Connecting People, Science and Regulation®

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Theory 1

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- 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 chemcial 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 senstive 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)

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

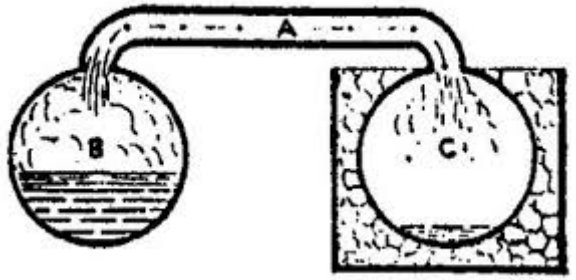
Vacuum freeze drying

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

→ Instant products

Aerospace food

Examples in daily life

Archeology

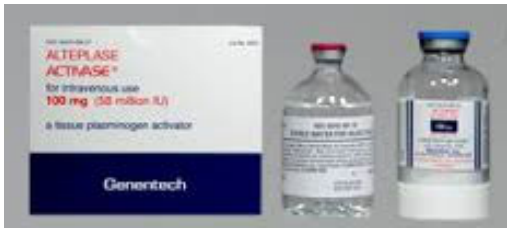
Documents after water damage

Conservation:

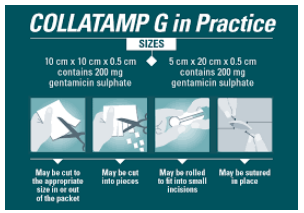
- Preparation of animals
- Decoration

Examples in Pharmaceutical Industry

<u>Biopharmaceuticals:</u>
Monoclonal antibodies, enzymes, peptides, other proteins, vaccines



<u>Special dosage forms:</u>
Sublingual tablets, implants



Collatamp® is a lyophilized collagen matrix with the antibiotics Gentamicin

Antibiotics, small molecules, probiotics

The Freeze drying process

Freezing

- Supercooling
- Nucleation: formation of first nucleation seed
- Ice crystal growth
- Complete solidification

