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Welcome to the PDA Freeze-Drying in Practice Course 2024!

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PDA Parenteral Drug Association

PDA TRAINING

Theory 1

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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

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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
- Standard pharmaceutical 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

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History and Development

Abb. 1: „Ötzi" (Foto: Archiv Südtiroler Landesmuseum, www.iceman.it)

Mummification by cold and dry air flow at reduced pressure (high altitude)

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 (13th to 16th century)

1st large scale freeze-dried pharmaceutical product

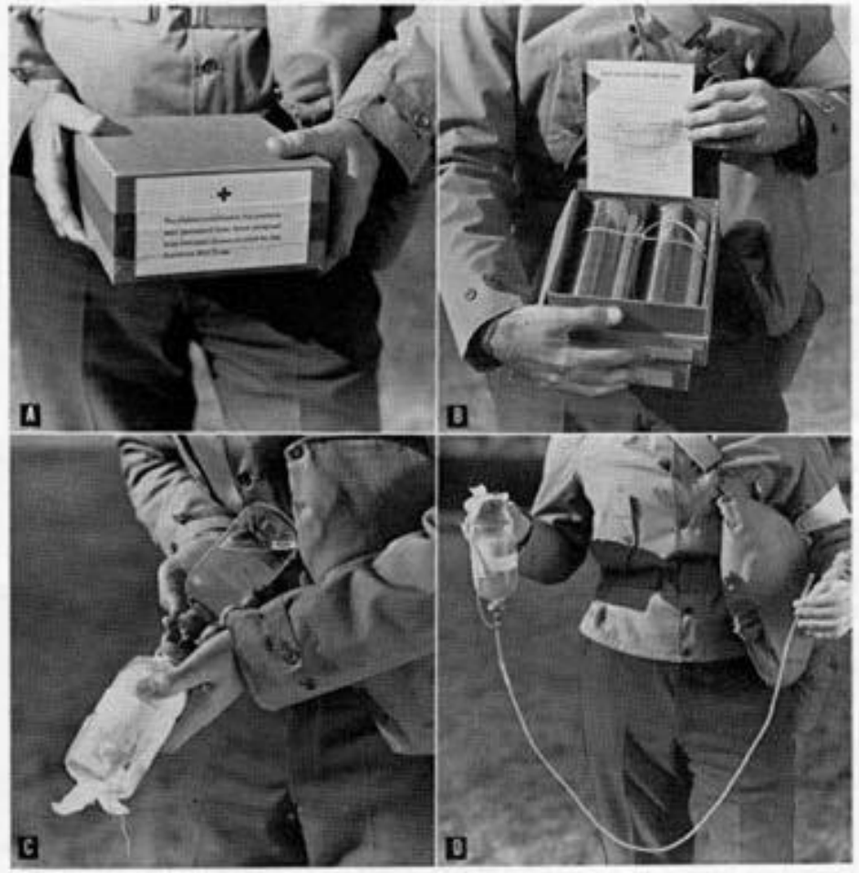

FIGURE 24.—Preparation for plasma transfusion. A. Army-Navy plasma package (250 cc.). B. Contents of package (dried plasma and sterile diluent). C. Reconstitution of plasma. D. Reconstituted plasma ready for injection.

Human blood plasma in World War II

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Examples from food industry

Preserve color and taste

Instant products

Aerospace food

Examples from other fields

Archeology

Z. Shaozhi et al. Journal of Cultural Heritage. 2016.
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Conservation:

- Preparation of animals
- Decoration

Document restoration

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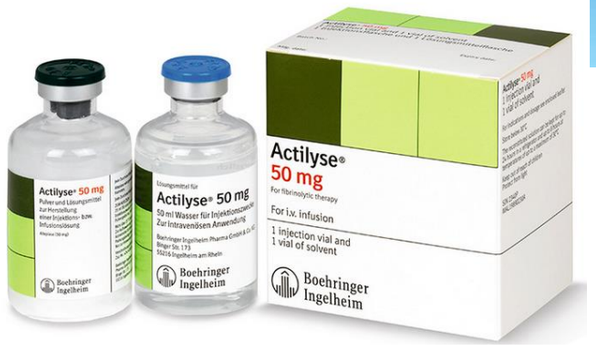
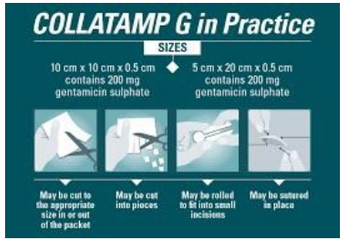
Examples in Pharmaceutical Industry

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

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Freeze drying process

Freezing

- Supercooling
- Nucleation: crystallization of water
- Ice crystal growth
- Complete solidification

