

# Outsourcing Lyophilized Products

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1

# Overview

- Involve your contractor in development.
- Minimize financial and critical timing risks.
- Three Example Studies:
  - If your Project Manager is named Murphy?
- Settle contractual issues before you start.

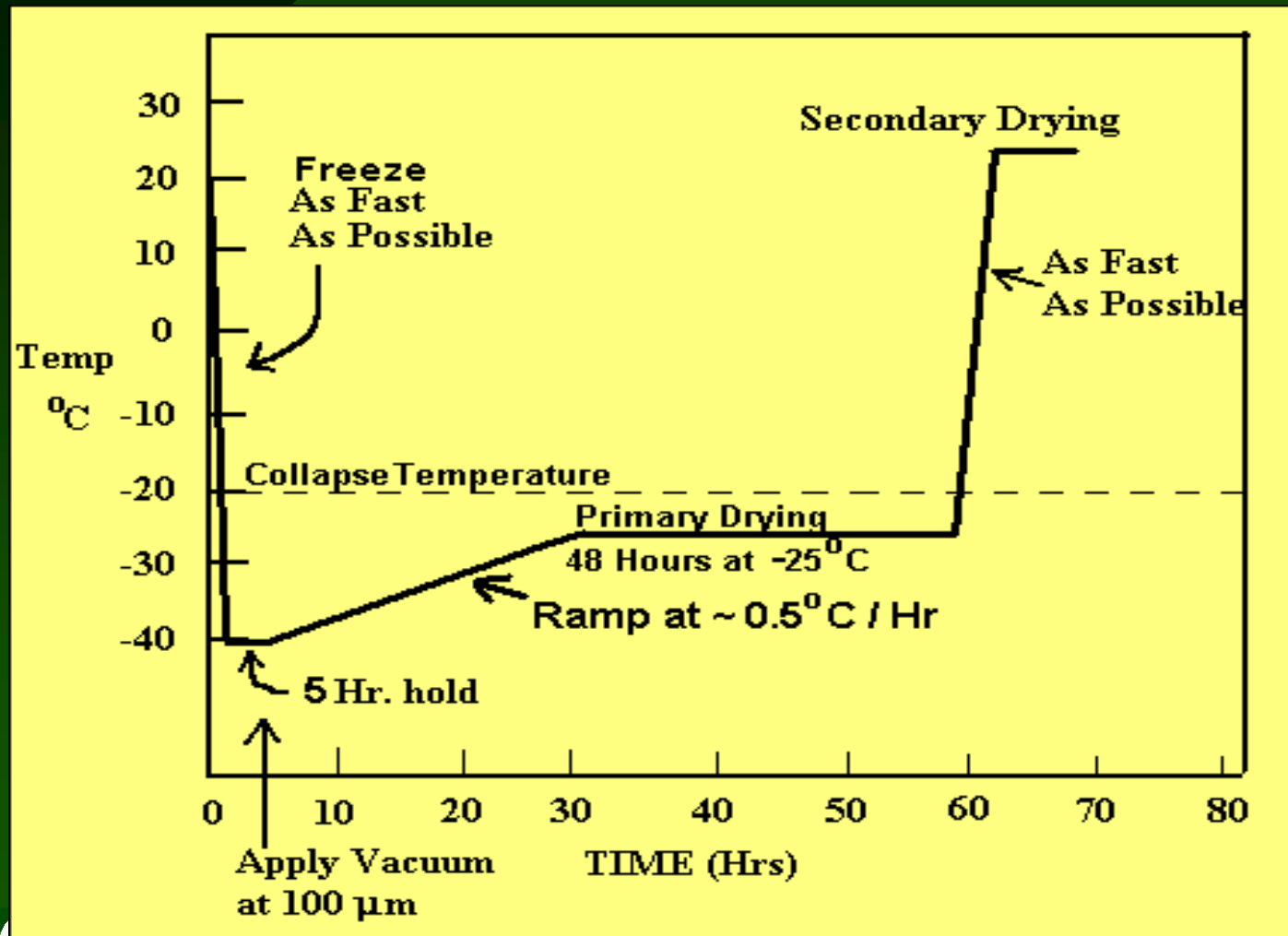
# Involve your contractor

## Everyman's Lyophilization Cycle.

- Lyophilizers Vary
- Condenser Capacity
- Freezing Temperature and Time
- Other Differences