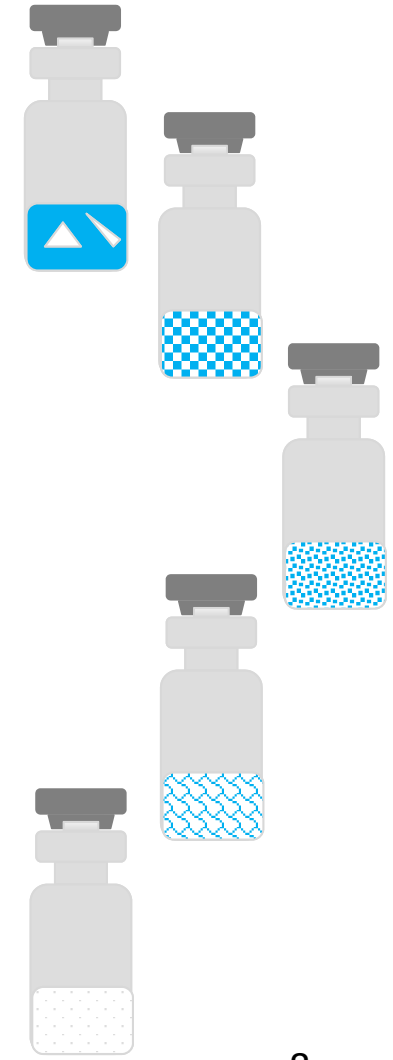
1° drying

- **Sublimation of ice**
  - Under vacuum
  - Continuous energy transfer

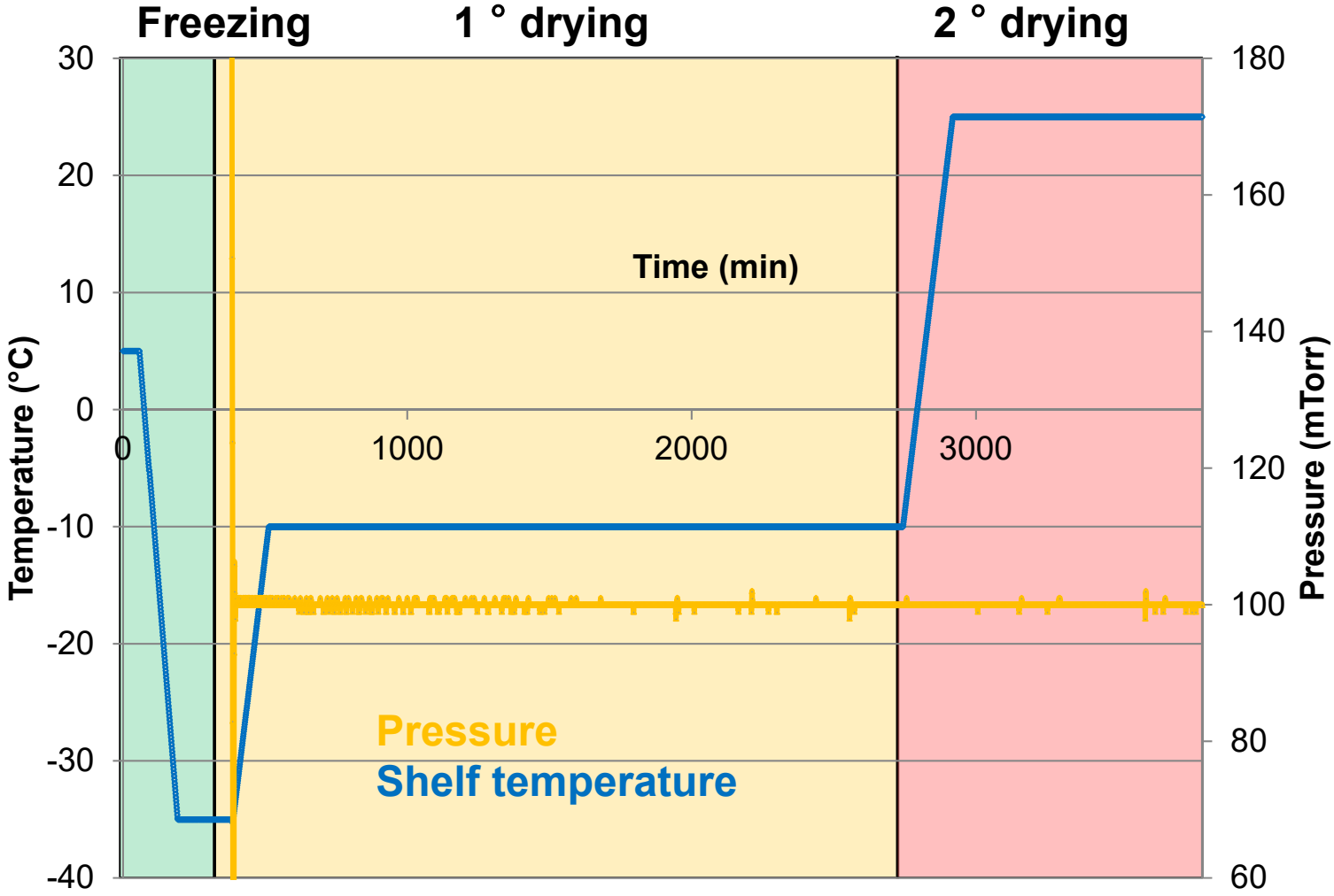
2° drying

- **Desorption** of adsorbed water
  - Under vacuum
  - Continuous energy transfer

