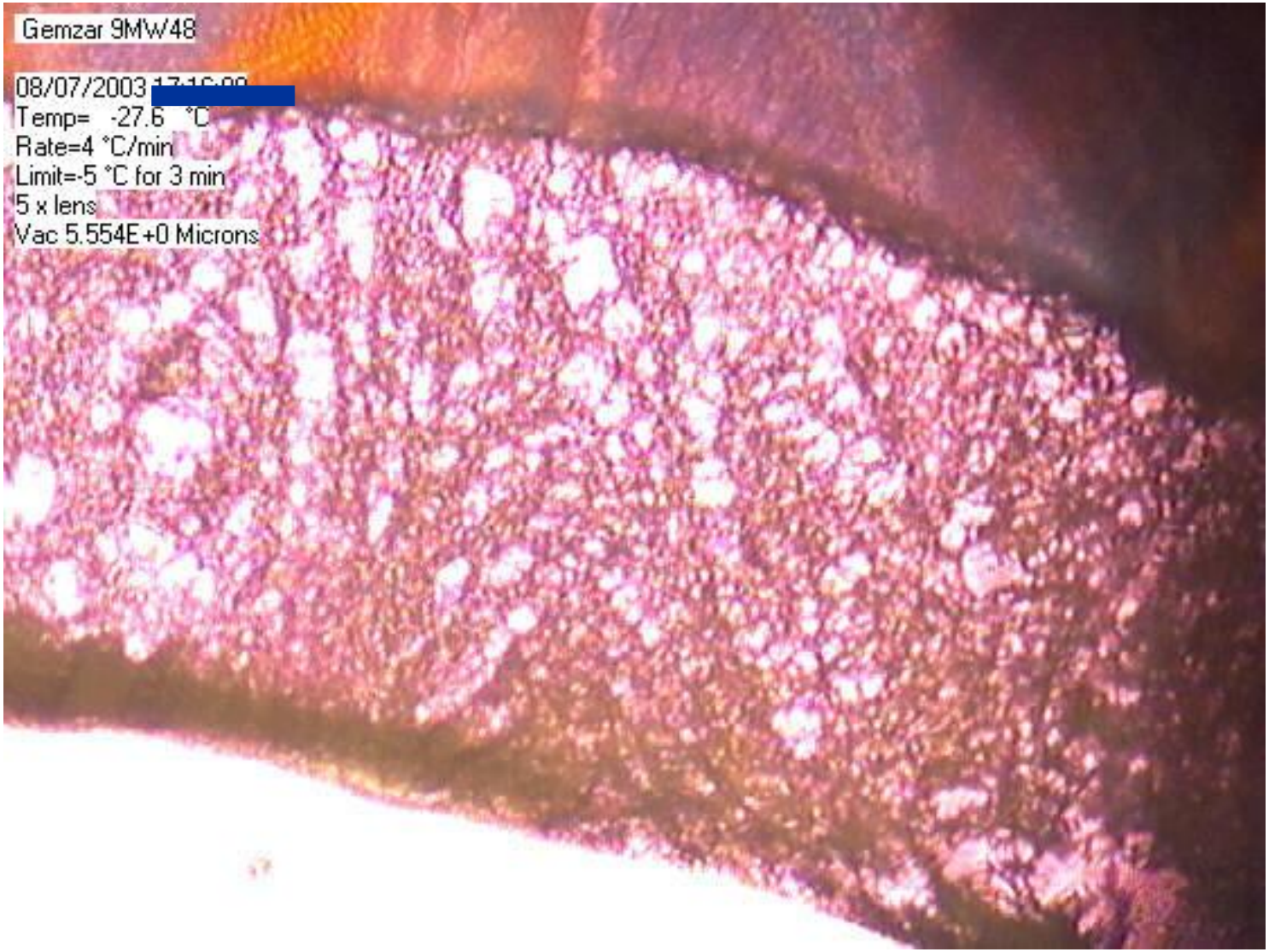
5 x lens
Vac 5.134E+0 Microns


Gemzar 9MW48
08/07/2003
Temp= -27.6 °C
Rate=4 °C/min
Limit=-5 °C for 3 min
5 x lens
Vac 5.554E+0 Microns

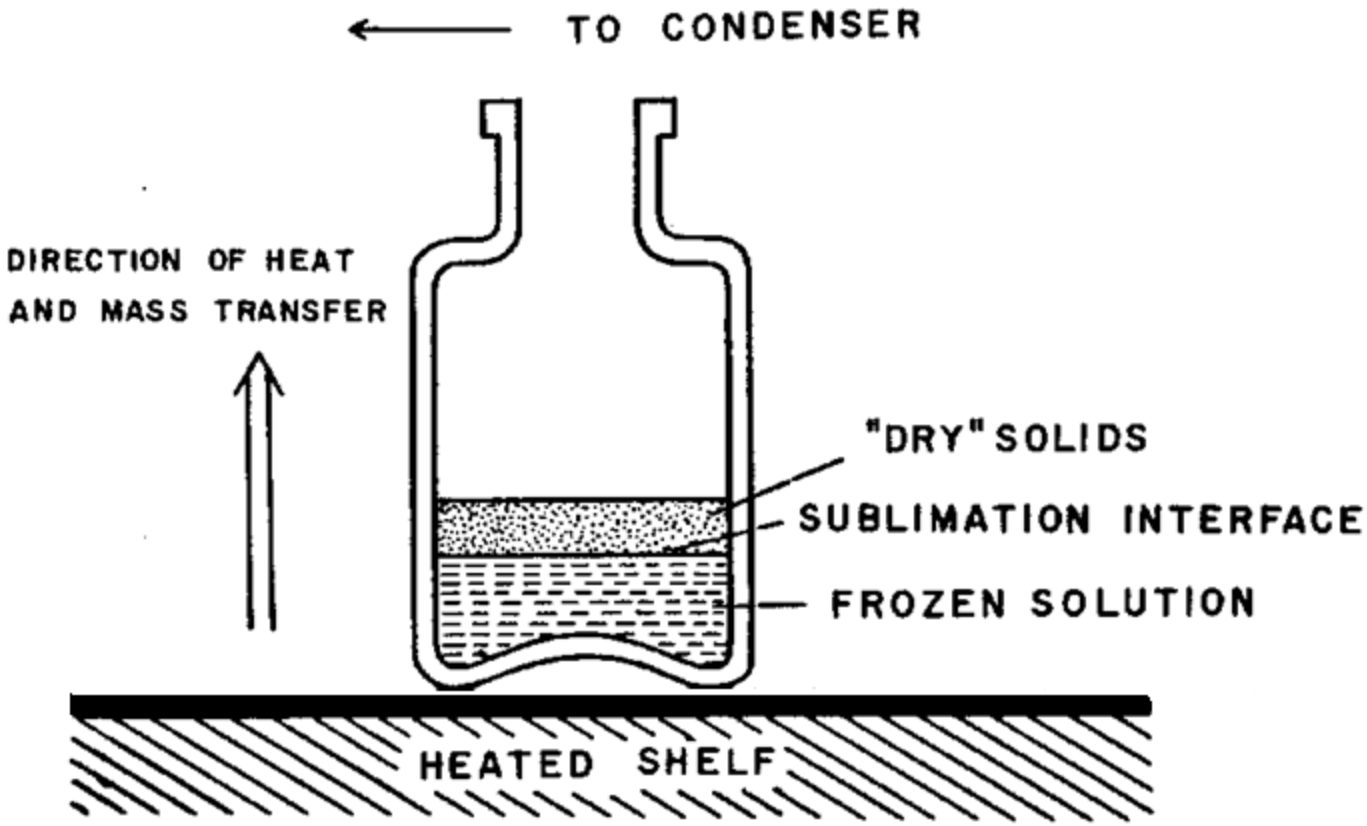
# Sources of Uncertainty in FD Microscopy