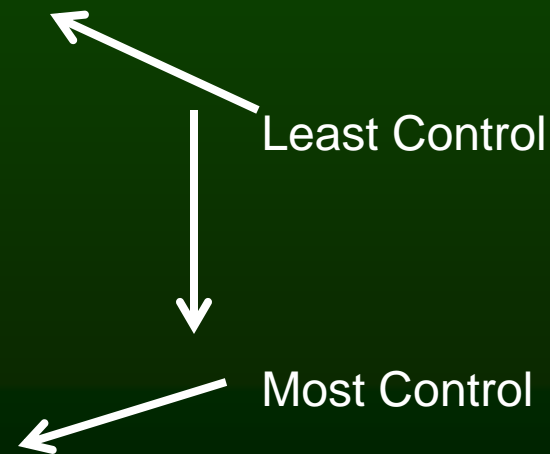
# Involve your contractor

## Everyman's Lyophilization Cycle



# Involve Your Contractor Lyophilizers Vary

- Condenser Capacity
- Condenser Temperature
- Product Freezing Temp. and Time
- Chamber Vacuum

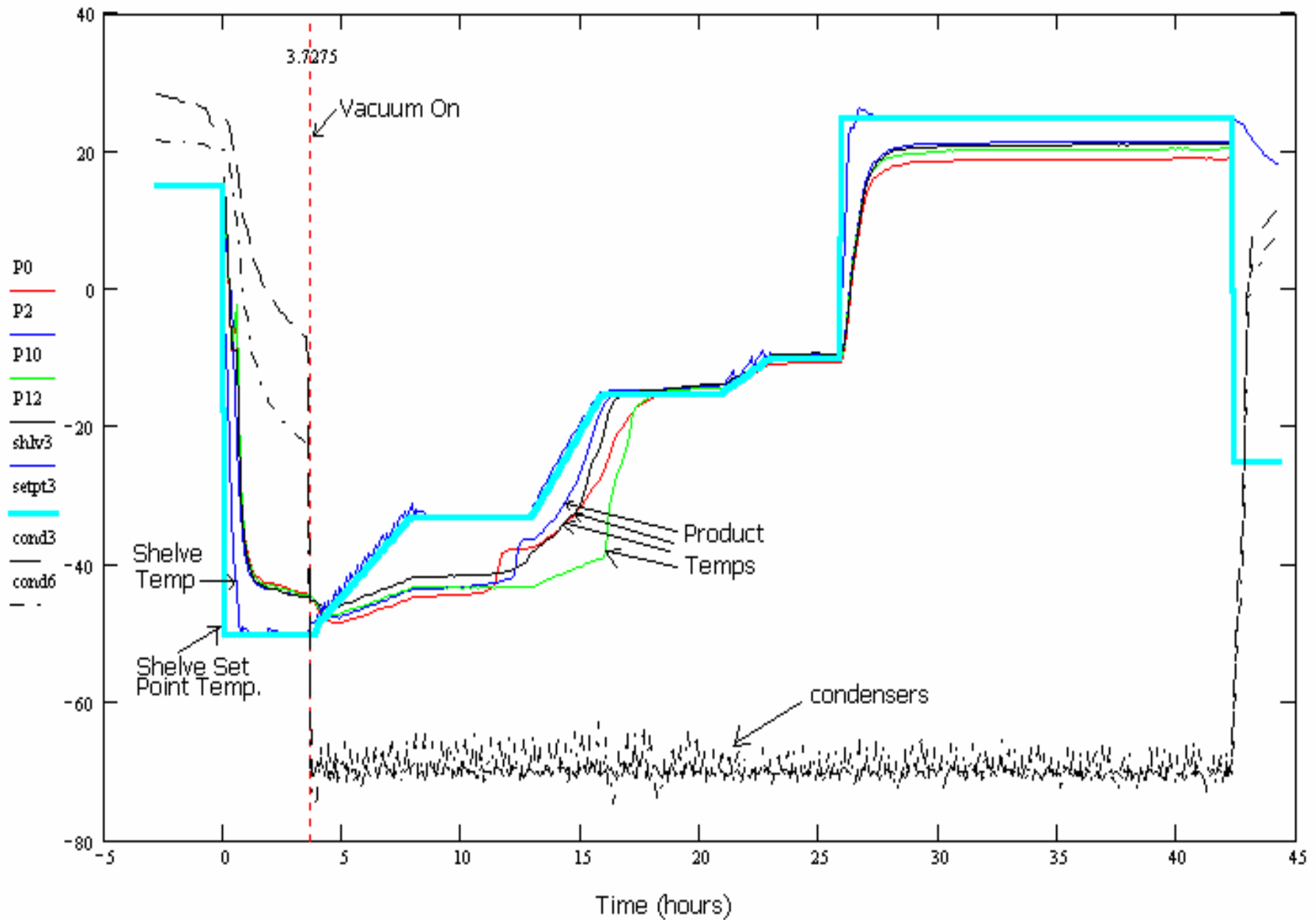


# Involve Your Contractor Condenser Capacity

- Ratio of Liquid to Condenser
- Geometry of the Lyophilizer  
Shape and Location
- Condenser Temperature

# Involve Your Contractor Freezing Temperature & Time

- Freezing is a function of compressor size.
- Product needs to all be approximately the same temperature at the start.





# Involve Your Contractor Other Changes

- Minor Changes in Formulation Matter?
- Changes in Components?

Glass

Elastomer

# Minimize Risk

- Cycle Development
- Cycle Compression
- Cycle Demonstration
- Cycle Validation

# Minimize Risk - 1

- Lyophilization Cycle Initial Development
  - Pharmaceutically elegant, dry, and stable product.
  - Initial formulation, pH, excipients, reconstitution.
  - Residual Moisture, Reconstitution time, Activity
  - Thermal characterization – eutectic/collapse

# Minimize Risk - 2

- Lyophilization Cycle Compression
  - Begin with a conservative cycle
  - Identify eutectic/collapse temperature
  - Assess results from shortened cycles
    - Appearance
    - Residual Moisture
    - Reconstitution time
    - Activity/Potency

# Minimize Risk - 3

- Lyophilization Cycle Demonstration
  - Cycle is already fully developed.
  - Use a small number of product vials in a full load cycle with placebo dummies.
  - Demonstrate validity of the cycle in the contractors lyophilizer.
  - Make adjustments as required.

