

Fundamentals of Freeze Drying

Lyo-Hub Summer School

LyoHUB

**ADVANCED
LYOPHILIZATION
TECHNOLOGY
CONSORTIUM**

**Part 1 – Introduction
and Process Overview**



Course Objective

The course objective is to expand your knowledge base and improve your critical thinking skills in the science and technology of freeze drying. Special emphasis is given to understanding the concepts behind the graphical design space.

Course Outline

- Introduction
 - Advantages and limitations of freeze drying
 - Product quality attributes
 - Process overview
 - Freezing
 - Primary drying
 - Secondary drying
- The Freezing Process
 - Supercooling and ice nucleation
 - Characterization of freezing behavior
 - Establishment of upper product temperature limit during primary drying

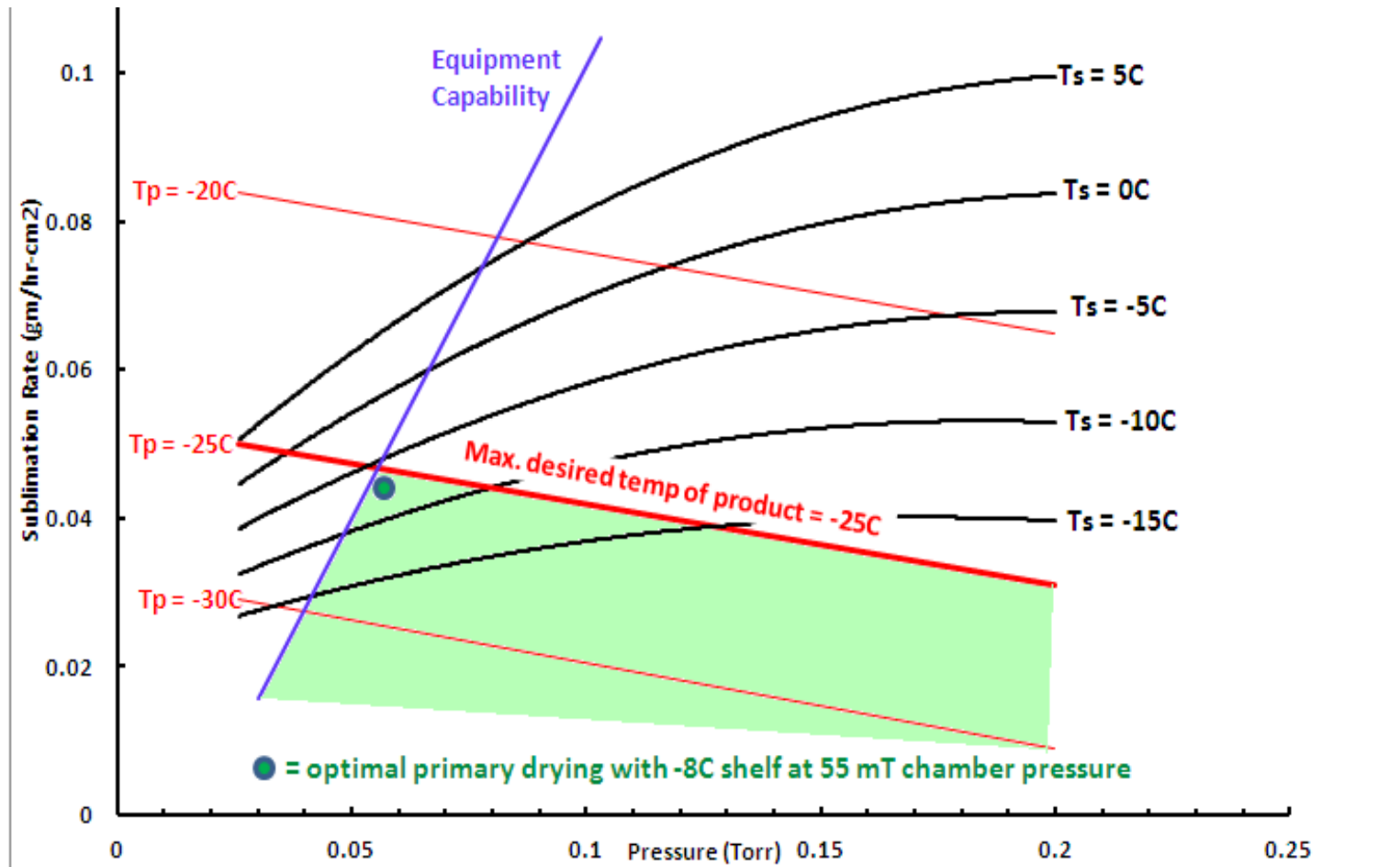
Course Outline (continued)

- Primary drying
 - Heat transfer considerations
 - Measurement of the vial heat transfer coefficient
 - Mass transfer considerations
 - Measurement of the resistance of the dried product layer
- Secondary drying
 - Critical process variables during secondary drying
 - How dry is “dry enough”

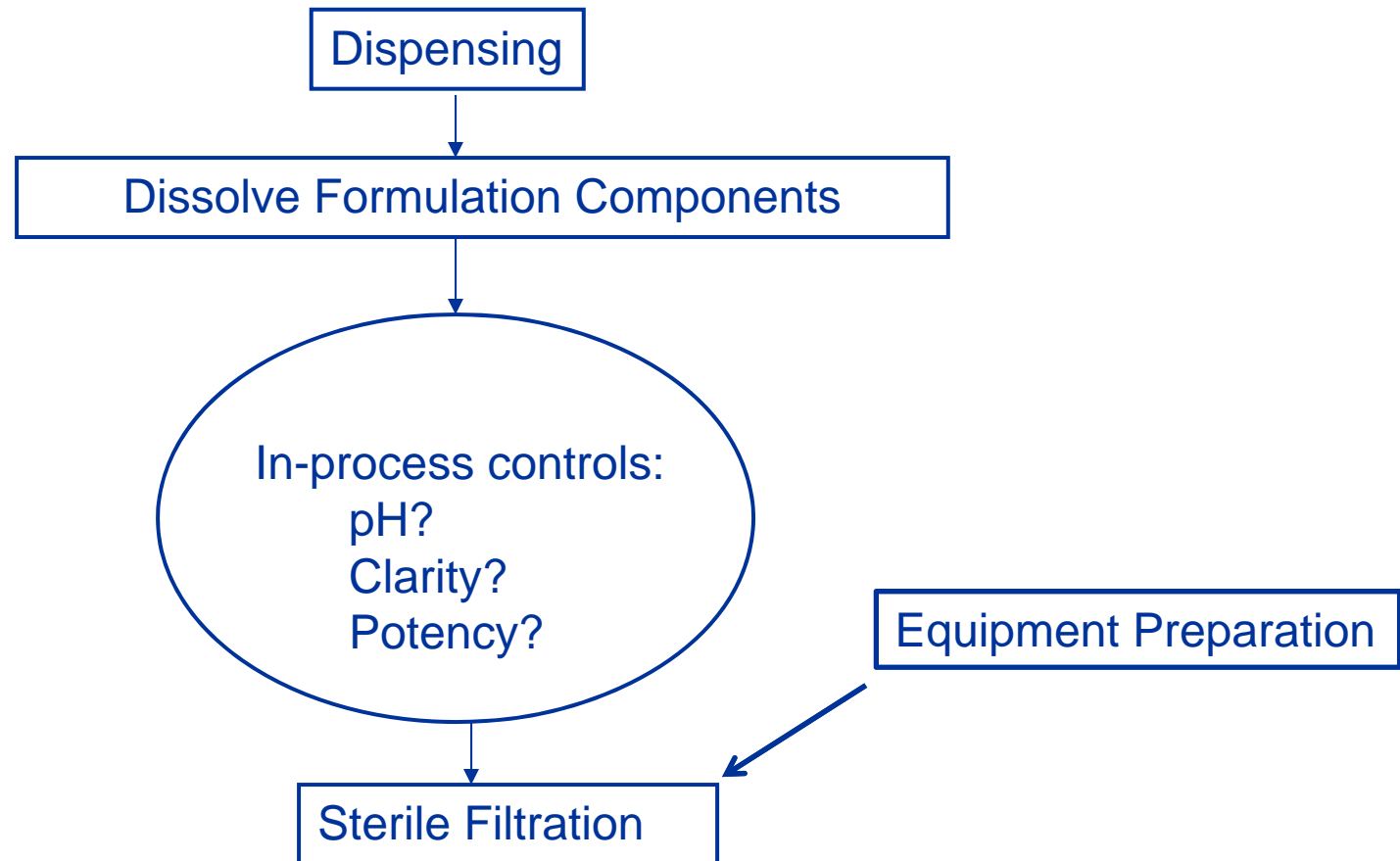
Course Outline (continued)