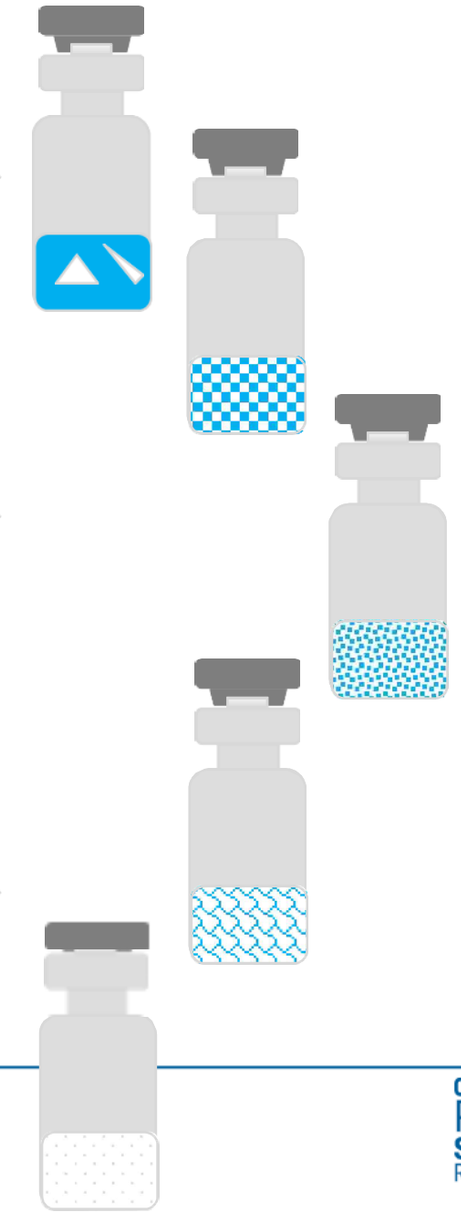
1° drying

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

2° drying

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

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



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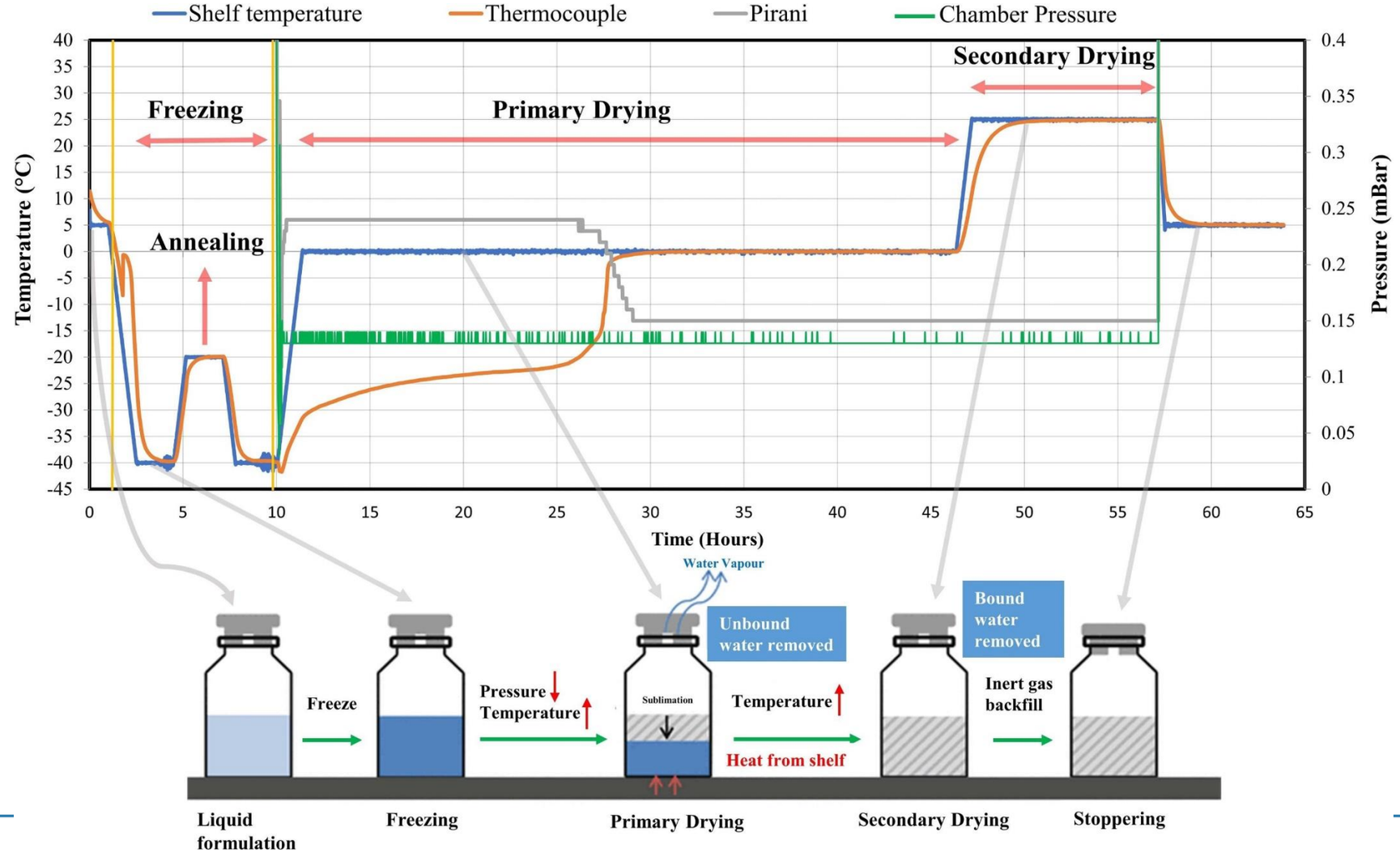
Freeze drying process