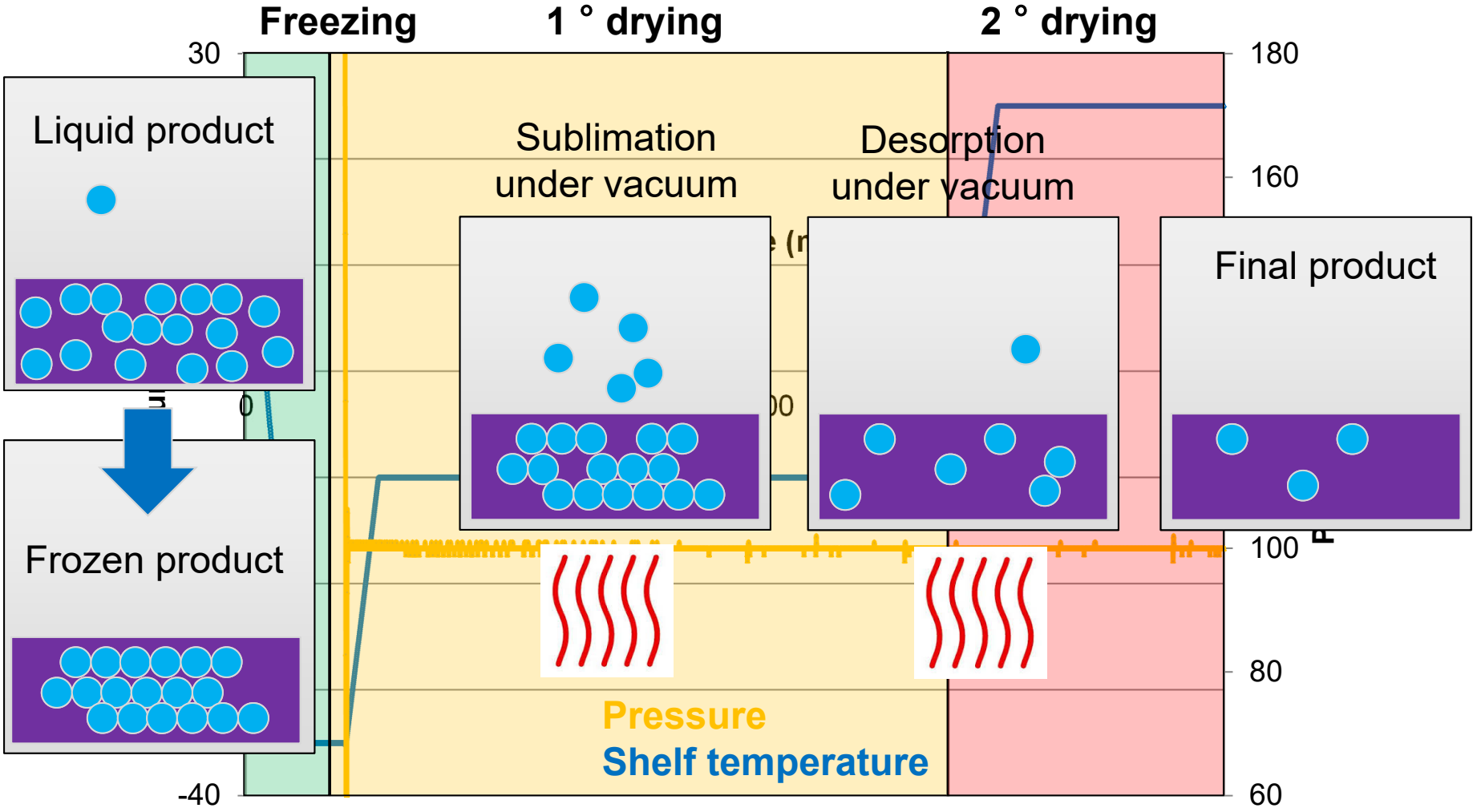
- (Partial) release of vacuum
- Stoppering
- Airation, complete release of vacuum
- Unloading