- It is often not clear what level of collapse, as observed by FDM, corresponds to collapse that can be observed in the vial of drug product
- Technology such as optical coherence tomography could allow more meaningful characterization by observing the formulation in a vial.

# Controlled Nucleation in Freeze Drying

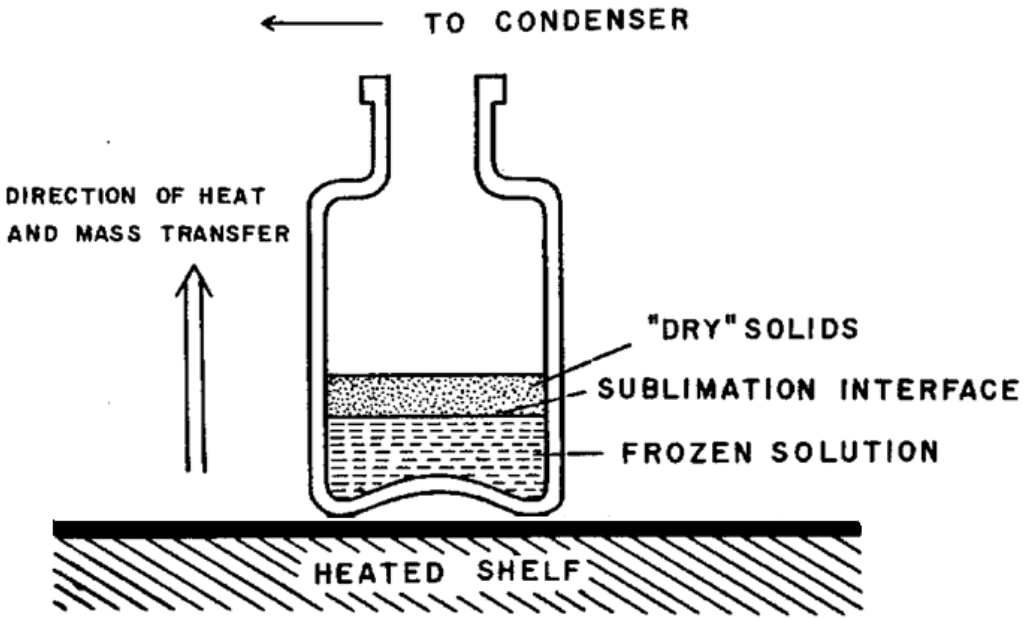
- **Rapid Depressurization (Praxair method)**
- **Ice Fog (IMA Life)**
- **Millrock method (uses condenser to generate ice fog)**

# Primary Drying: Removal of Ice by Direct Sublimation



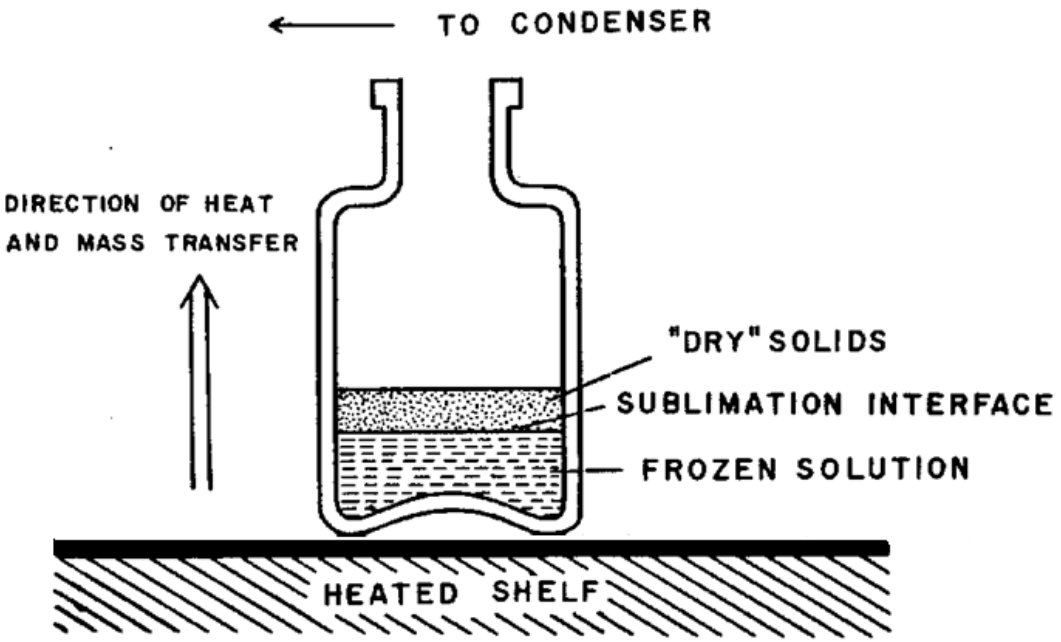

**The driving force for primary drying is the vapor pressure of ice. every 5°C increase in ice temperature increases the vapor pressure by about 75%!!**

# Primary Drying: Removal of Ice by Direct Sublimation




**There are two rate processes in primary drying: Heat transfer from shelf to sublimation front, and mass transfer from the sublimation front to the condenser. Heat transfer is very inefficient. Could we re-design the process for more efficient heat transfer?**

# Cycle Development: Why Do We Pay Particular Attention to Primary Drying?




Choosing process conditions for primary drying requires balancing two objectives: 1) Carry out the process at the highest practical product temperature, and 2) don't ruin the product by exceeding the critical temperature.