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Freeze drying process

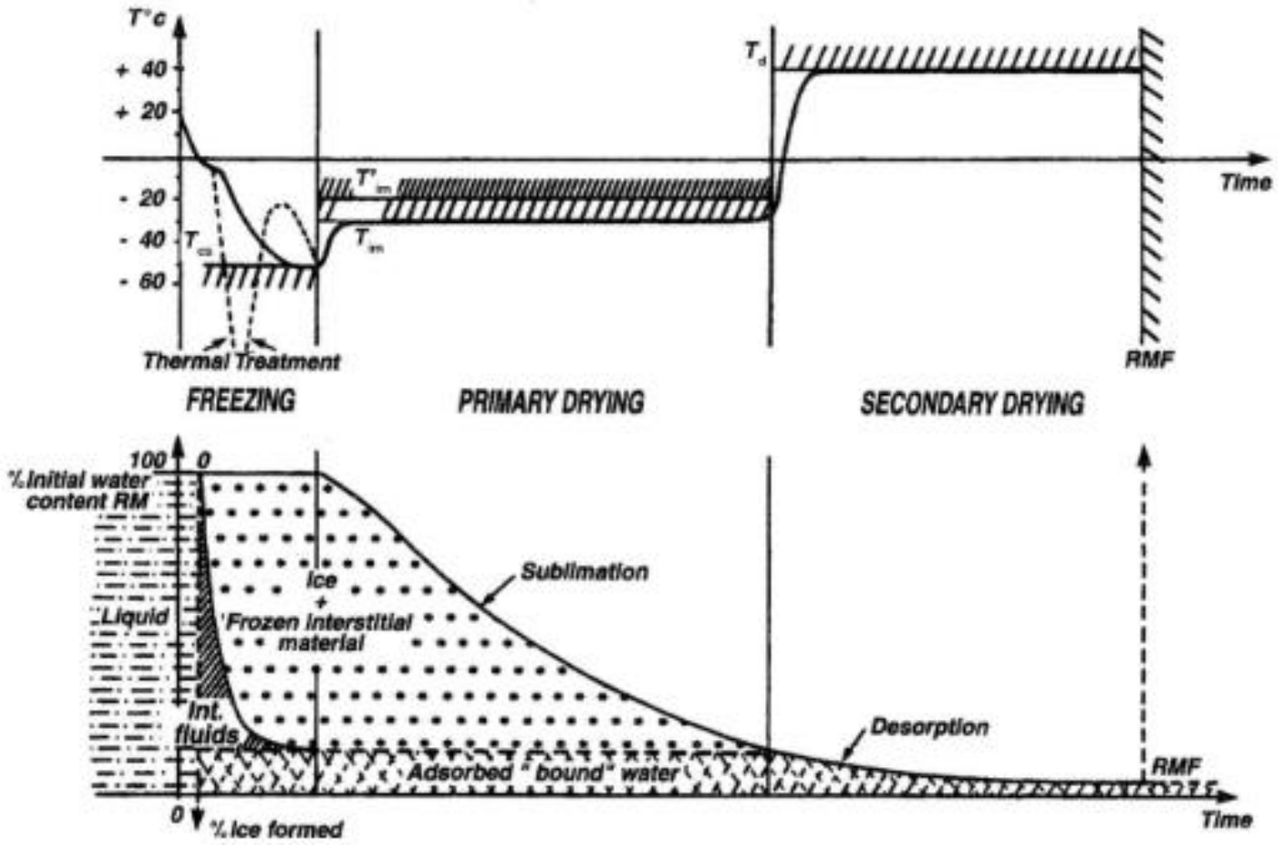

FIGURE 1 Schematic evolution of the freeze-drying process. Temperatures (*upper curve*) and water content (*lower curve*) versus time are indicated. *Abbreviations*: T_{cs}, maximum temperature of complete solidification; T_{im}, minimum temperature of incipient melting; T'_{im}, absolute limit for fast process; T_d, maximum allowed temperature for the dry product; RMF, final requested residual moisture.

