



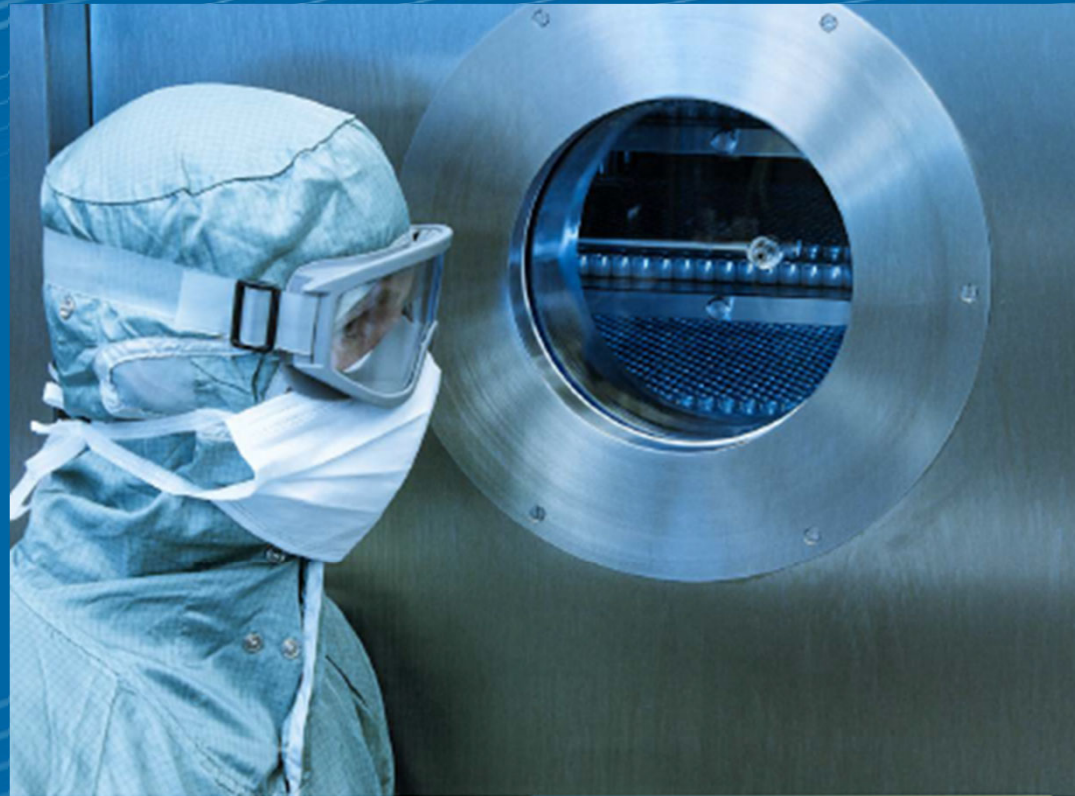
Connecting People, Science and Regulation®

# Theory 1

**Dr. Andrea Allmendinger**

*Late-stage Pharmaceutical and  
Processing Development  
Hoffmann-La Roche, Basel*

[andrea.allmendinger.aa1@roche.com](mailto:andrea.allmendinger.aa1@roche.com)



25-29 MARCH 2019  
OSTERODE (HARZ), GERMANY

[pda.org/eu/fdp2019](http://pda.org/eu/fdp2019)



2019 PDA EUROPE TRAINING

## Freeze Drying in Practice



# Theory 1

- Why lyophilization?
- History and Development
- Examples in daily life and pharmaceutical industry
- The freeze drying process
- Freeze drying equipment
- Pros and Cons for Lyophilization



# Why drying?

- Drying for stabilization of products for long-term storage:
  - Reduced mobility decreases tendency for physical instabilities
  - and decreases chemical degradation, e.g. hydrolysis
- Drying techniques
  - A. Evaporation  
(not suitable for sensitive biologics)
  - B. Spray drying
  - C. Vacuum drying
  - D. Freeze drying / lyophilization**
    - Gentle procedure for thermo sensitive molecules to remove water
    - Basic principle: Removal of water after freezing under vacuum by sublimation (and desorption)





# History and Development



Abb. 1: „Ötzi“ (Foto: Archiv Südtiroler Landesmuseum, [www.iceman.it](http://www.iceman.it))

Mummification by cold  
and dry air flow

## Freeze drying



### Chuño = frozen potatoe

- Freeze dried, long-life food from the Andes made from potatoes
- Produced at low water vapor pressure at high altitude
- Origin already during Inca's time

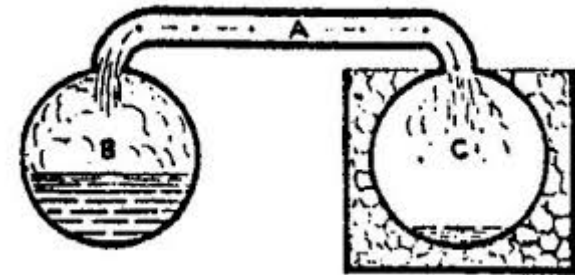
## Vacuum freeze drying

PHILOSOPHICAL  
TRANSACTIONS:

### On a Method of Freezing at a Distance

William Hyde Wollaston

*Phil. Trans. R. Soc. Lond.* 1813 **103**, 71-74, published 1 January 1813



William Hyde Wollaston:  
Cryophorus



# Examples in food industry



→ Preserve color and taste

Aerospace food



→ Instant products





# Examples in daily life

## Archeology



Documents after water damage

## Conservation:

- Preparation of animals
- Decoration

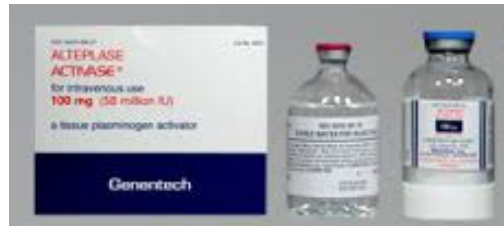




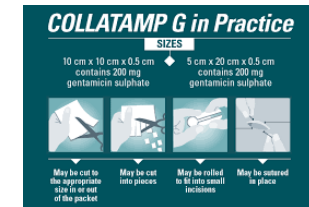
# Examples in Pharmaceutical Industry

## Biopharmaceuticals:

Monoclonal antibodies, enzymes, peptides, other proteins, vaccines



## Special dosage forms: Sublingual tablets, implants



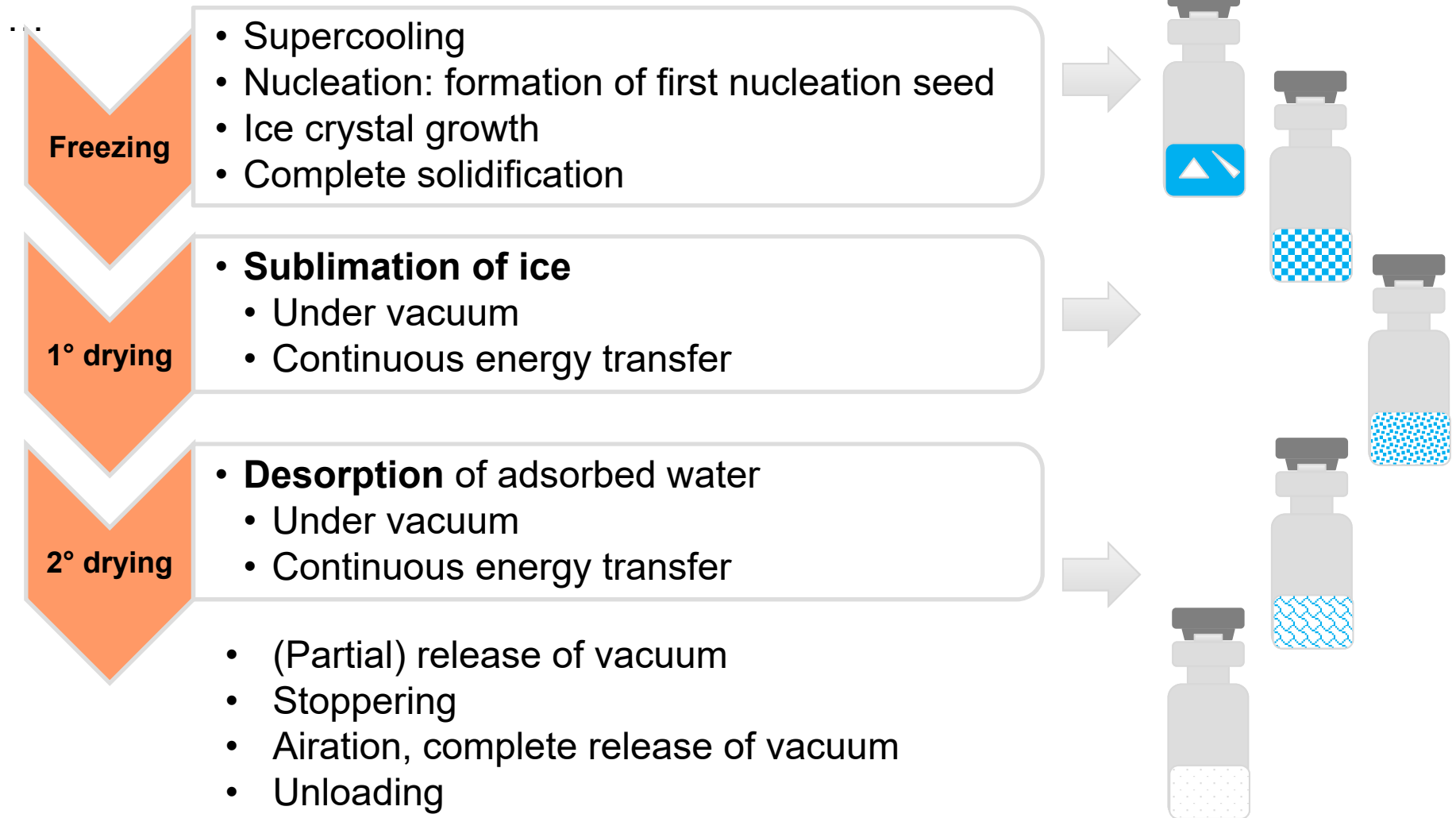
Collatamp® is a lyophilized collagen matrix with the antibiotics Gentamicin