# Process Development for Primary Drying: What's the Objective?

- We want to develop process conditions that result in 1) a pharmaceutically acceptable product that 2) takes no longer than necessary and is 3) within the capability of the equipment.
- We know at this point that there is an upper product temperature limit that we cannot exceed without damaging the product. However, we don't control product temperature directly – we control the shelf temperature and the chamber pressure. The main question we have to address is **"What combination of shelf temperature and chamber pressure result in an appropriate product temperature profile?"**

# “Traditional” Approach to Freeze-Dry Cycle Development

- **Largely by trial and error: identify freeze-dry process conditions that produce an acceptable product.**
- **Establish “proven acceptable ranges” around shelf temperature and chamber pressure set points.**

# QbD Approach to Cycle Development

- **Identify optimal processing conditions based on a thorough understanding of the process, and *find the edges of failure.***
- **There are two edges of failure. One is associated with the product (usually the collapse temperature), and one is associated with the equipment.**
- **Any freeze dryer has a limit as to the sublimation rate that it will support. In order to optimize the process, we need to know what this is.**

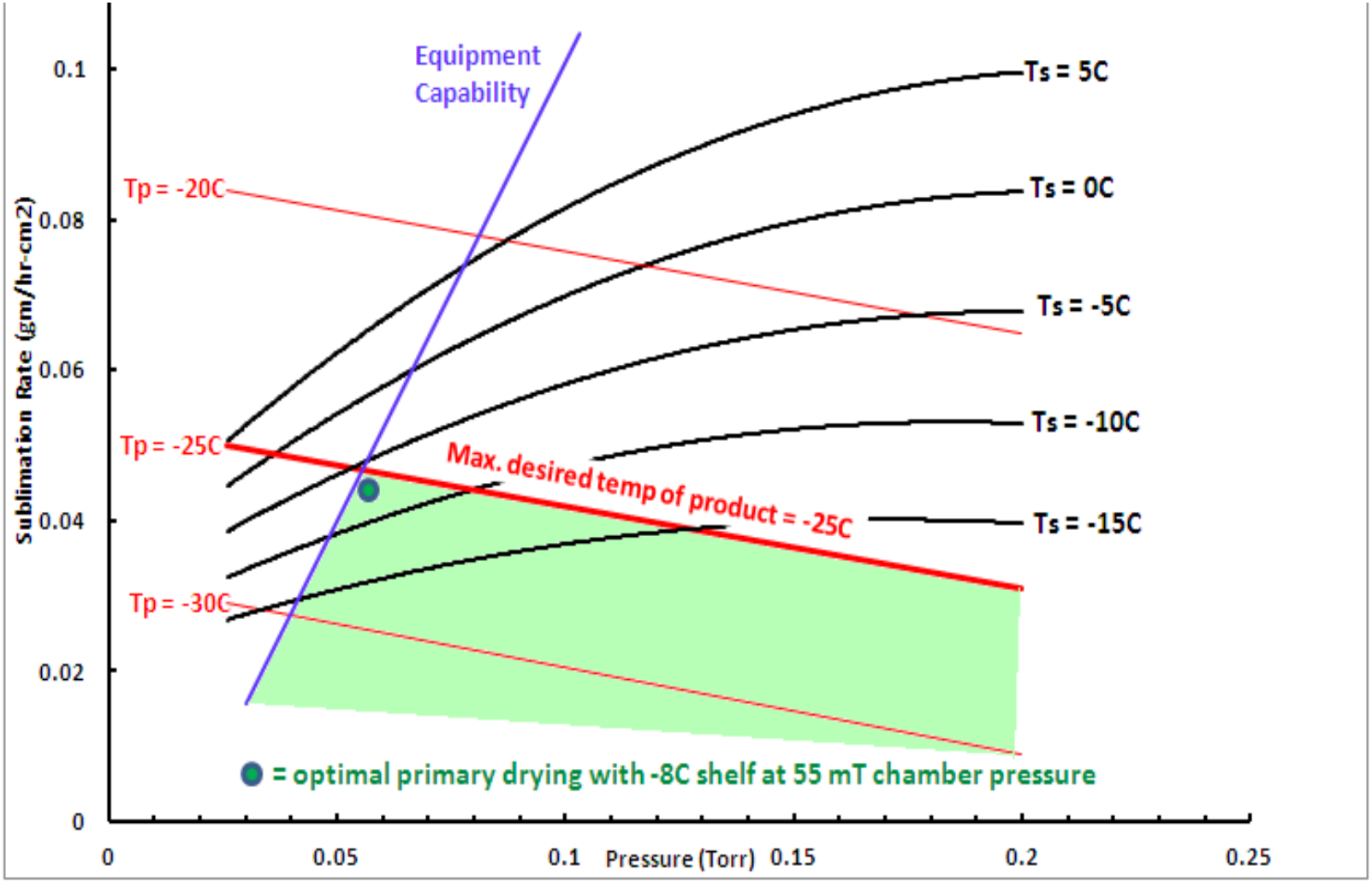
# Outline of Steps

- Characterize the formulation and identify the failure mode
  - Eutectic melting (“melt-back”)
  - Collapse
  - Powder ejection from the vial?
  - Others?
- Determine the upper product temperature limit during primary drying
  - Low temperature thermal analysis
  - Freeze dry microscopy

# Outline of Steps

- **Establish the relationship between the process variables you control (shelf temperature and chamber pressure) and the one you don't directly control (product temperature).**
  - **Measure the vial heat transfer coefficient, $K_v$, as a function of chamber pressure**
  - **Measure the resistance of the dried product layer, $R_p$, to flow of water vapor**

# The Graphical Design Space



# Limitations of This Approach

- It's based on batch average values for both the vial heat transfer coefficient and the dried layer resistance
- It assumes that the value of $R_p$ is constant across the design space.
- Demand for equipment capability is highest early in primary drying, but risk to product is greatest late in primary drying.

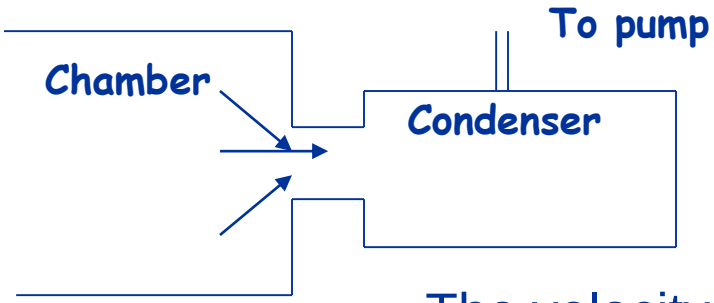
# Where Are We With The Graphical Design Space Approach?

- It's still a work in progress. As we continue to develop this approach, we need to:
  - Recognize that truly optimizing a cycle requires constantly changing the shelf temperature and the chamber pressure during primary drying – from high shelf temperature and chamber pressure early in primary drying to lower shelf temperature and chamber pressure as primary drying proceeds.
  - More rigorously account for sources of process variability, such as the position dependence of the vial heat transfer coefficient, as well as, perhaps vial-to-vial variability in $R_p$.
  - Develop a much better understanding of equipment capability of manufacturing scale freeze dryers.