- Understanding equipment capability
 - Factors that could limit equipment performance
 - Sonic velocity and “choked” flow
 - Measuring equipment capability
 - Choke point test
 - Minimum controllable pressure
- Process monitoring and control
- Formulation Considerations
- Putting this together – construction of the graphical design space for primary drying
 - Case studies

Graphical Design Space



Overview of Unit Operations in Manufacture of a Freeze-Dried Injectable Product - Formulation



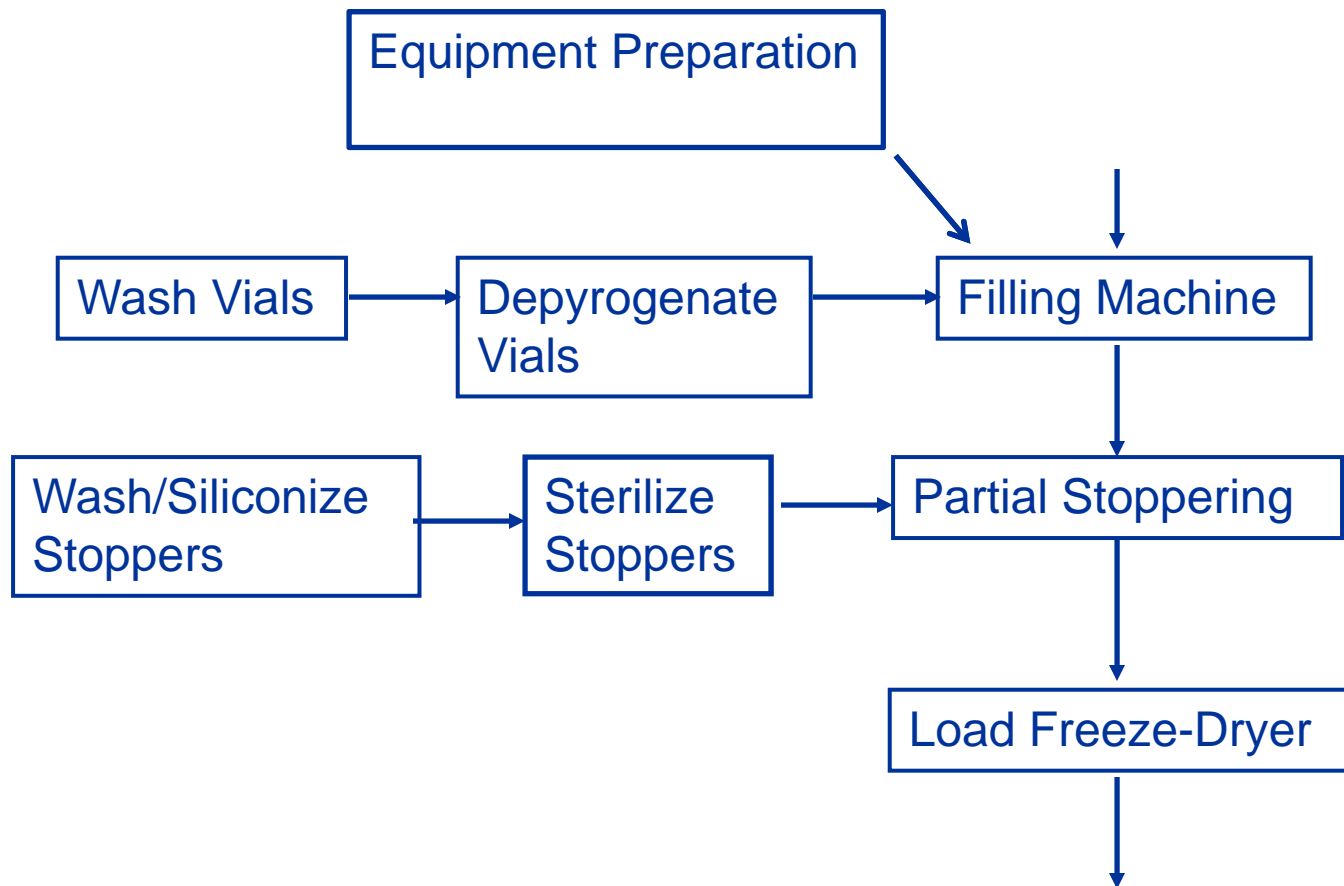
Formulation/Filtration

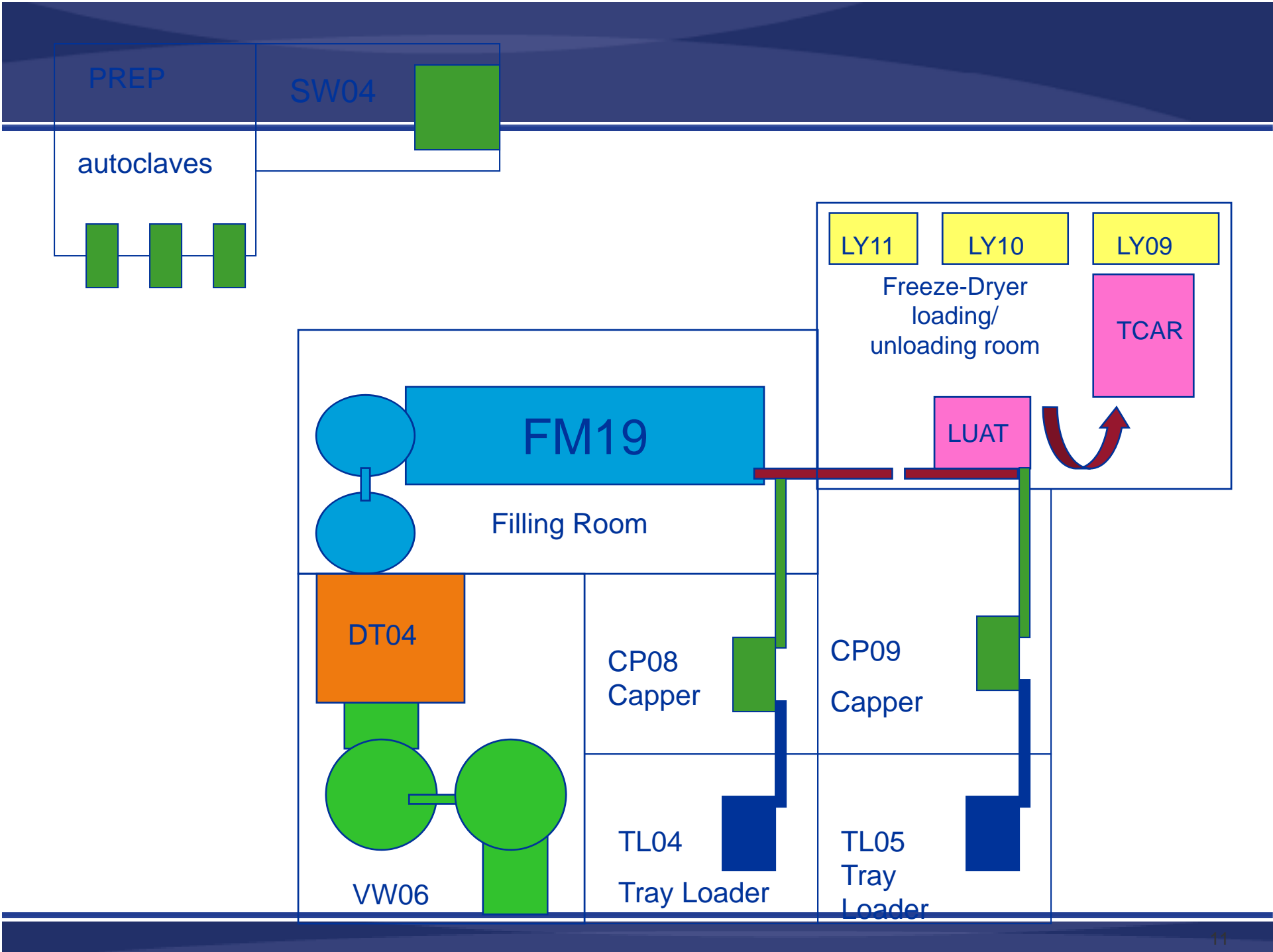


Formulation/Filtration



Overview of Unit Operations in Manufacture of an Injectable Drug Product - Filling



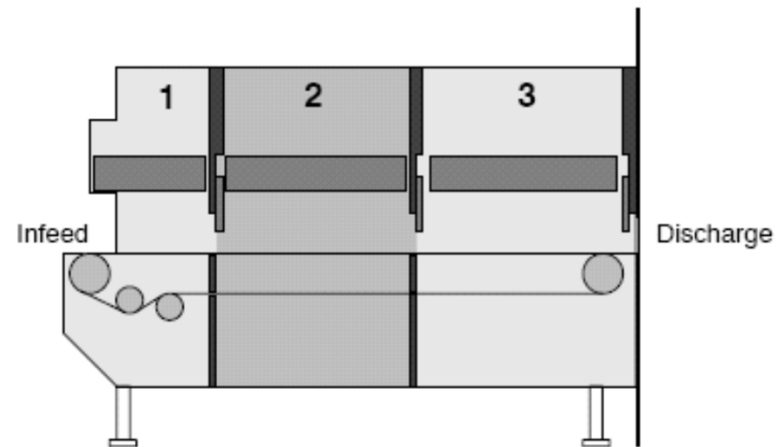


VW06 & DT04

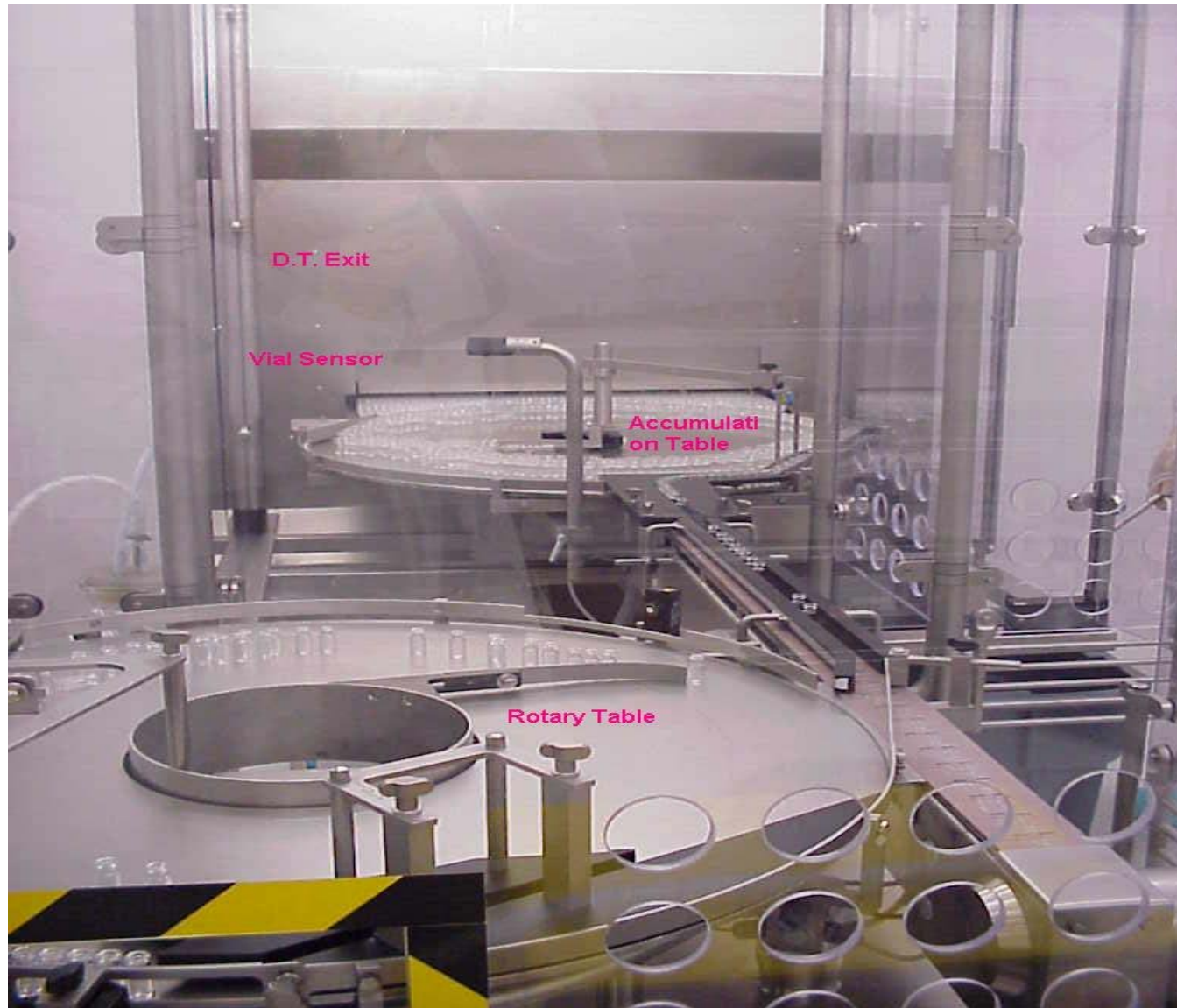


Depyrogenation Tunnel (DT04)

- Depyrogenation Temperature and Time (Belt Speed)
- 3 zones
 - Preheat
 - Drying & Sterilizing
 - Cooling Zone