## Antibiotics, small molecules, probiotics





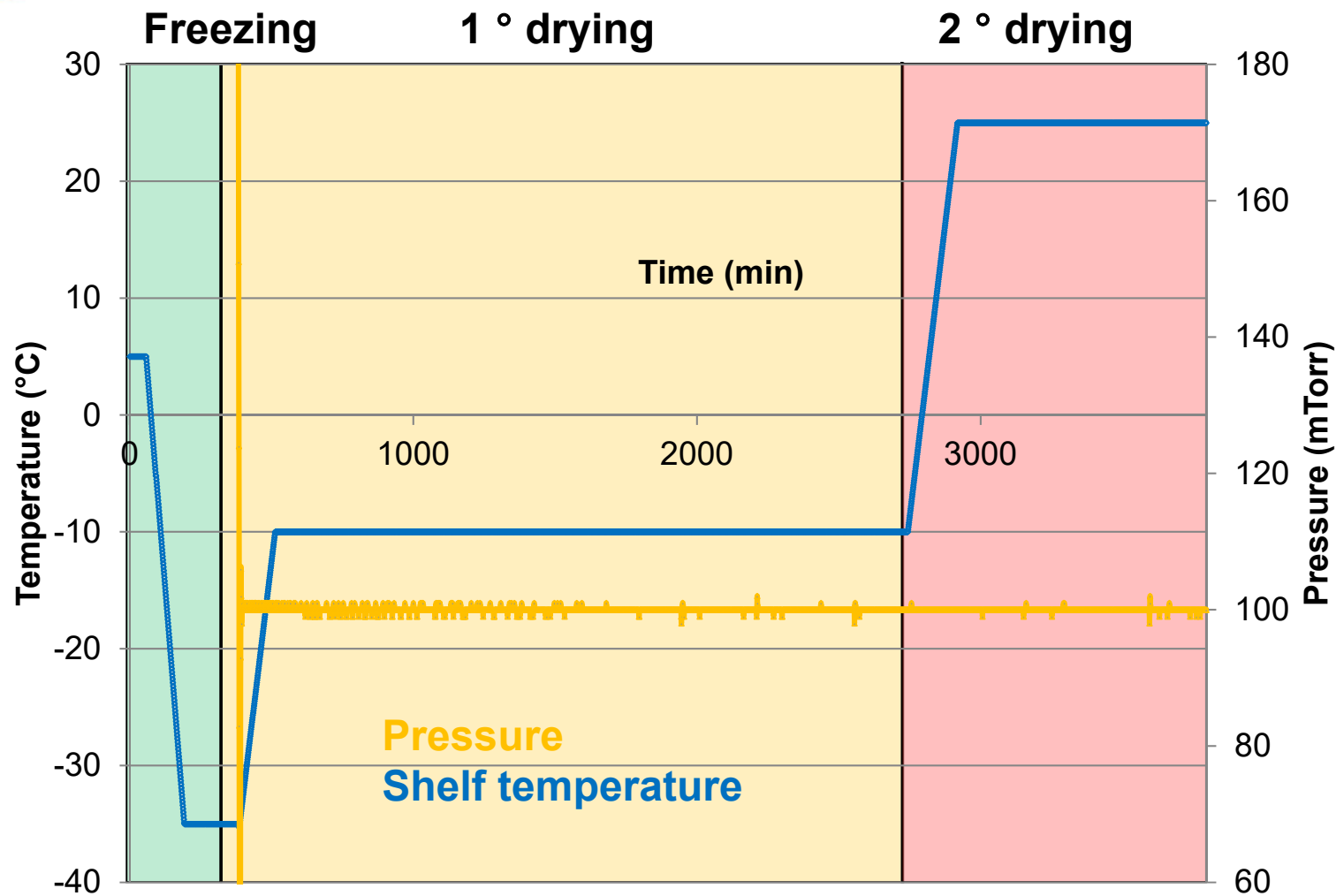
# The Freeze drying process





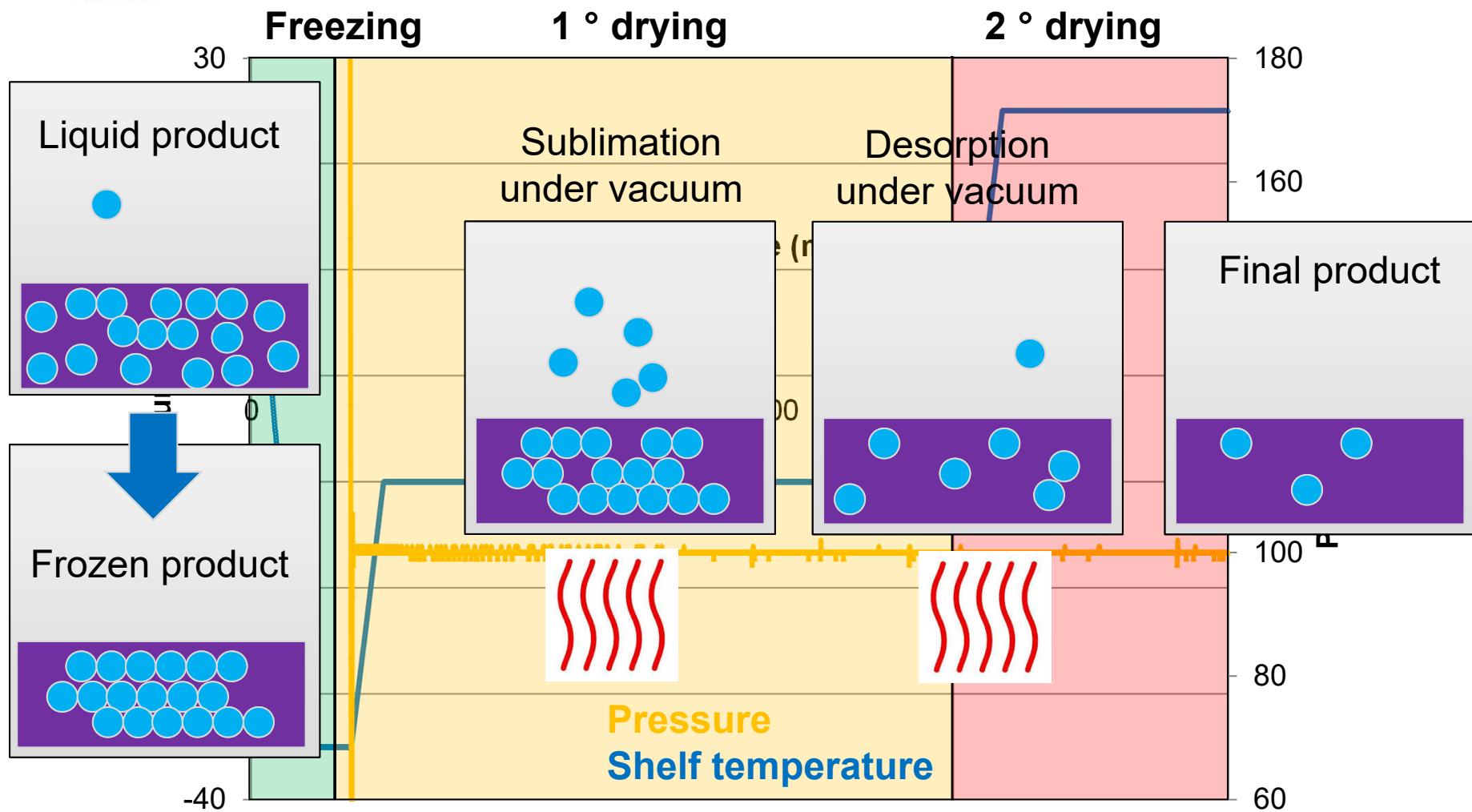


# The Freeze drying process



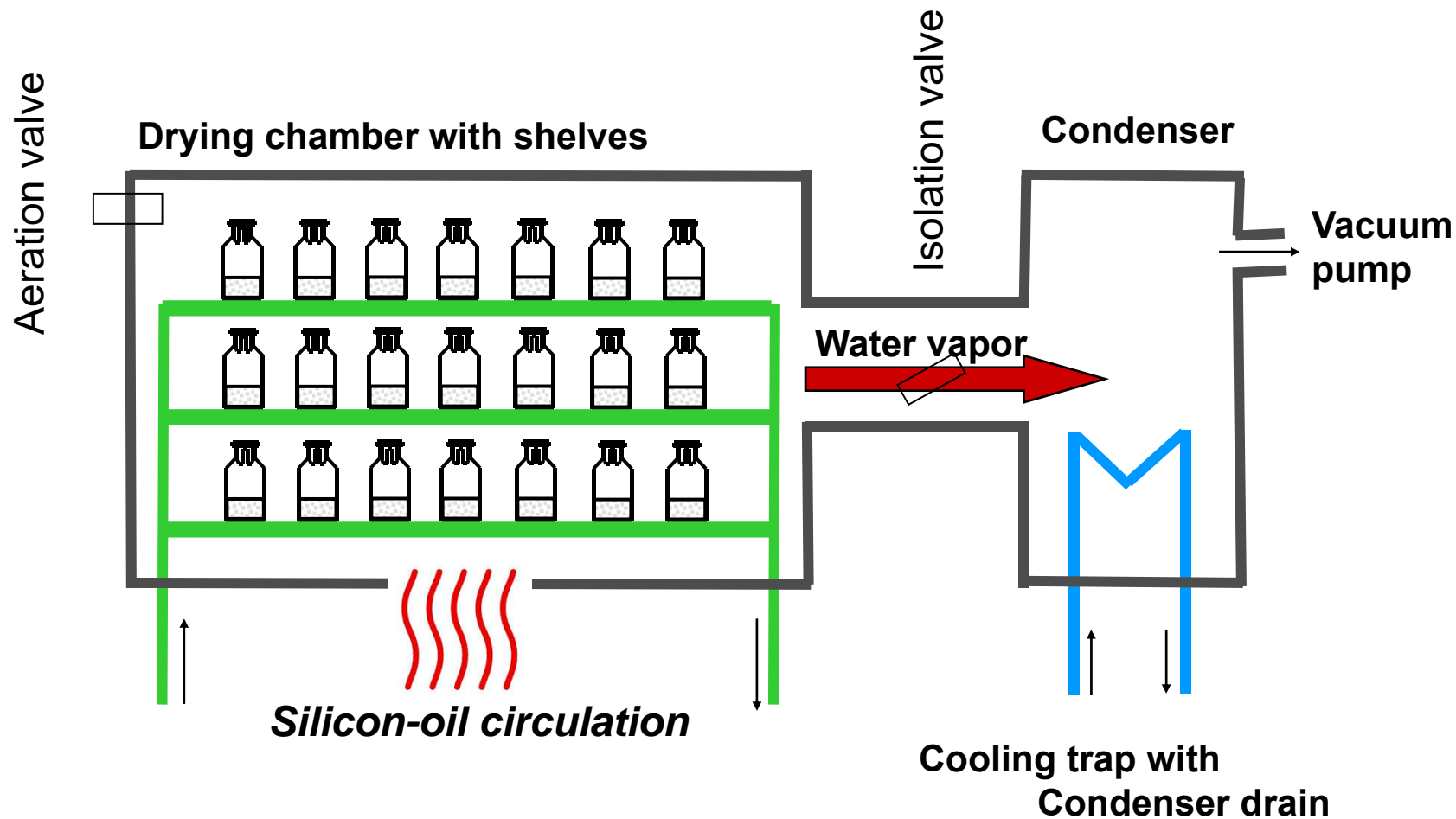