# The Equipment Capability Curve

- Any freeze dryer has a limit to the sublimation rate that it will handle. It is very important to understand equipment capability, both at the laboratory and the production scale
- Factors that can limit performance
  - Refrigeration capacity
  - Condenser surface area
  - Upper limit of shelf temperature
  - Dynamics of vapor flow from chamber to condenser

# Dynamics of Vapor Flow as a Limiting Factor in Equipment Capability

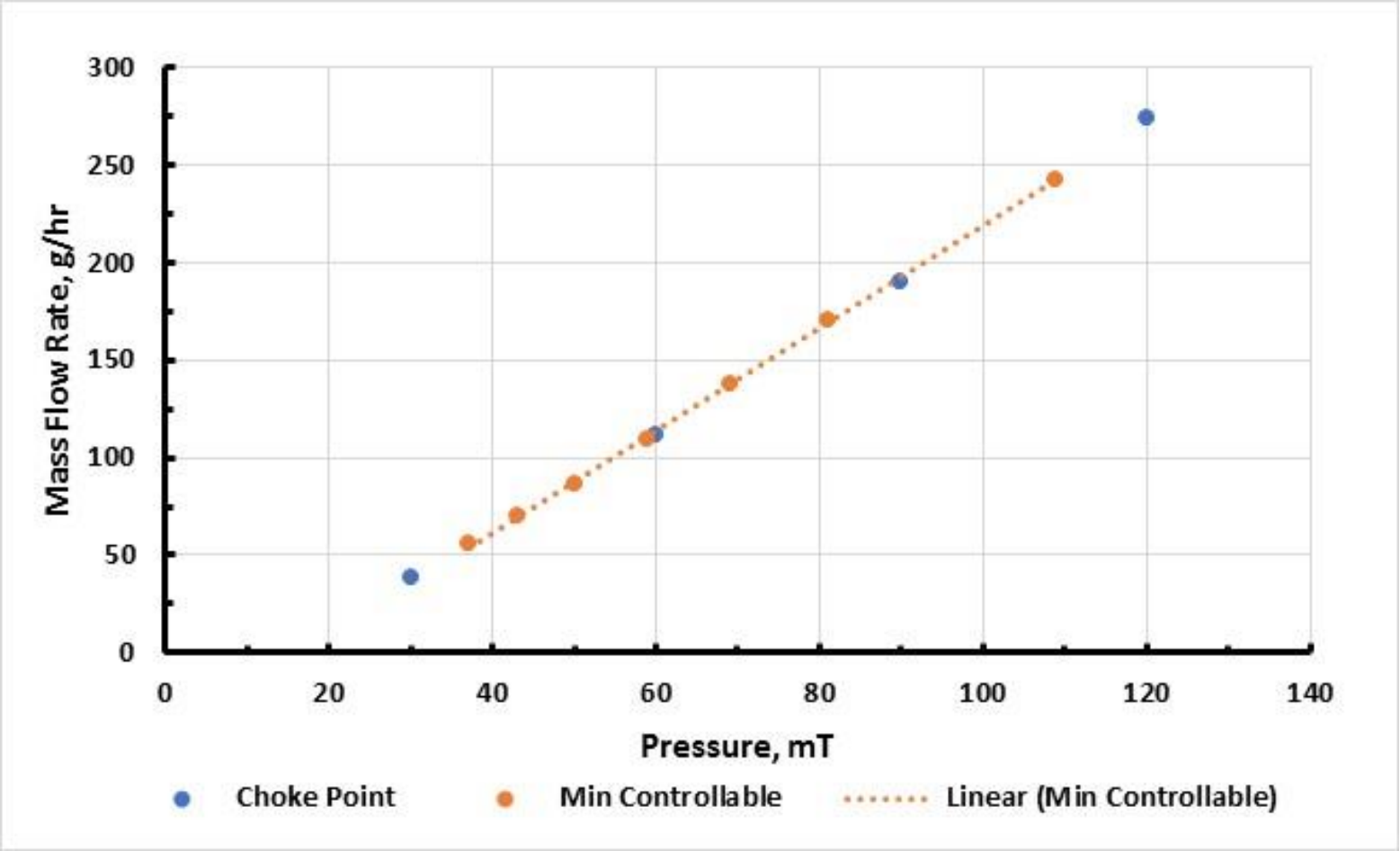



The velocity of vapor through the “throat” of the system is limited by the speed of sound in that vapor stream. This Is called “choked flow.”

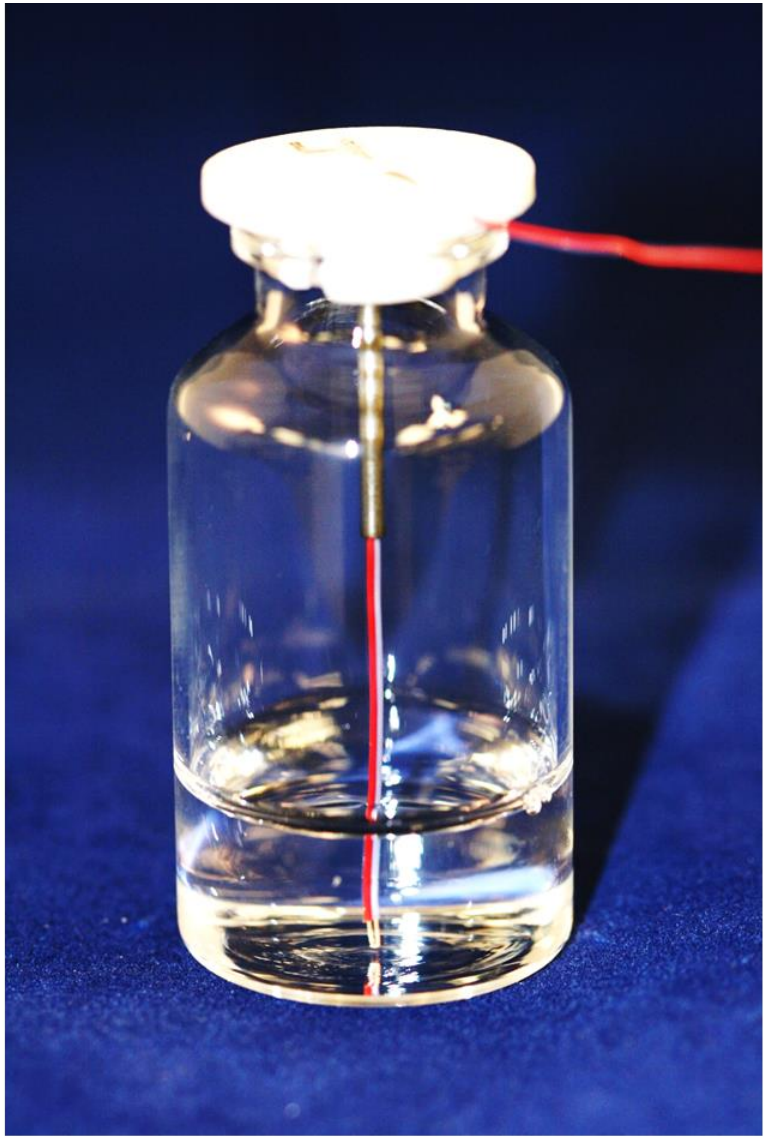
# Measuring the Equipment Capability Curve