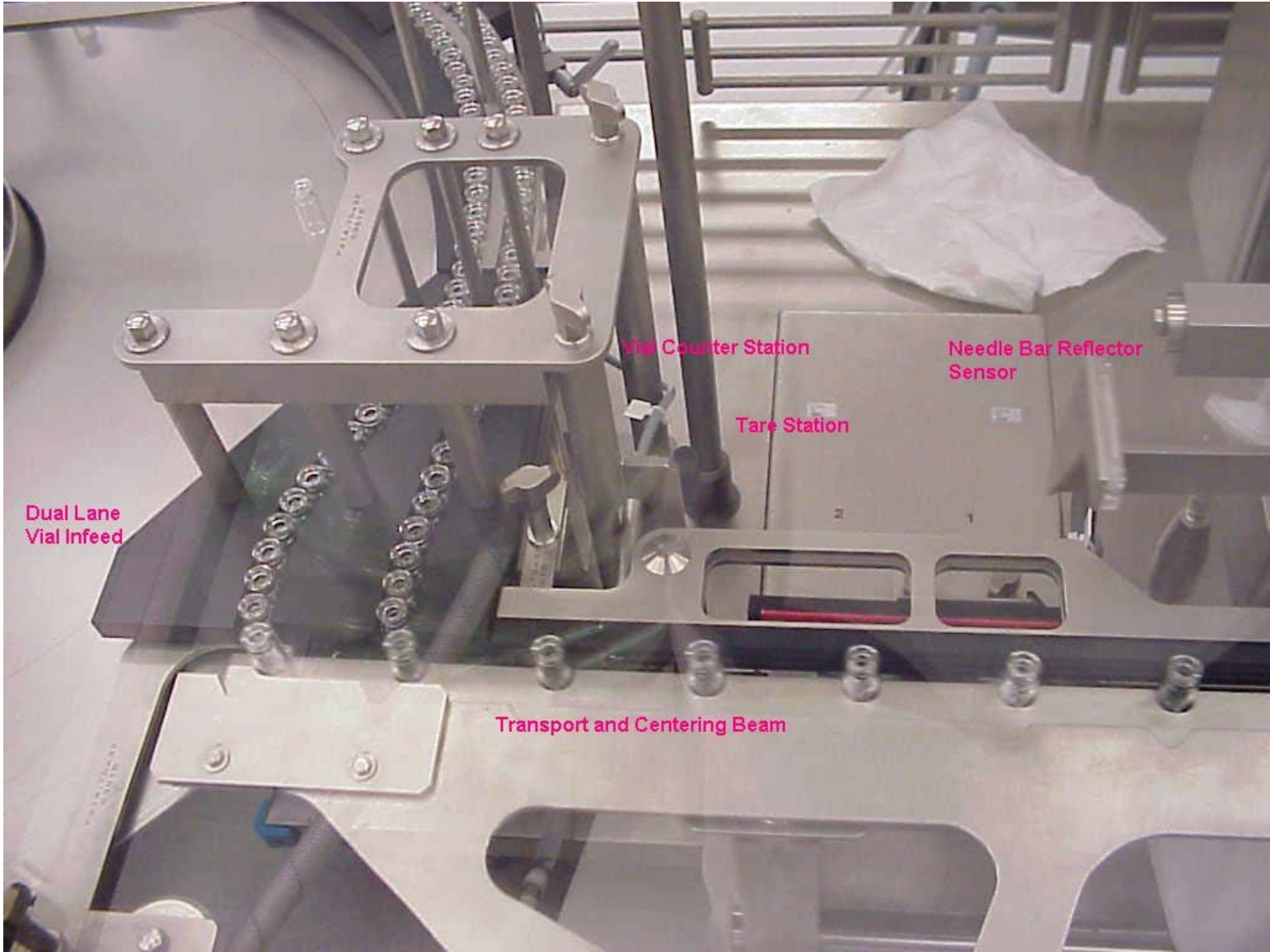


FM19

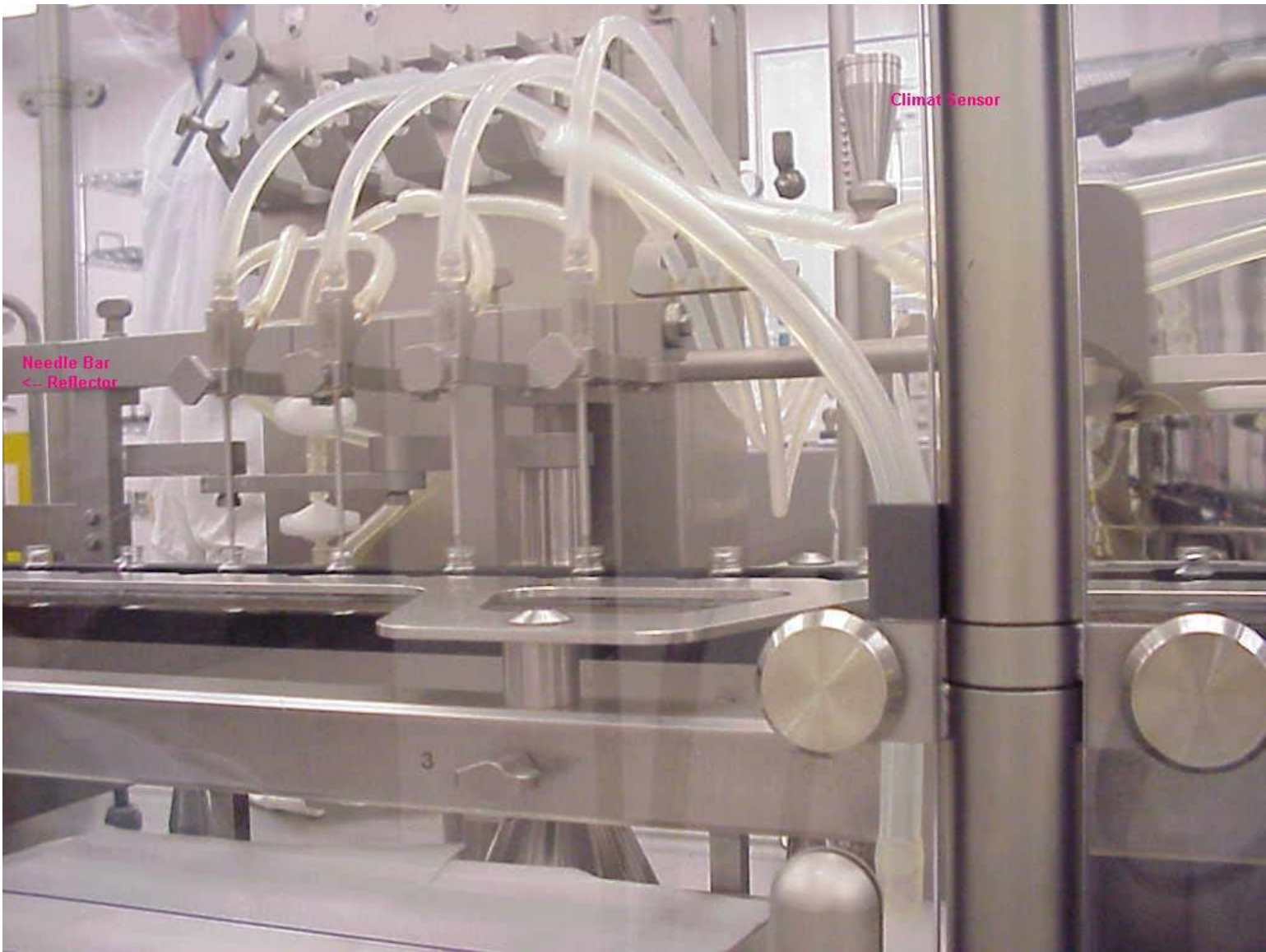


Stopper Washing (SW04)