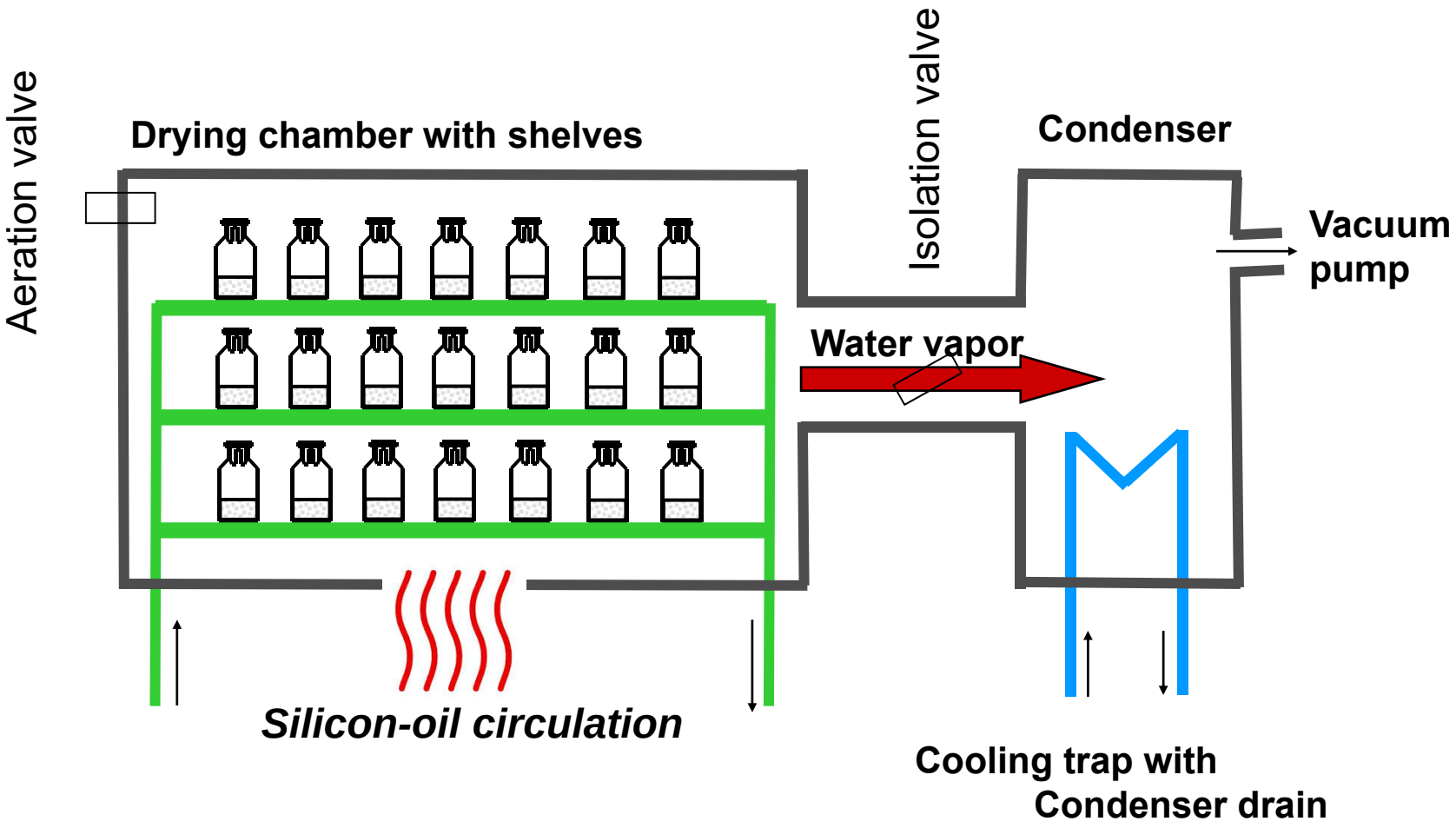
The Freeze drying process



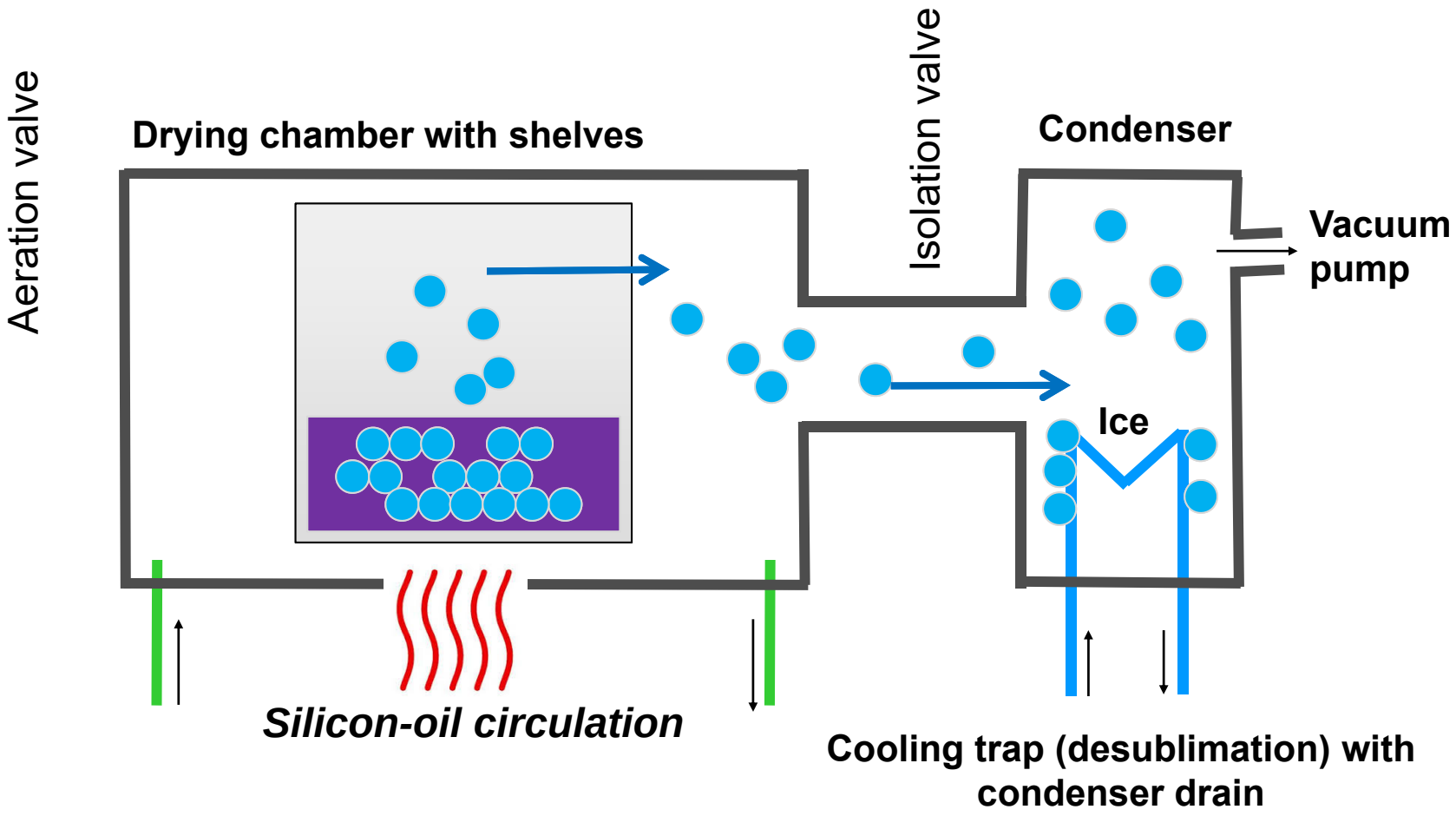
The Freeze drying process