- Two methods can be used.  Both are done with ice slabs covering the entire shelf area

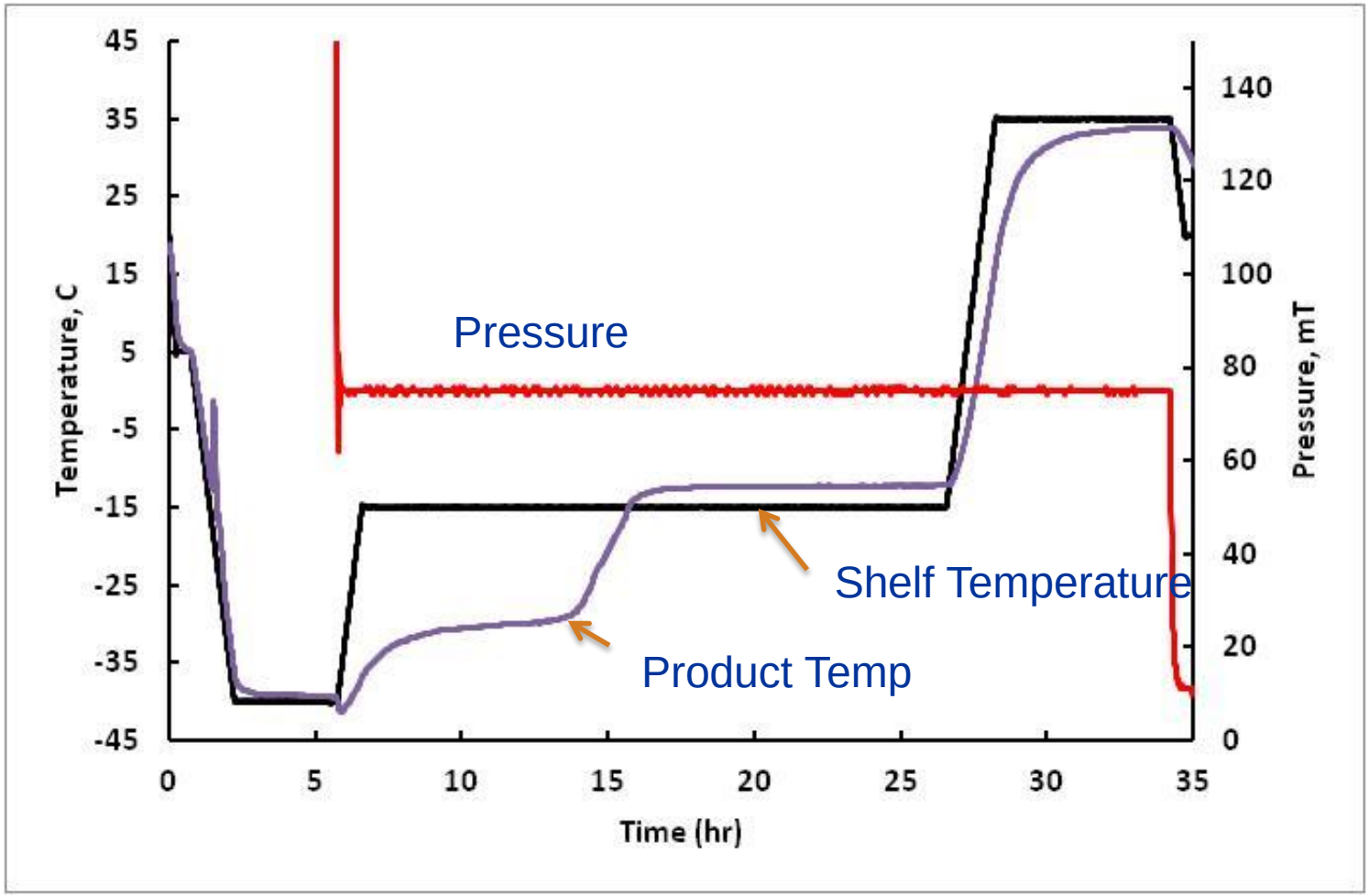
# Both Methods Give the Same Result



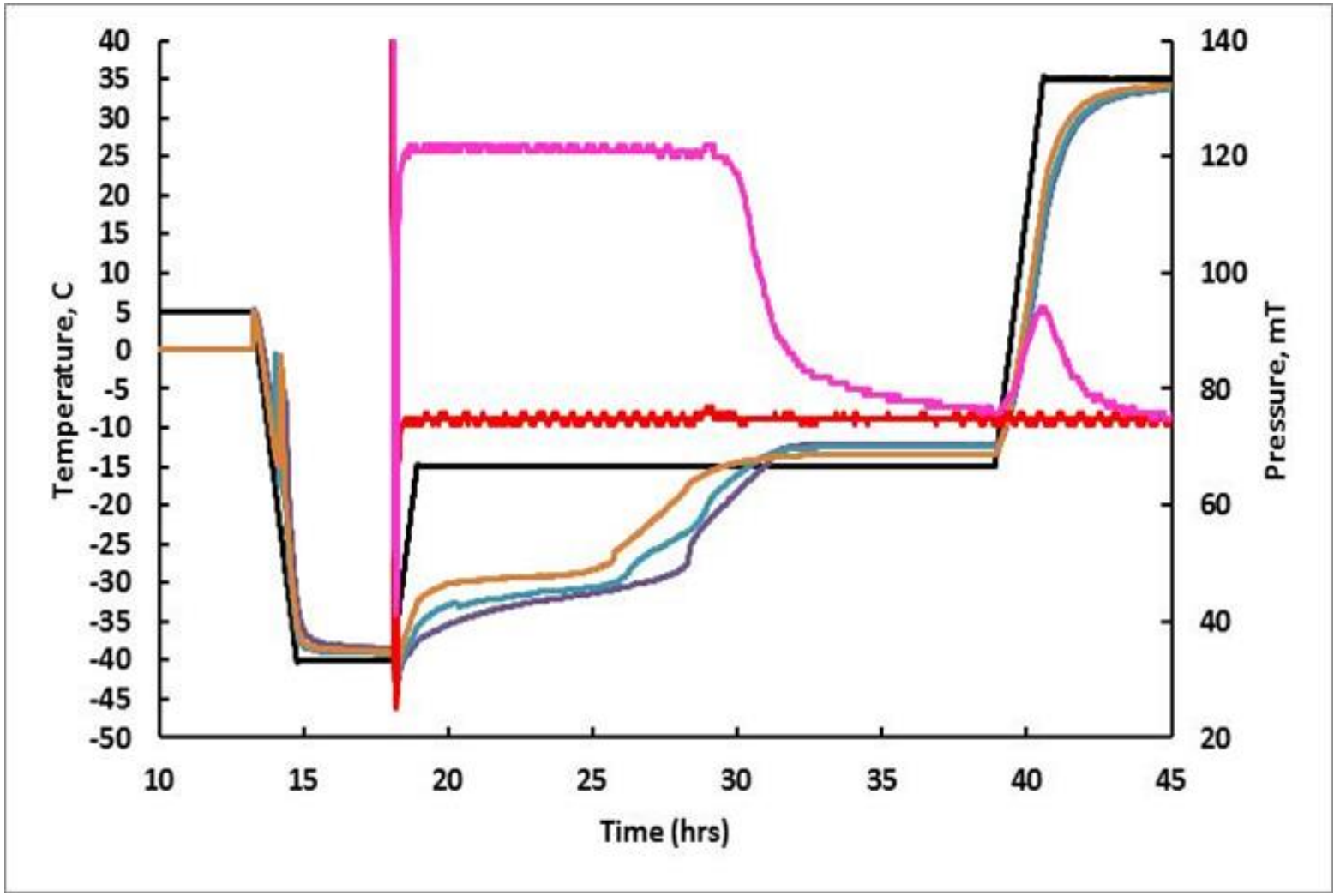
# Product Temperature Measurement in Development Lab