# The Freeze drying process



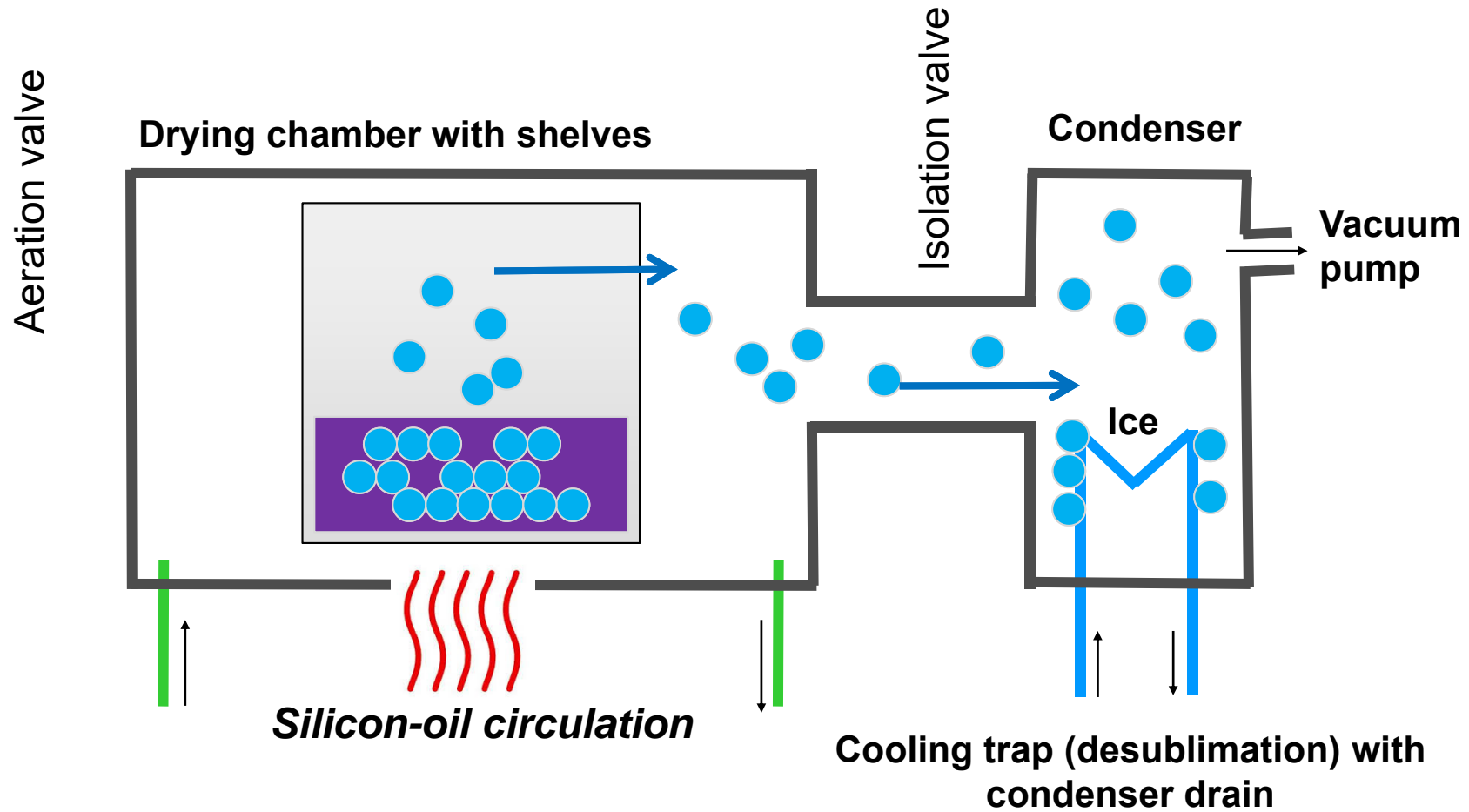


# Freeze drying equipment



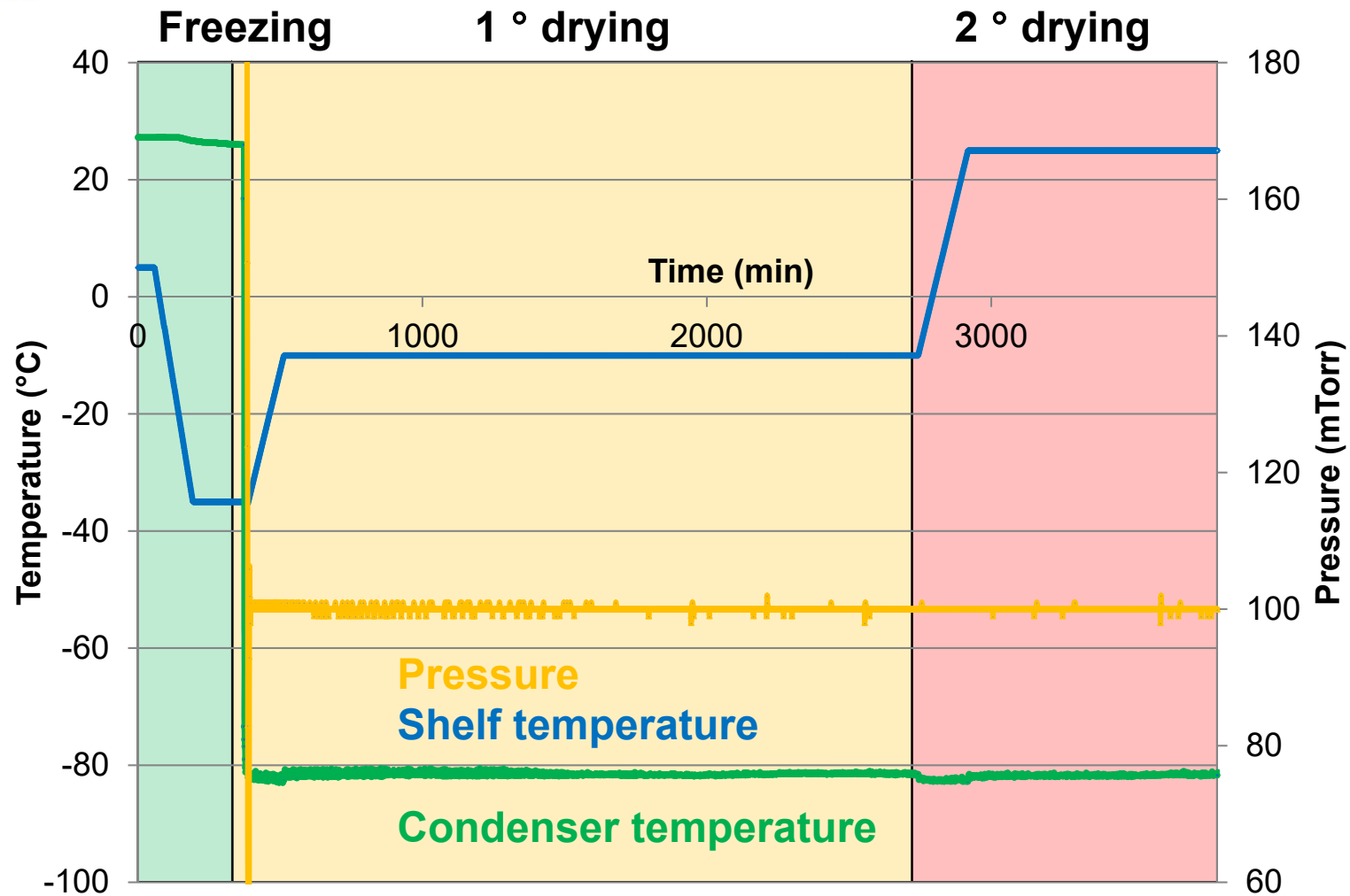


# Freeze drying equipment





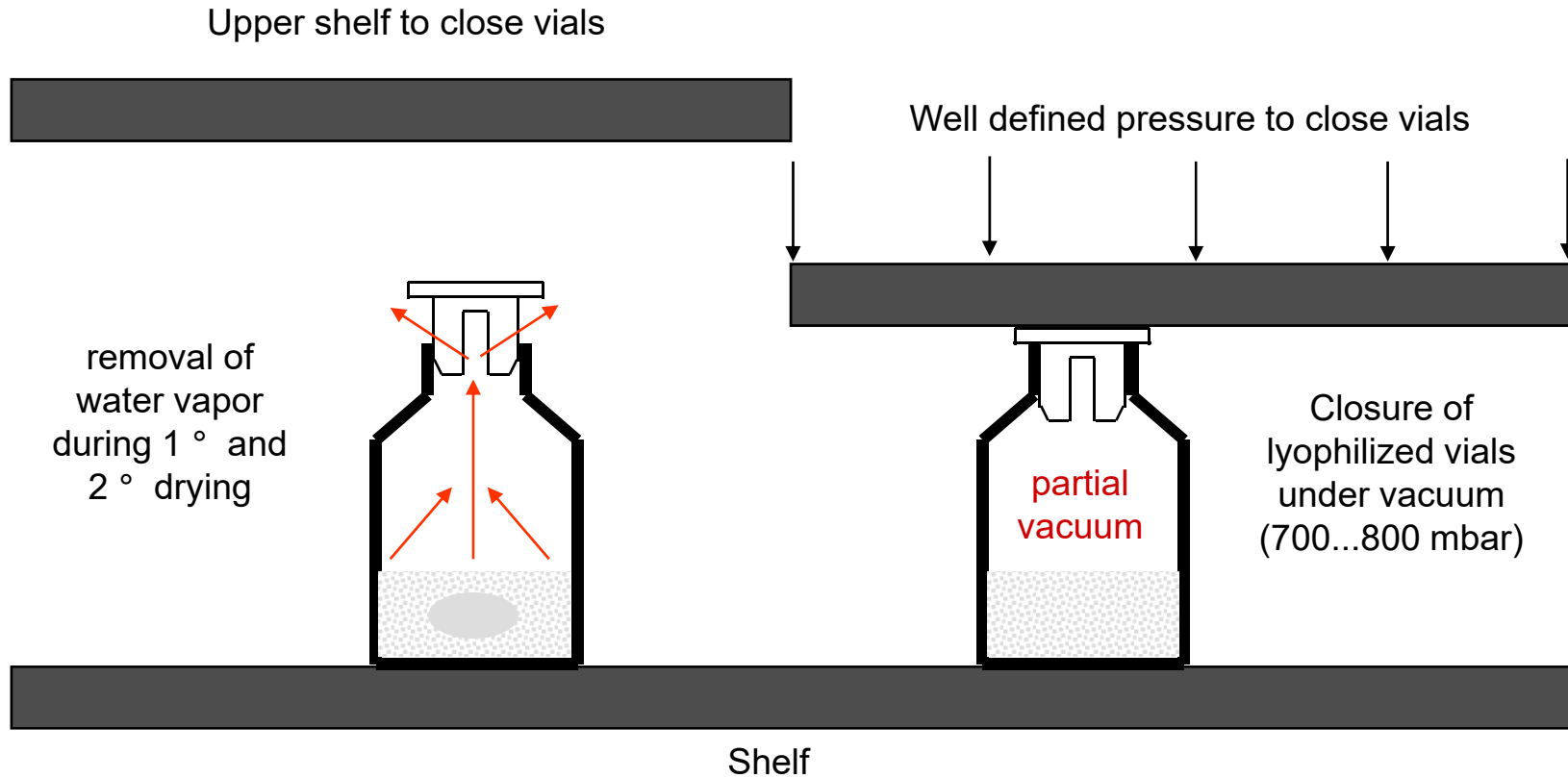