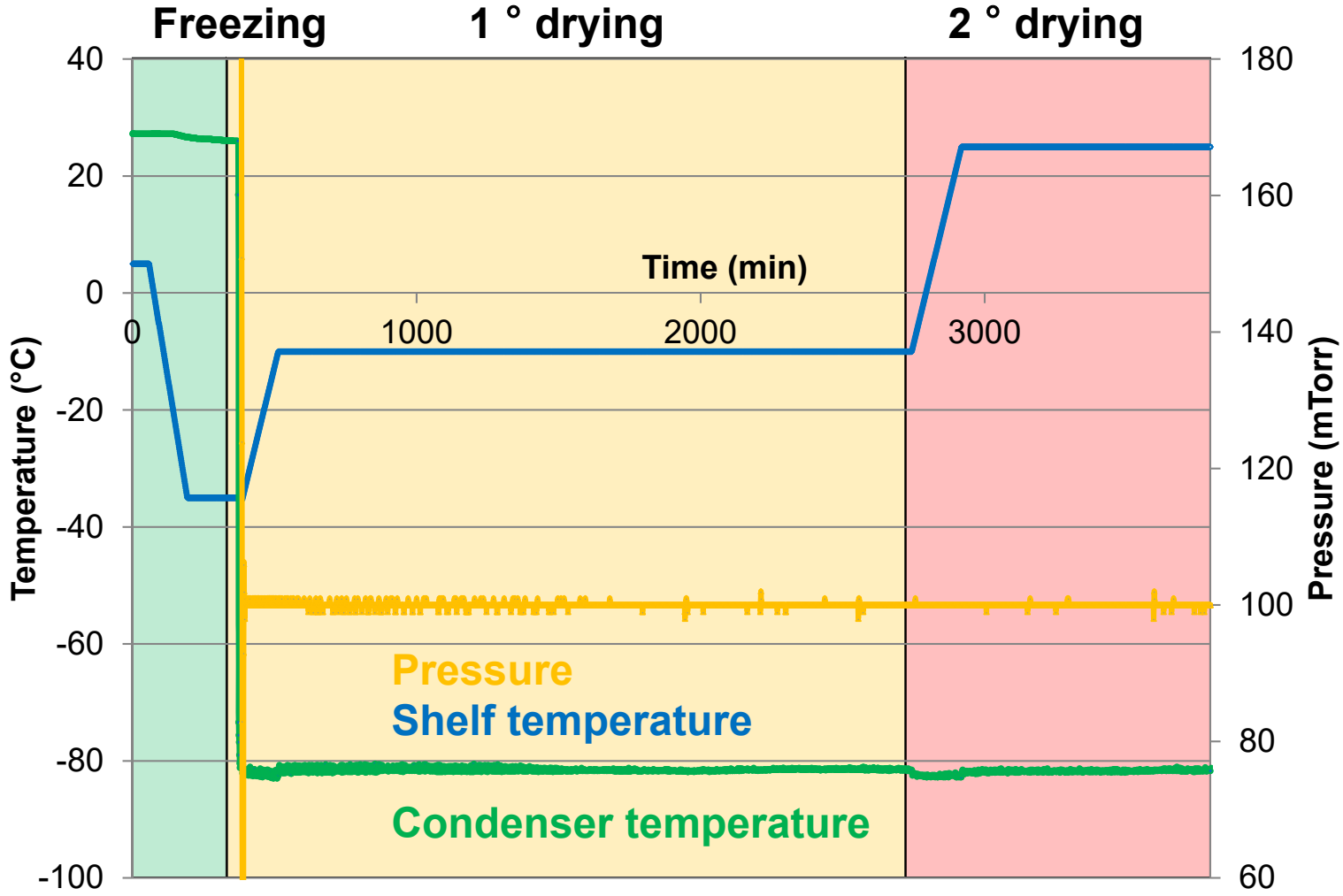
Freeze drying equipment



Freeze drying equipment

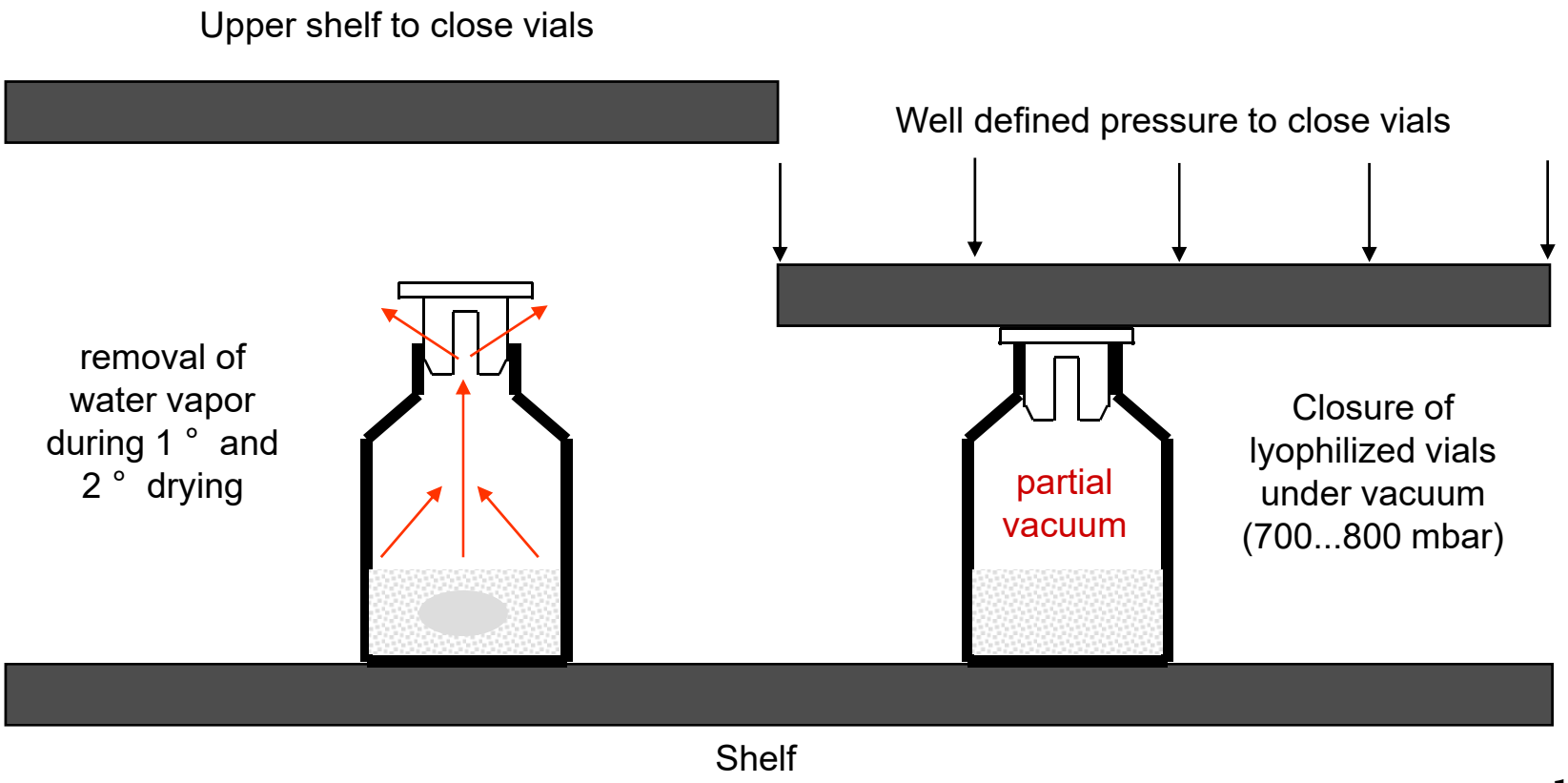


The Freeze drying process



Stopper position

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

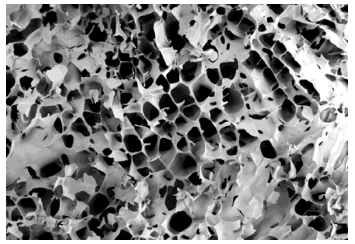


The Freeze drying process

Freezing

- Supercooling
- Nucleation: formation of first nucleation seed
- Ice crystal growth
- Complete solidification