# Review of a Representative Process Data Chart



# Secondary Drying



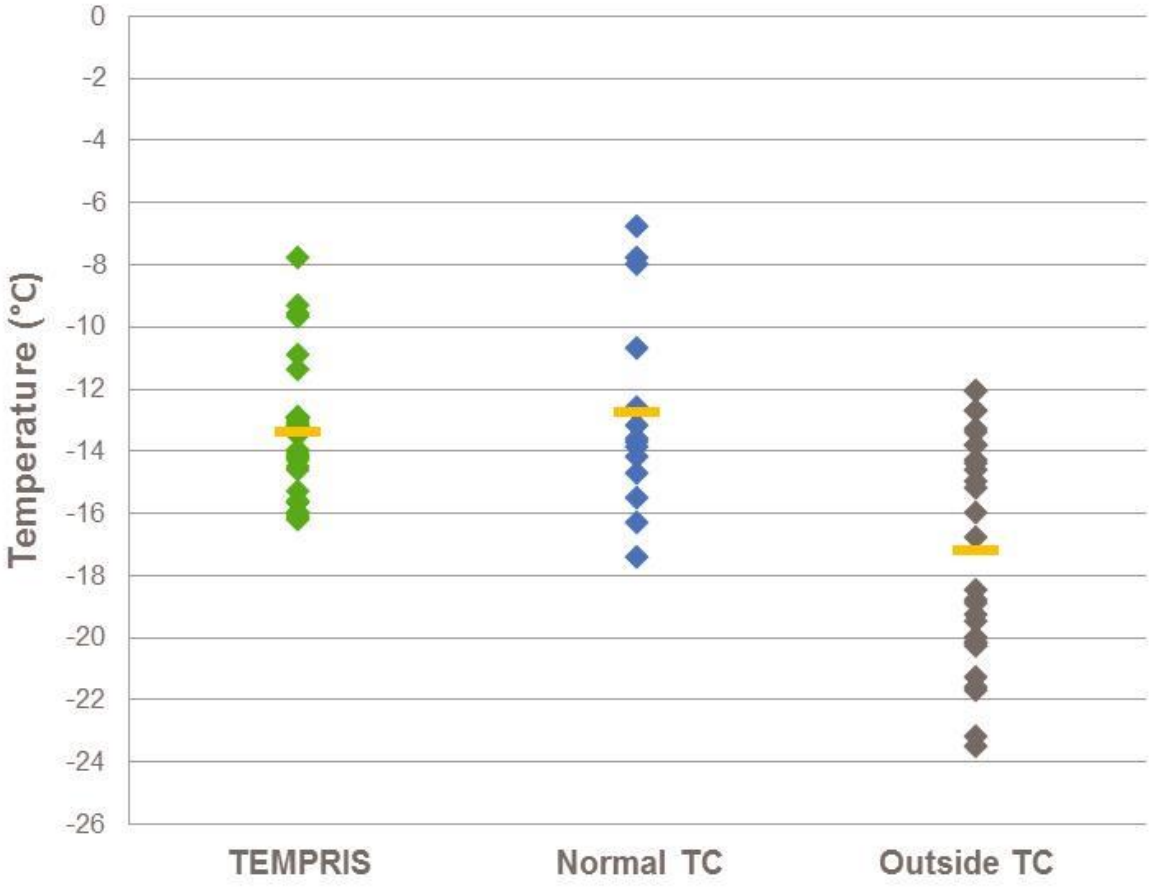
# Why Do We Care About Product Temperature Measurement?

- Product temperature is the process variable that has the greatest potential impact on product quality (yet we don't control it directly).
- Needed for laboratory scale development work
- Can be very useful at manufacturing scale for:
  - Scale-up studies
  - Validation
  - Transfers between manufacturing sites
  - Monitoring of routine production batches?

# Disadvantages of All Product Temperature Measurement Methods

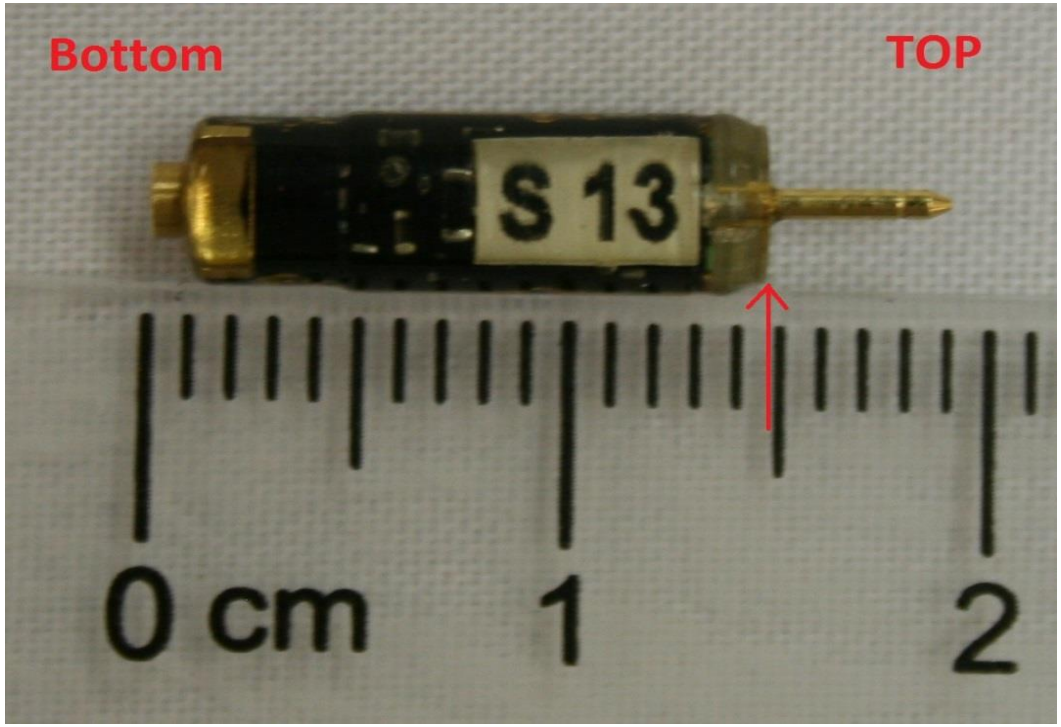
- Monitored vials are biased
  - supercool less
  - freeze slower
  - have larger average ice crystal size
  - freeze-dry faster than rest of batch (on average, about 10%)
- Must have a way of dealing with “bad” data
- Not compatible with automated material handling systems
- Compromise asepsis