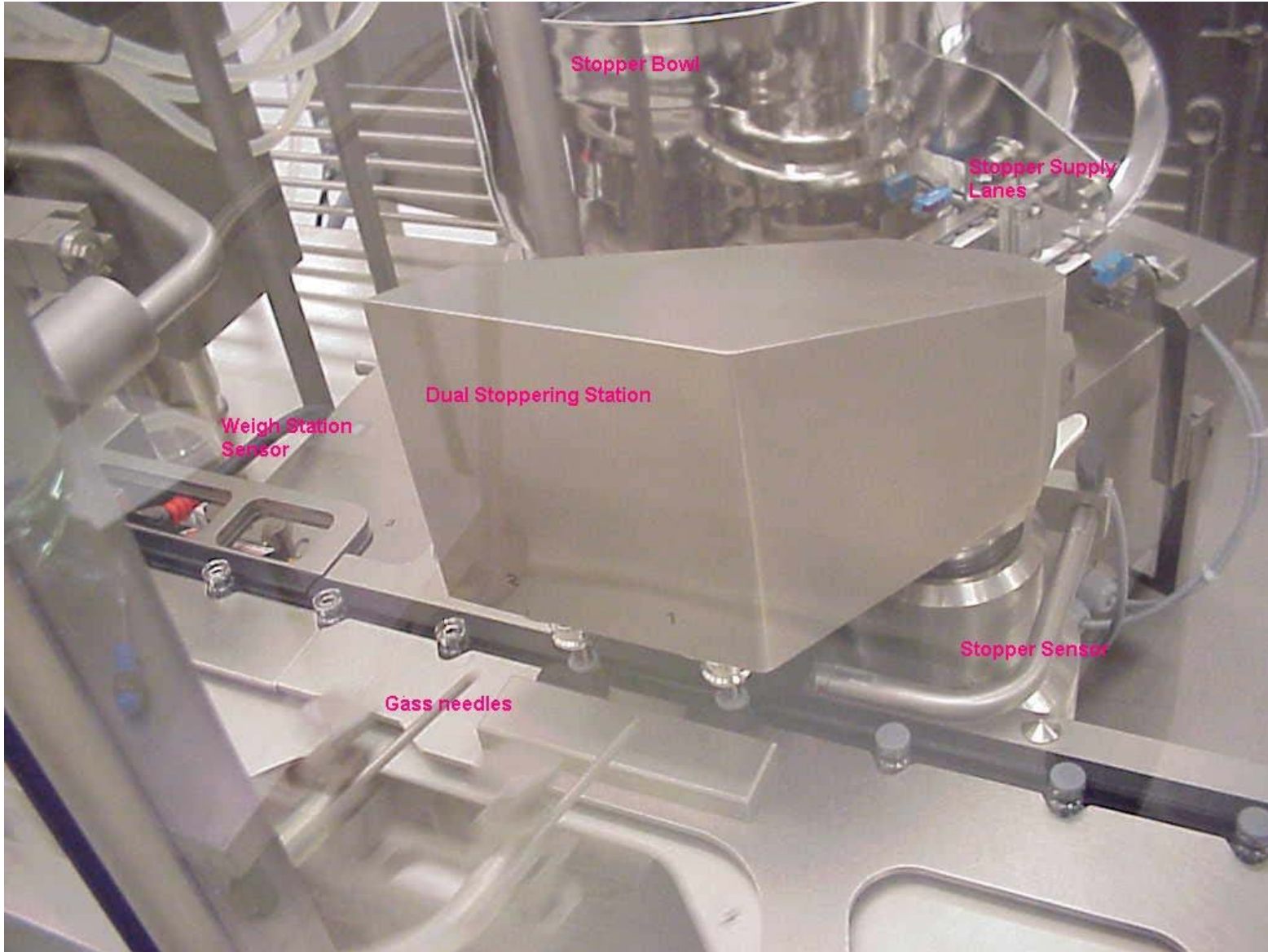


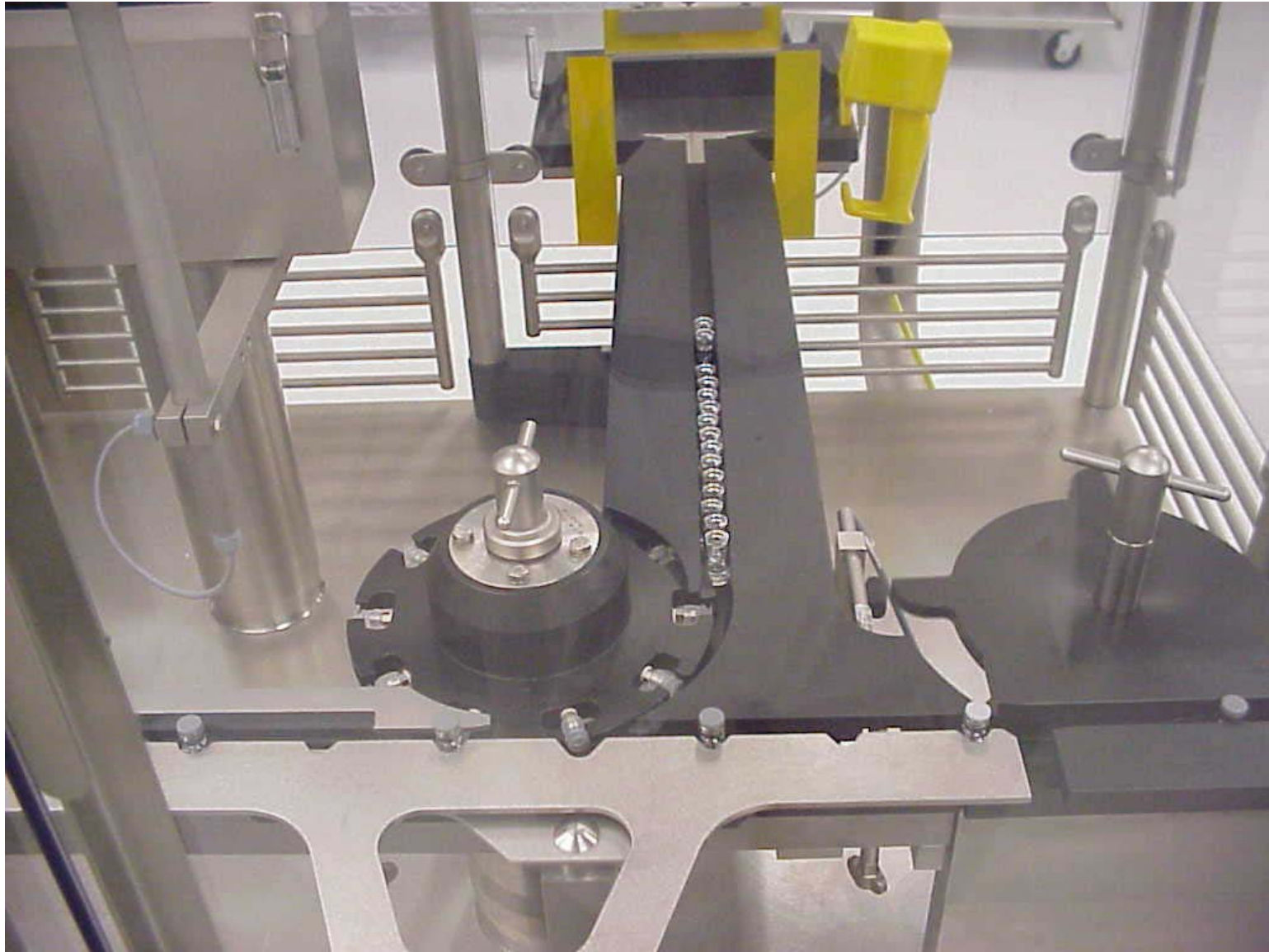


Needle Bar
<- Reflector

Climat Sensor

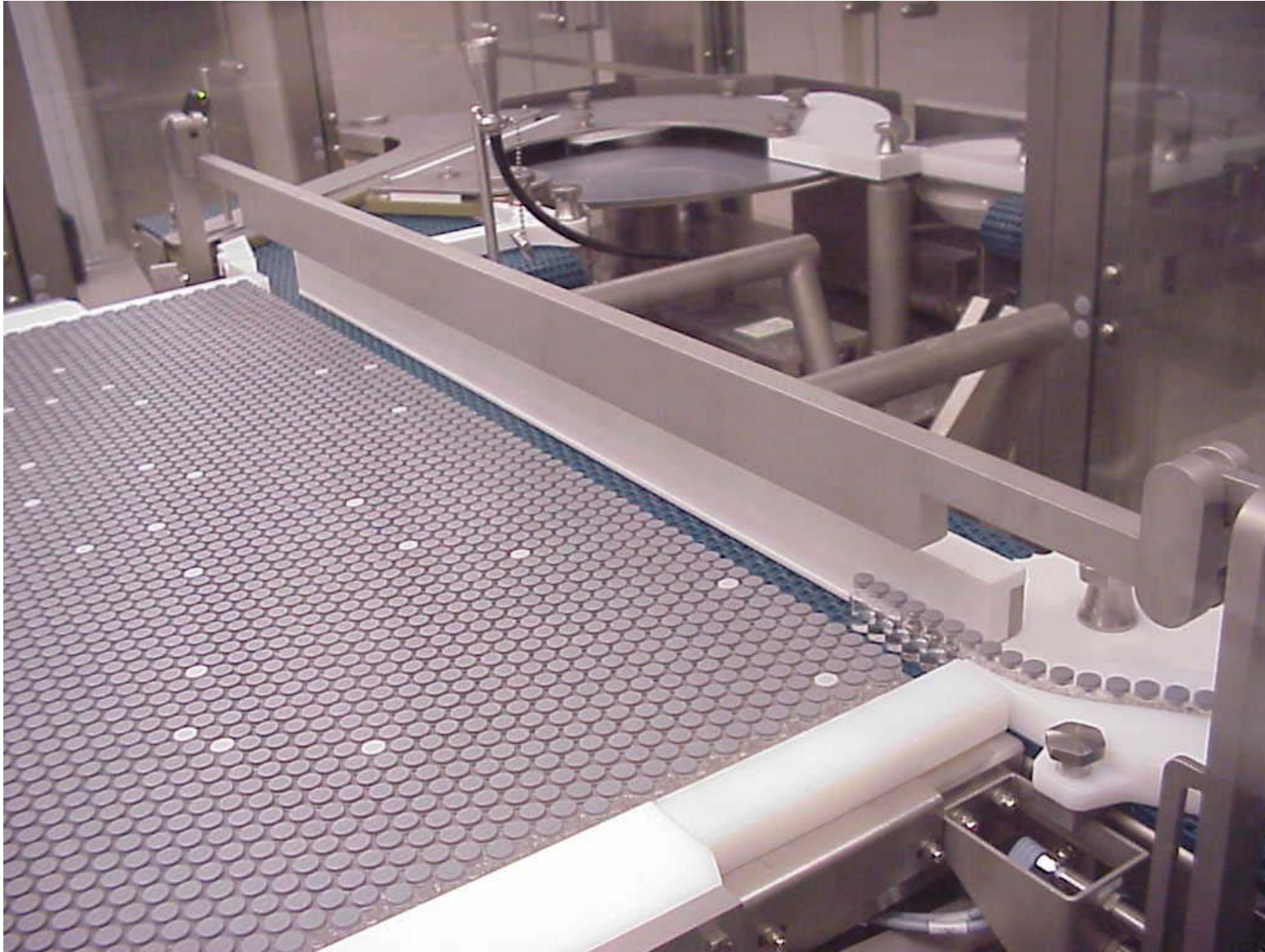








LUAT





LY04



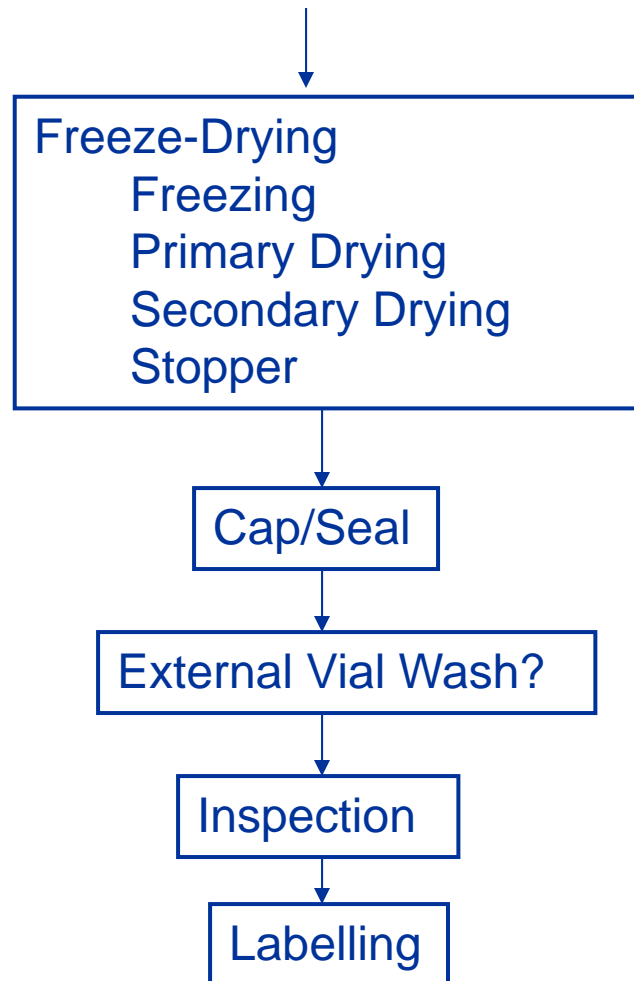
LY04



T-Car



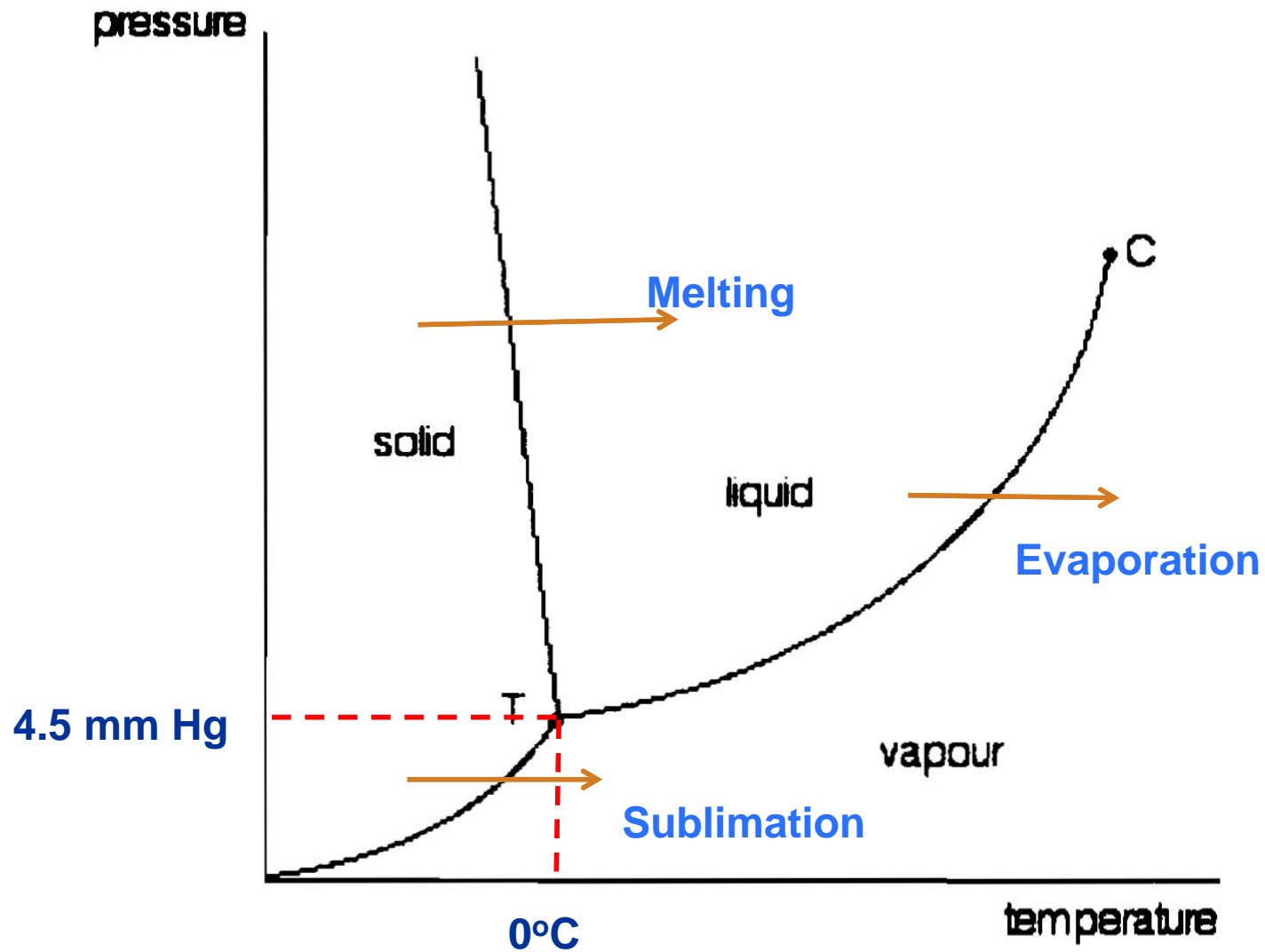
Overview of Unit Operations in Manufacture of a Freeze-Dried Injectable Product