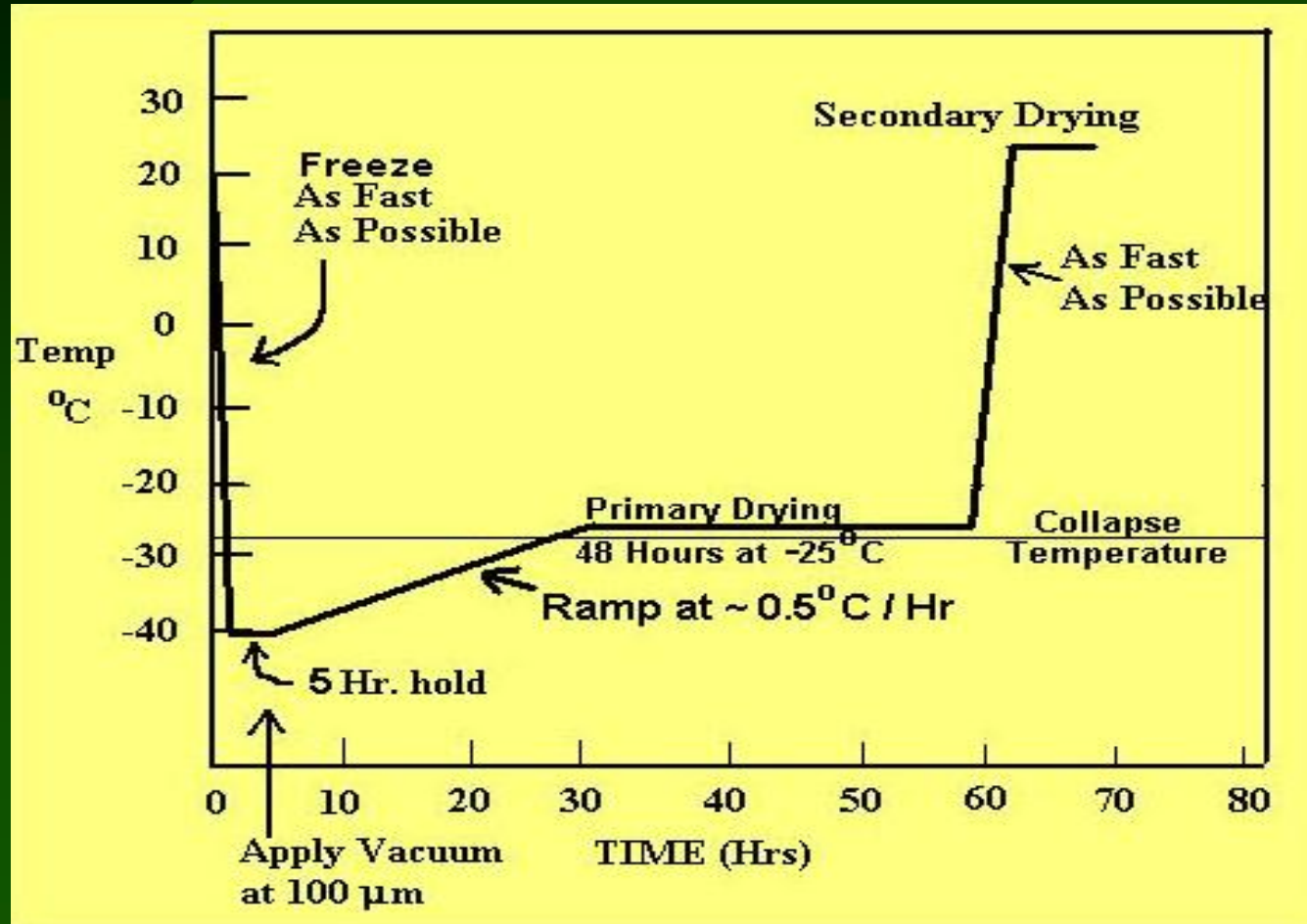
# Minimize Risk - 4

- Lyophilization Cycle Validation
  - Performed as part of Process Validation
  - Not an IQ/OQ
  - 3X Full Scale Demonstration
  - Required for Commercialization