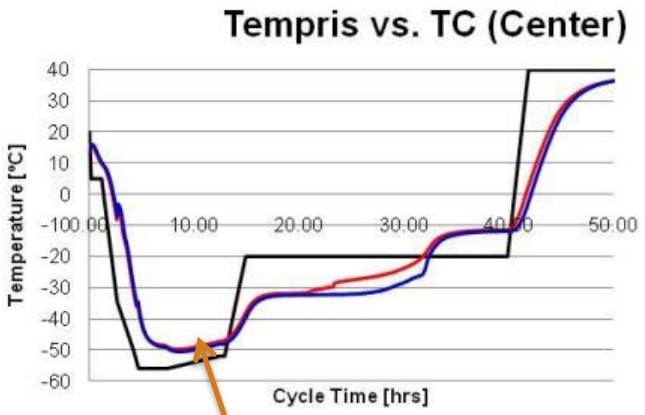
# Influence of a Temperature Sensor on Ice Nucleation Temperature



# Wireless Sensor in a Production Environment

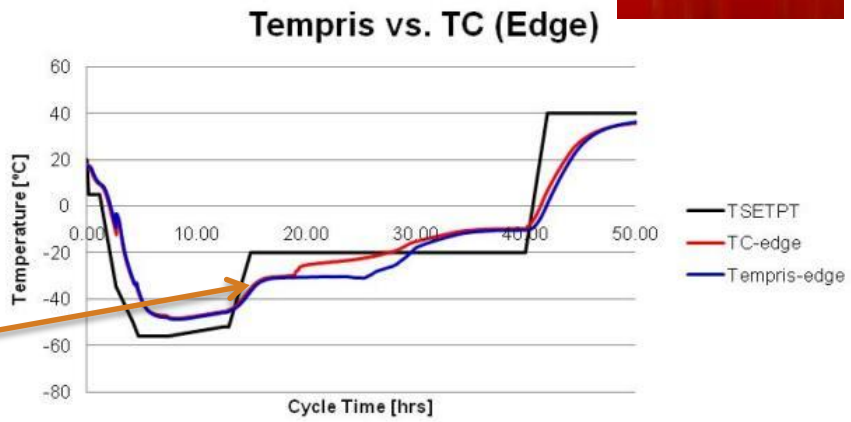
# Close-Up of Sensor





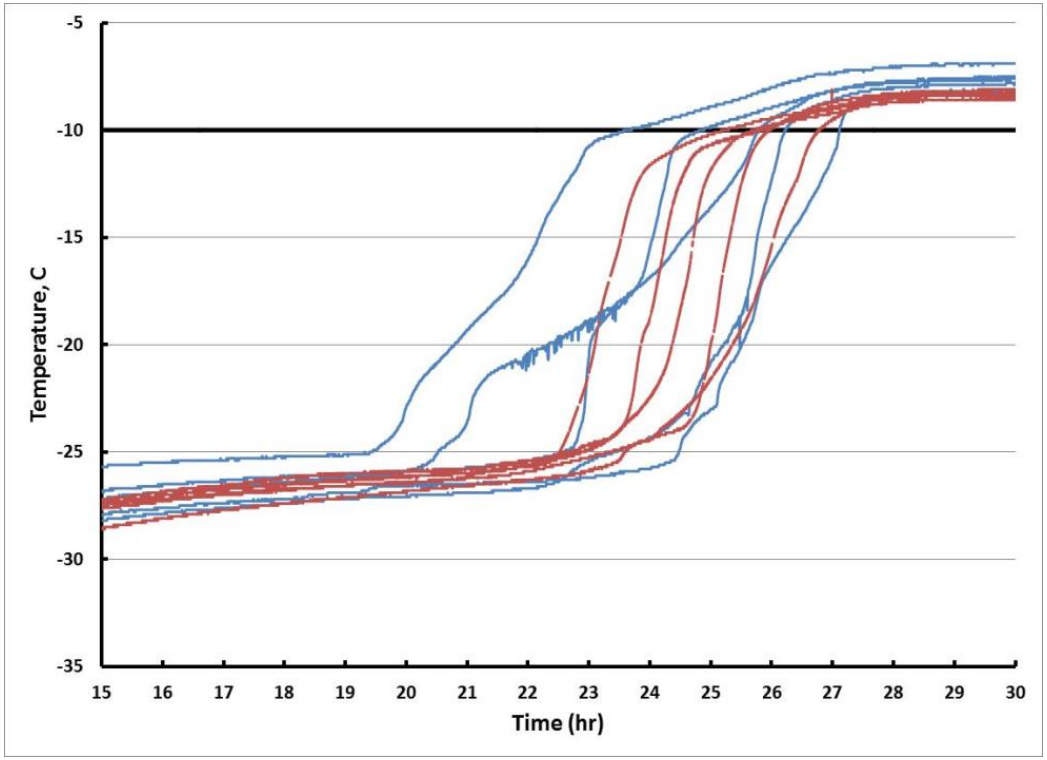

Very good overlay for SD

Excellent overlay for freezing



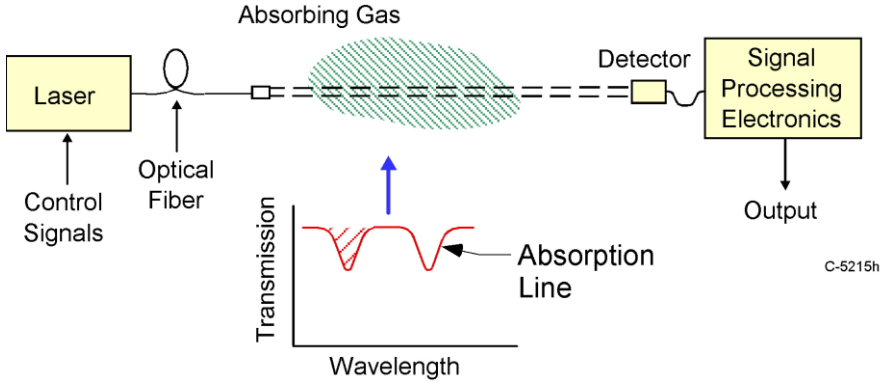

Excellent overlay for PD until TC loses contact with ice

# Process Data – Tempris vs. Thermocouples

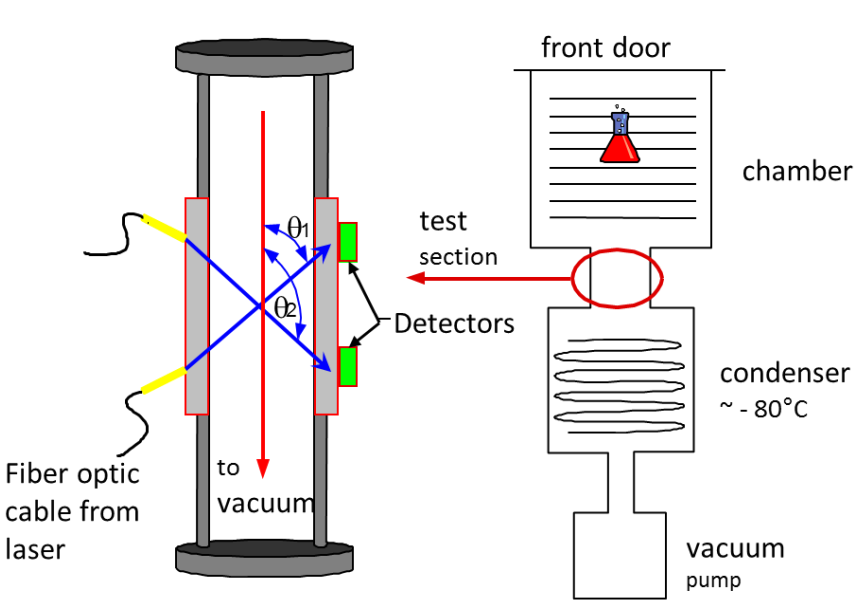


# Tunable Diode Laser Absorption Spectroscopy (TDLAS) Mass Flux Measurements

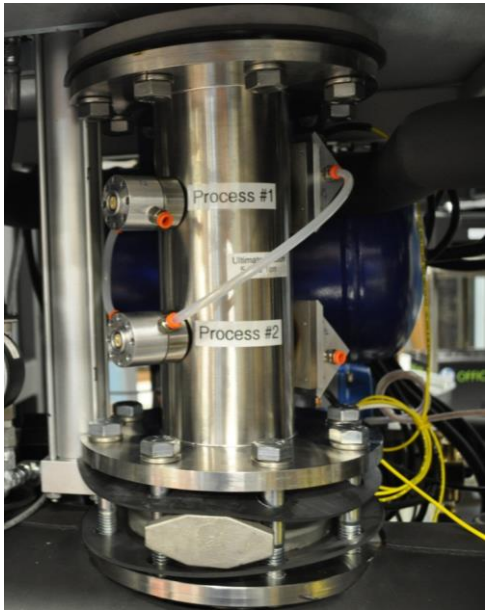
- Optically measure water vapor concentration
- Optically measure gas velocity
- Use the concentration and velocity measurements to determine the water vapor removal rate from the product vials (grams/second)
- Integrate the water removal rate during the process to predict the total amount of water removed (mass balance)




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

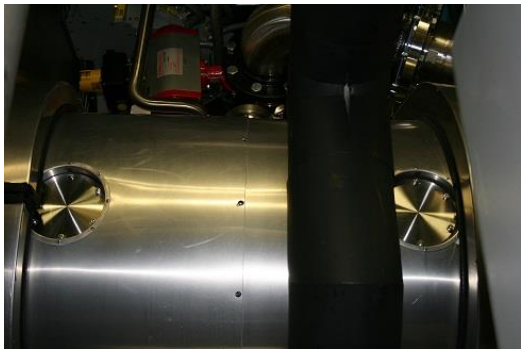


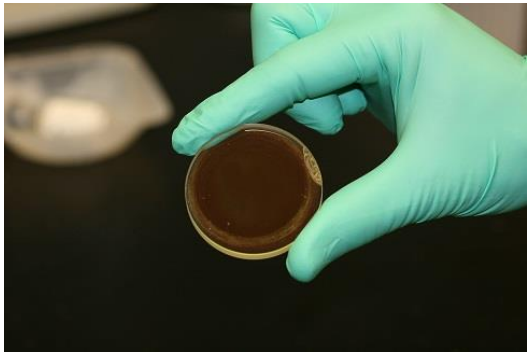

LyoFlux 100 Optical Spool

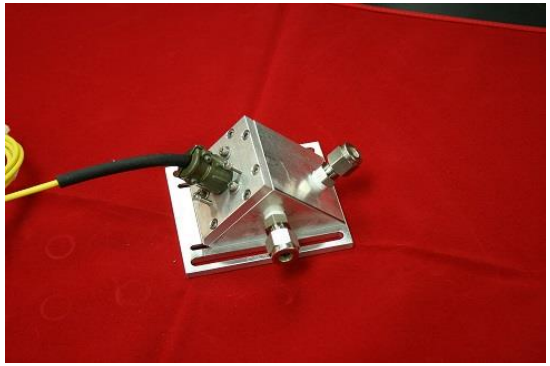



LyoFlux 200 Optical Spool
Installed in a Lyostar III lyophilizer

# TDLAS at Manufacturing Scale







# Application of TDLAS in Pharm. Development

- Measurement of vial heat transfer coefficient
- Measurement of resistance of dry product layer to flow of water vapor
- Measurement of equipment capability
- Construction of a primary drying design space.

# Application of TDLAS in a Manufacturing Environment

- It’s still developing.
- Quantitative accuracy at production scale is still questionable
- Robustness of instrumentation can be an issue
- To date, there does not seem to be a critical mass of interest.
- TDLAS does have the potential to provide batch average product temperature without the need to put any probes in vials.

# Formulation Considerations for Therapeutic Proteins

- What makes freeze drying of proteins special?
  - Both the short-term and long-term stability can be affected significantly influenced by seemingly small changes in the composition of the formulation.
  - Concentration of the protein in the formulation can significantly influence stability.
  - Integrity of the drug product, particularly stability, can be influenced by differences in the thermal history of freezing.
  - For small molecules, dryer is generally better in terms of product stability.  This isn't always the case with proteins.