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
- From a pharmaceutical development perspective, a freeze-dried drug product has a higher probability of technical success than a sterile, ready-to-use solution

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.

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
- Rapid, complete reconstitution
- Suitably stable at the anticipated storage conditions
- Adequately low level of residual moisture
- Appearance of the freeze dried solid – how much do we care?

Cake Collapse



Partial collapse



Cake Shrinkage Not Associated with Collapse



Cake Cracking/Breaking



Powder Ejection



“Skin” Formation



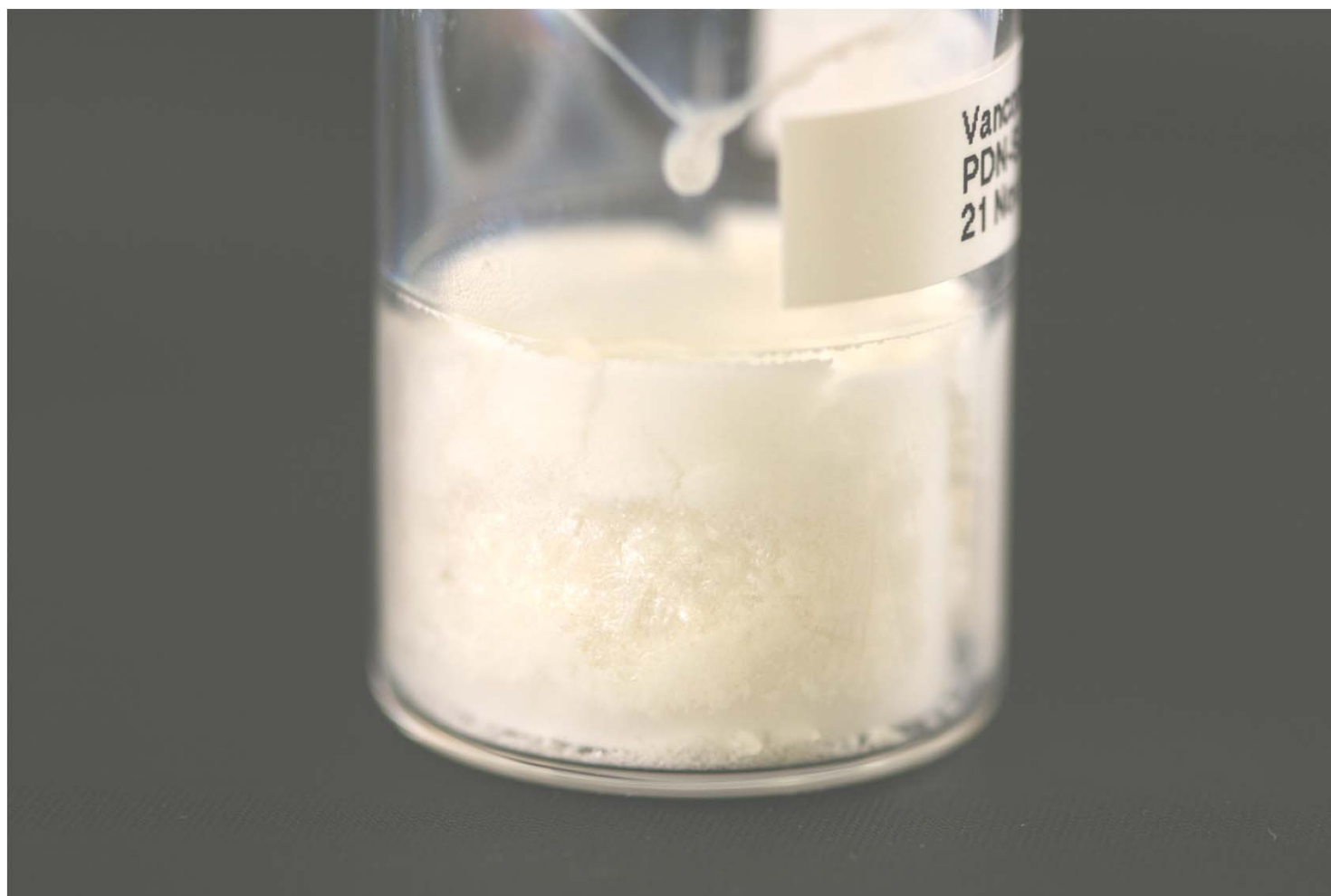
“Puffing”