# Three Examples:

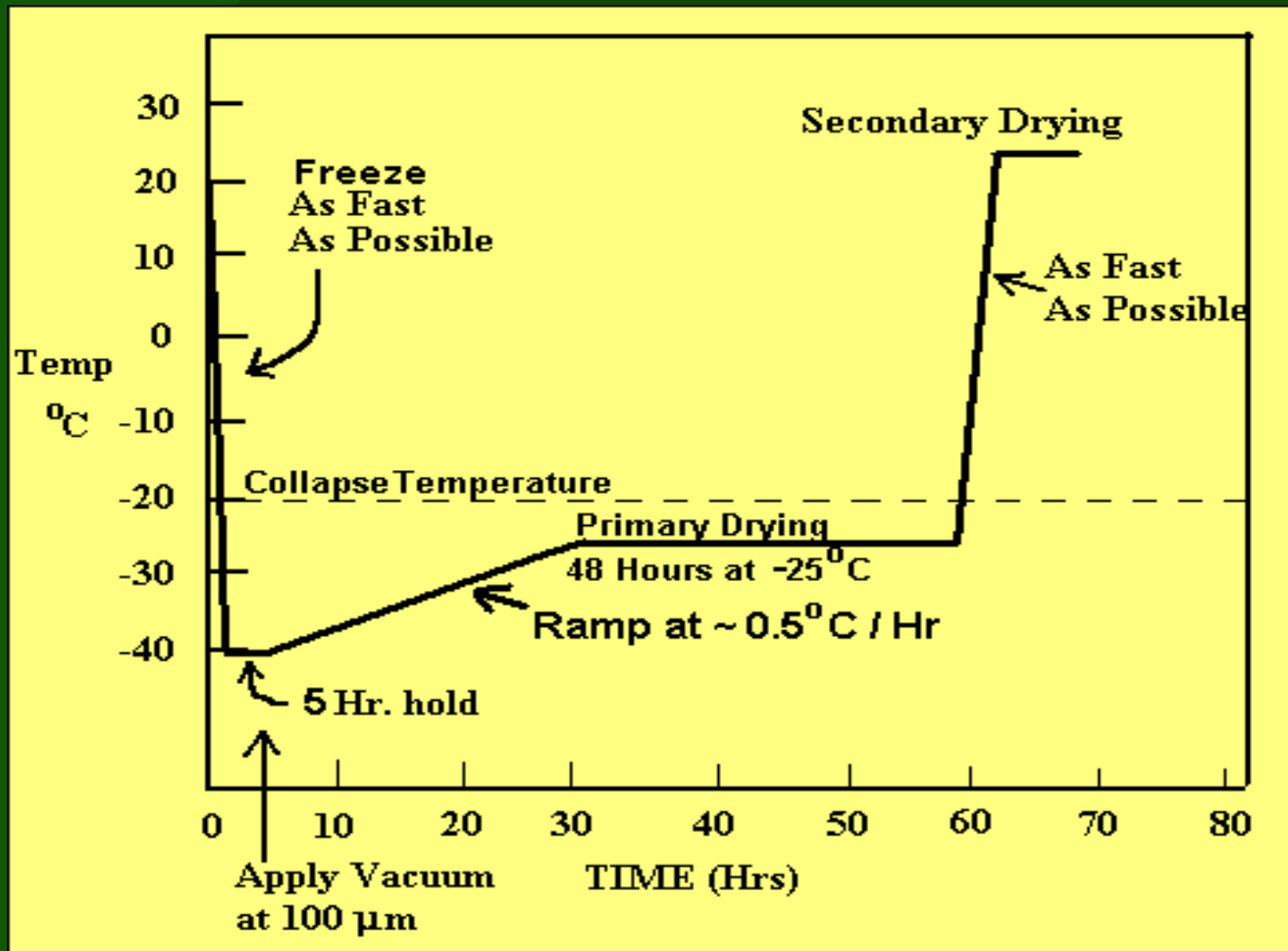
- What Could Have Gone Better?
- What Was the Resolution?
  - Science
  - Business