# The Freeze drying process





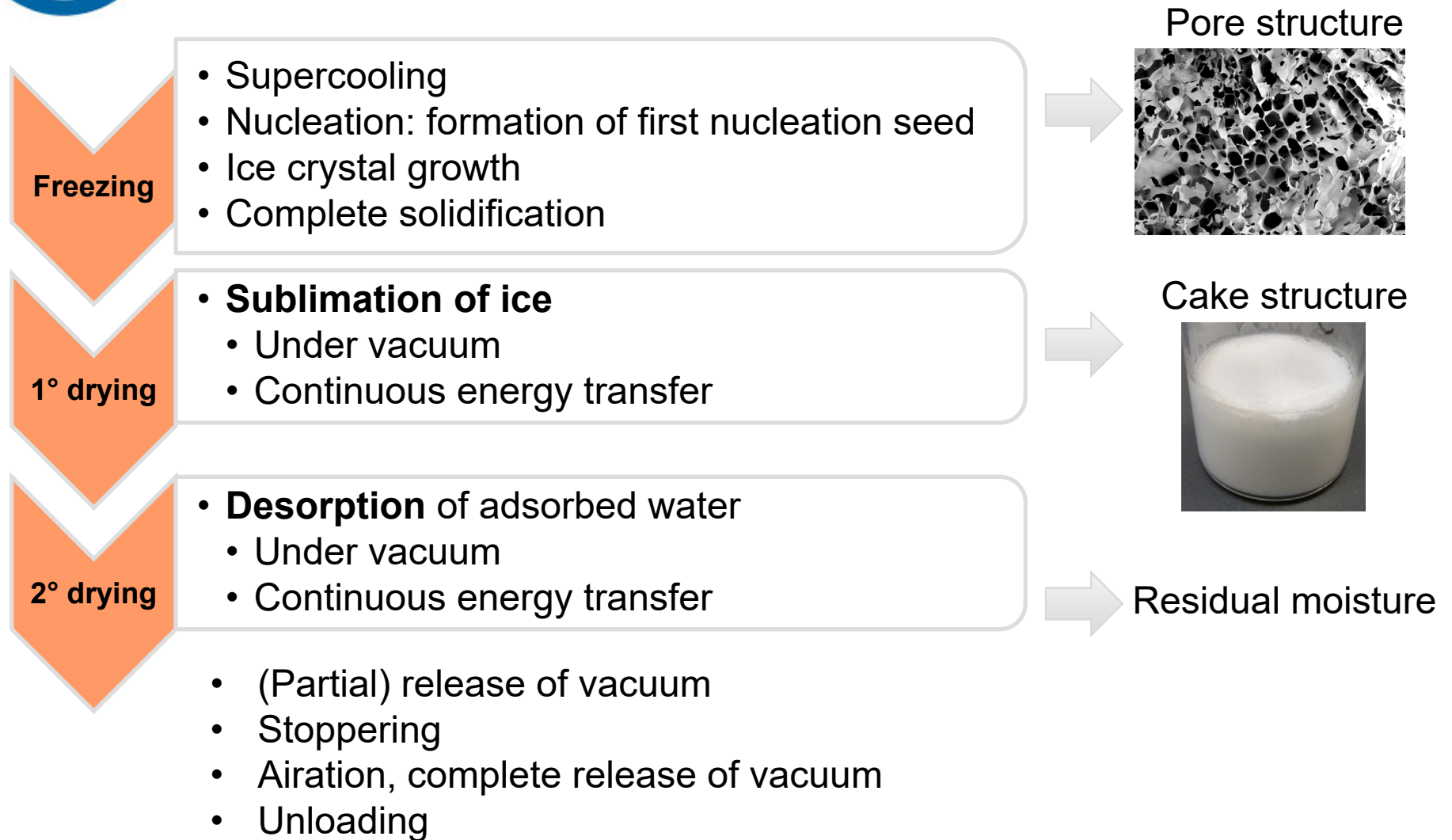
# Stopper position

The upper shelf is used to close the vials of the lower shelf in lyophilizers with several shelves.



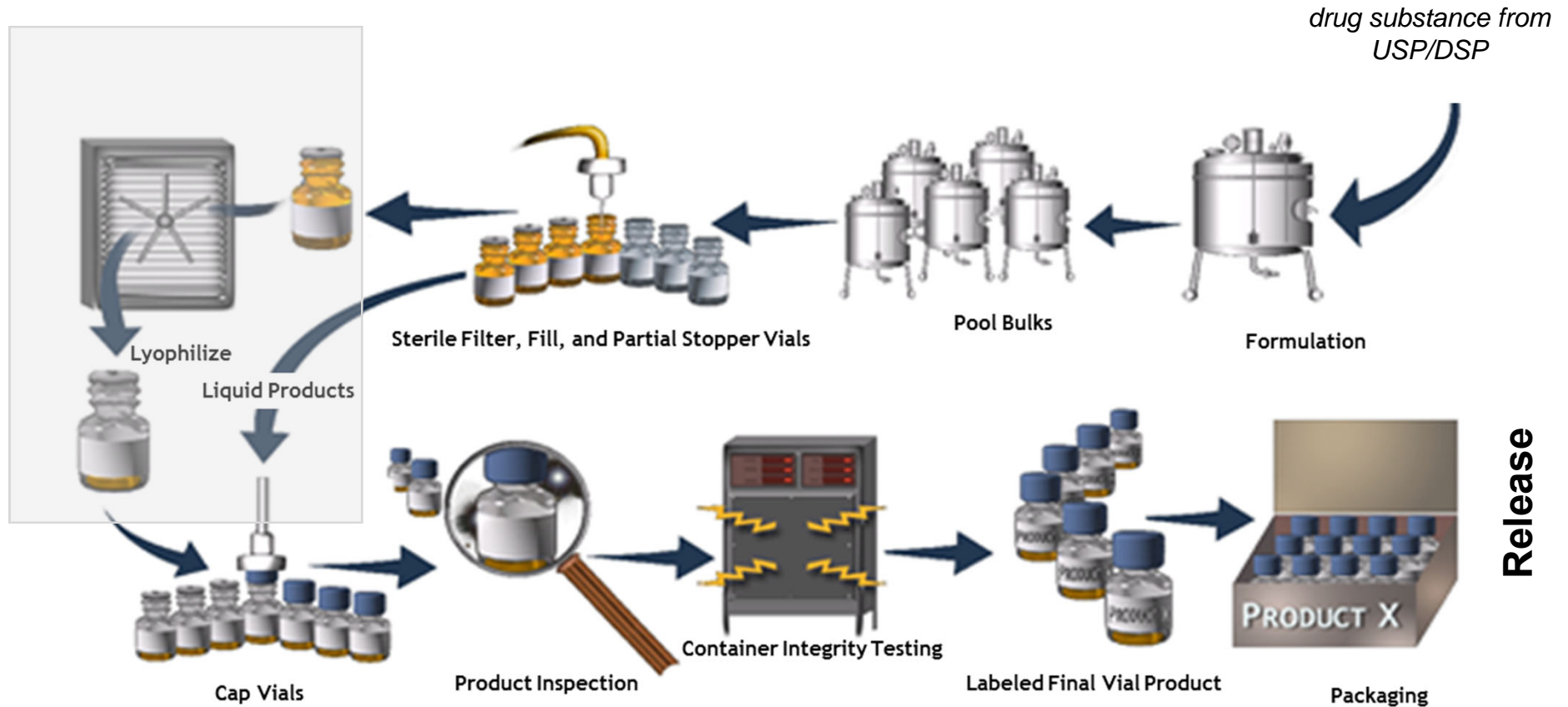


# The Freeze drying process





# Fill-Finish Manufacturing DP







# Pros and Cons for Lyophilization

- **Pro**
  - (in most cases) better stability of e.g. proteins in comparison to liquid formulations
- **Con**
  - Additional process step/ unit operation
  - Time consuming (several days)
  - Energy intensive (>>>90% of constituent are removed)  
→ expensive process!!
  - Batch process (limited batch size)
  - Scale-up and technical transfer needed → highly complex process!
  - For many biologics, the amorphous state has to be maintained in order to have adequate stability
  - Water sensitive (hygroscopic)
  - Handling: Reconstitution step required → Liquid formulations are more convenient/ easier to handle and can be combined with different injection devices