“Fogging”



Inconsistent Texture of Dried Solids



Lifted Cake

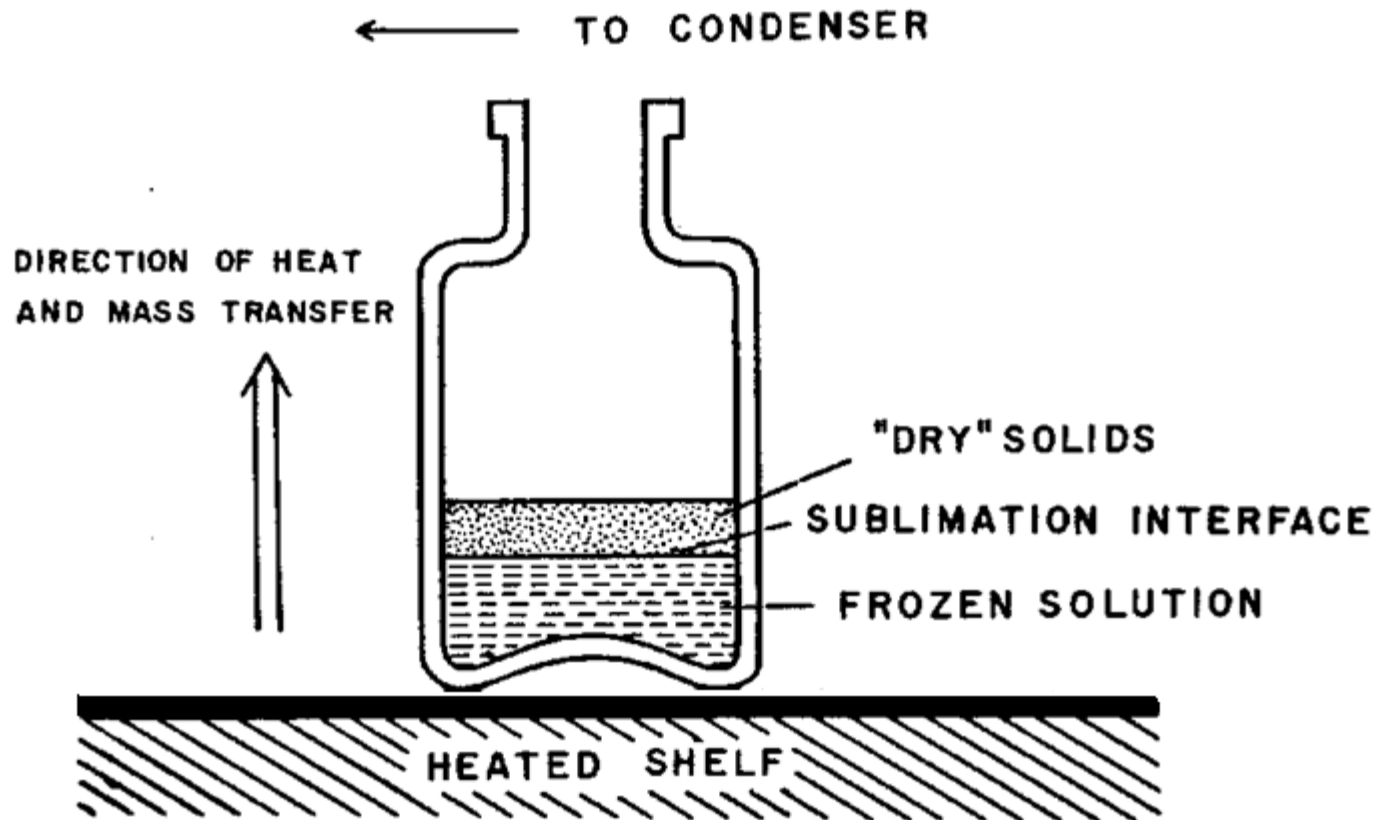


A Closer Look at the Freeze-Dry Process

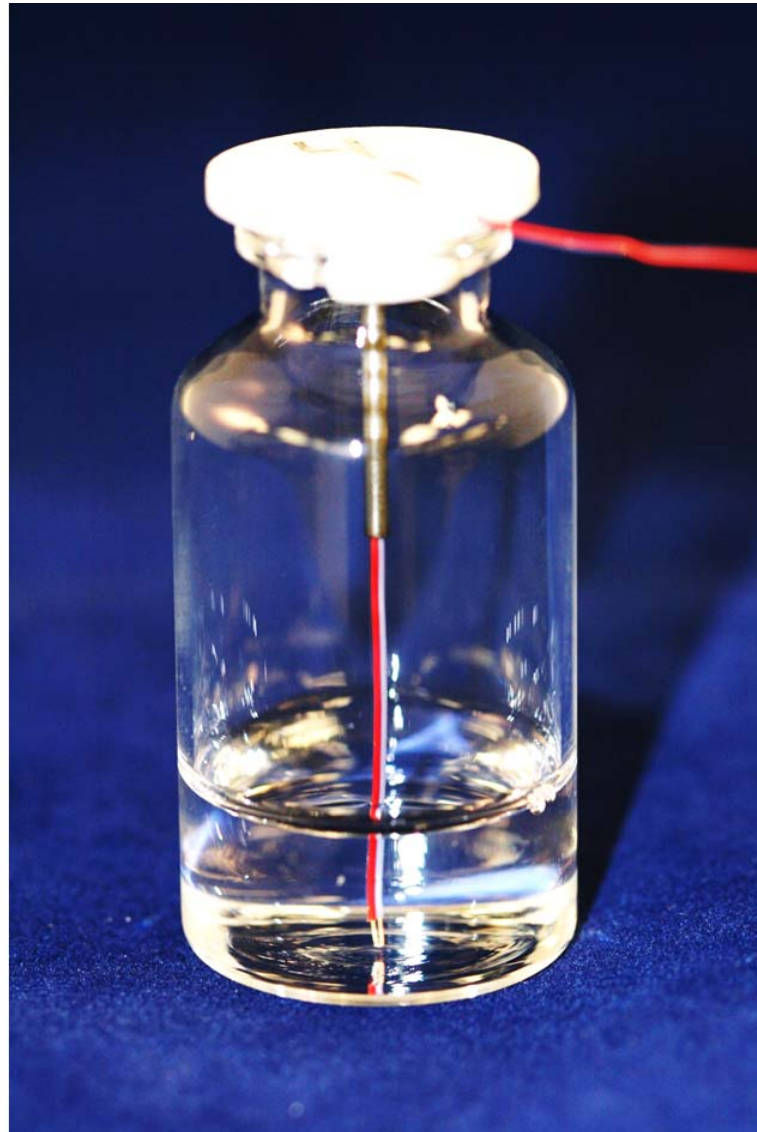
- Freezing
 - Solidify the contents of every vial
- Primary drying
 - Remove, by sublimation, the ice from the frozen matrix. This occurs by bulk flow from a region of higher pressure (the surface of the ice in the product vial) to a region of lower pressure (the chamber).
- Secondary drying
 - Remove 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).



There Are Two Rate Processes in Freeze-Drying – Heat Transfer and Mass Transfer



Product Temperature Measurement in Development Lab



Review of a Representative Process Data Chart