# Case 1: Chewing Gum Happens

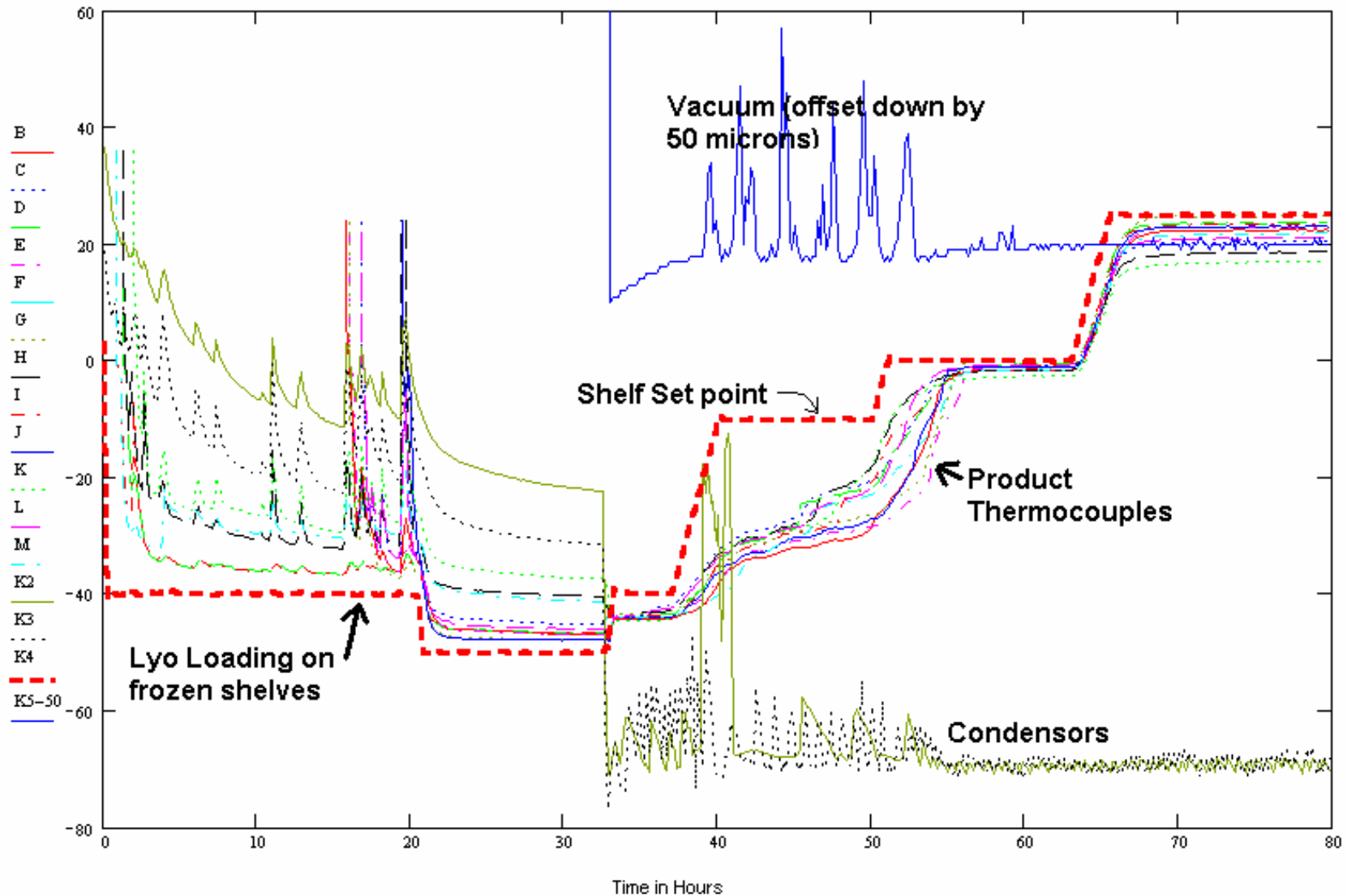




# Case 2: Vials Break



# Case 3: Clients Get Their Way:



# Less Obvious Problems:

- Failure to become dry.
- Lack of Potency
- Lyophiles break
- Failure to Reconstitute (in time)
- Insufficient Stability

# Contractual Issues:

- Direct Contractor Fault
  - Equipment Failure
  - Operator Failure
  - Contamination Issues