Pore structure



1° drying

- **Sublimation of ice**
  - Under vacuum
  - Continuous energy transfer

Cake structure

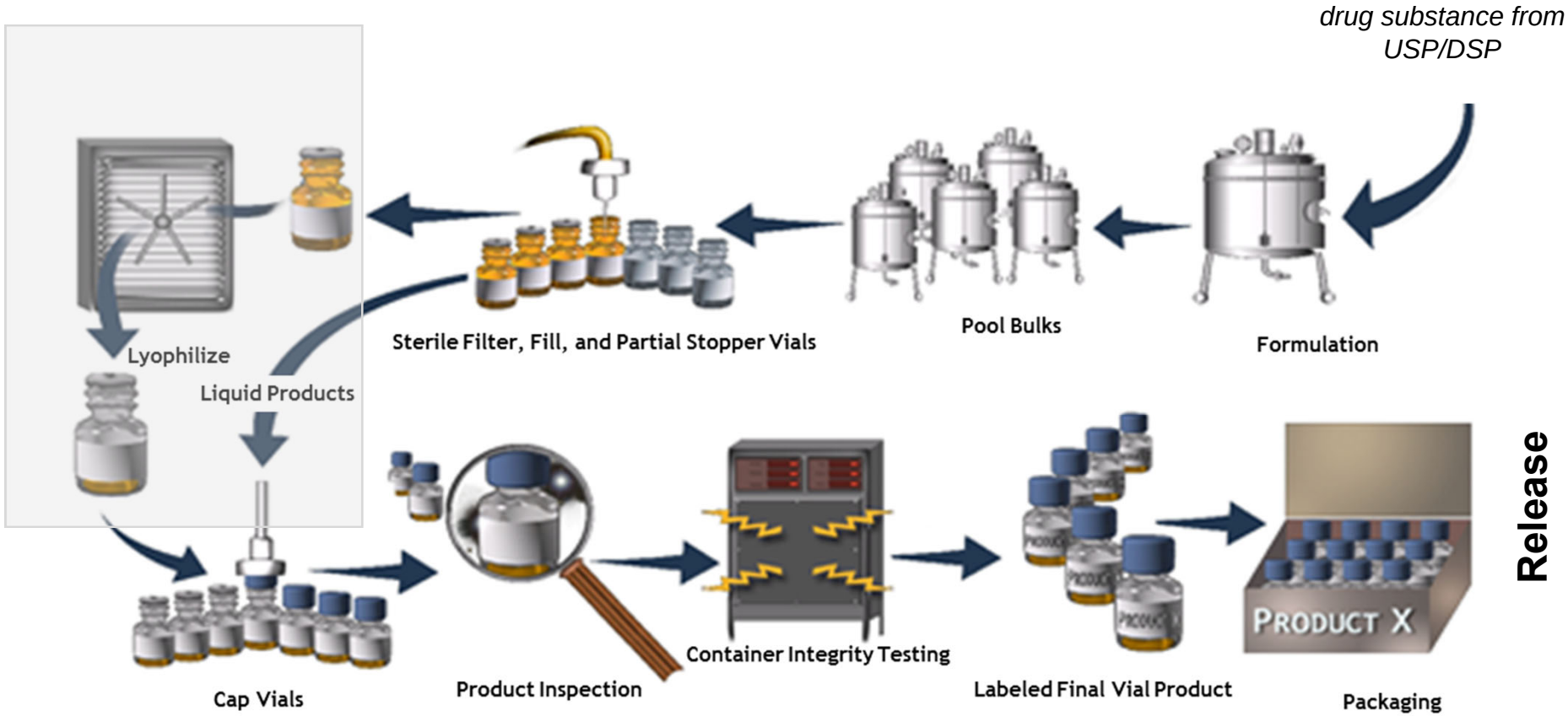
2° drying

- **Desorption** of adsorbed water
  - Under vacuum
  - Continuous energy transfer

Residual moisture

- (Partial) release of vacuum
- Stoppering
- Airation, complete release of vacuum
- Unloading

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 techical 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 wth different injection devices