# Contractual Issues:

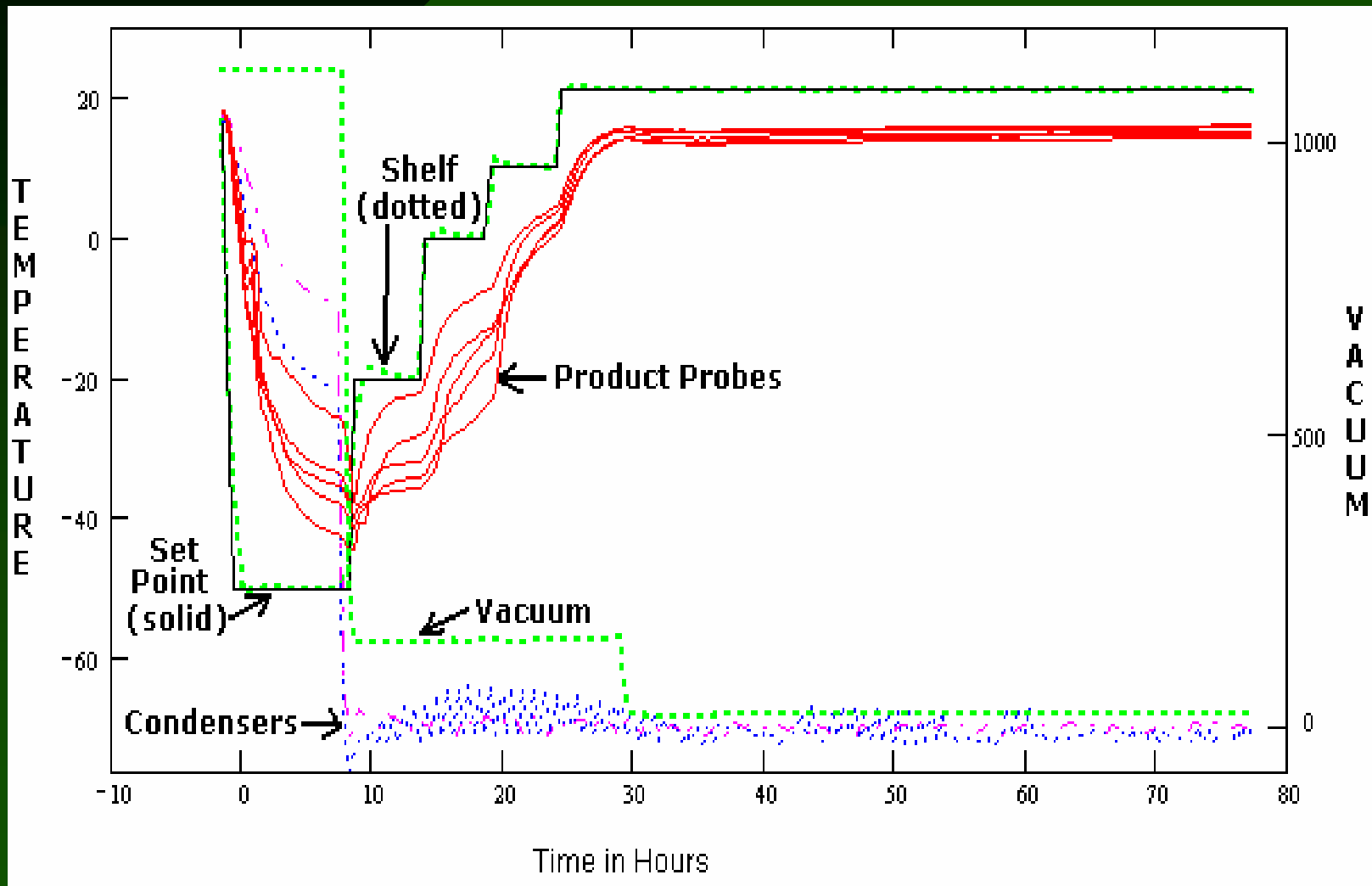
A Contractor will not be responsible for unexpected results that can be attributed to a process or procedure either supplied by, or requested by the Customer, that have not been fully validated.

# Contractual Issues:

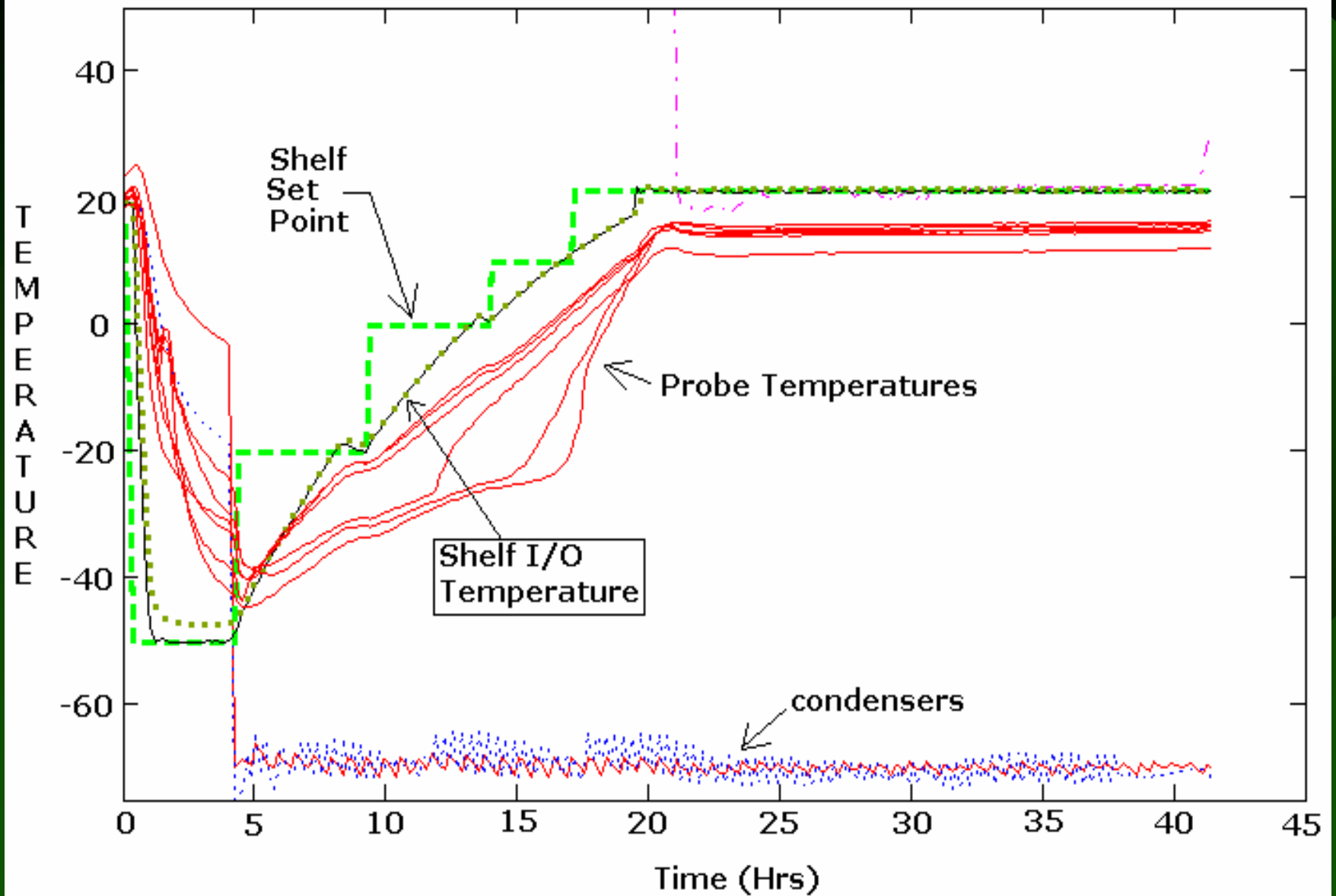
The Contractors liability to the Customer is limited to the value of the amounts invoiced. Any additional claims are either the responsibility of the customer or must be separately identified and covered by insurance.

# Contractual Issues:

The best, and least expensive, insurance is time spent developing the process and later validating the process.







# Summary

- Work with your contractor prior to commercialization.
- Minimize Risks – Development before Validation
- Try to stay away from edges in the Lyo Cycle
- Help yourself to avoid non-scientific errors
- Understand your contract