Reprinted from "Freeze Drying/Lyophilization of Pharmaceutical and Biological Products" edited by Louis Rey and Joan C. May, © 2010 Informa Healthcare

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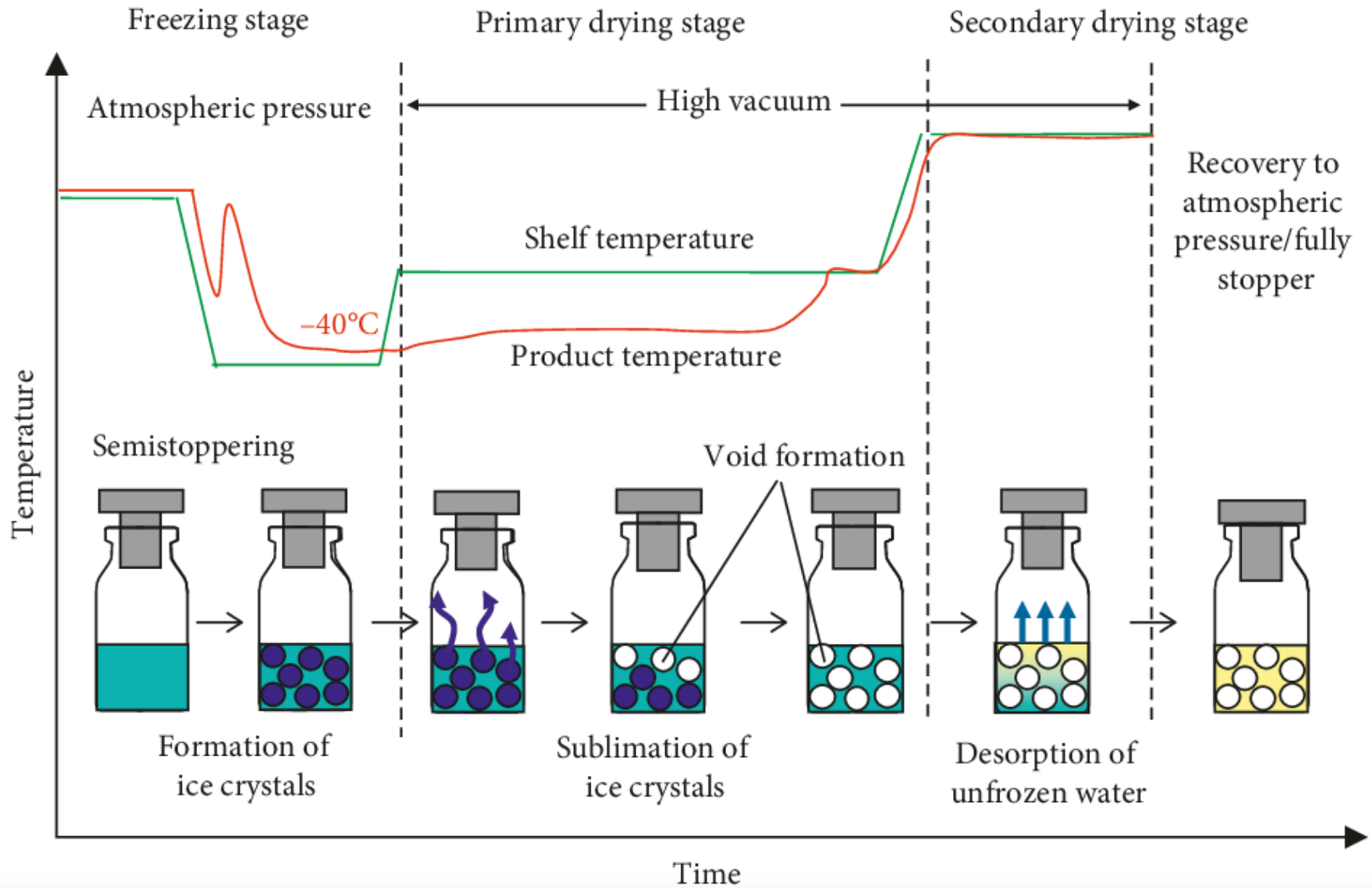
Freeze drying process



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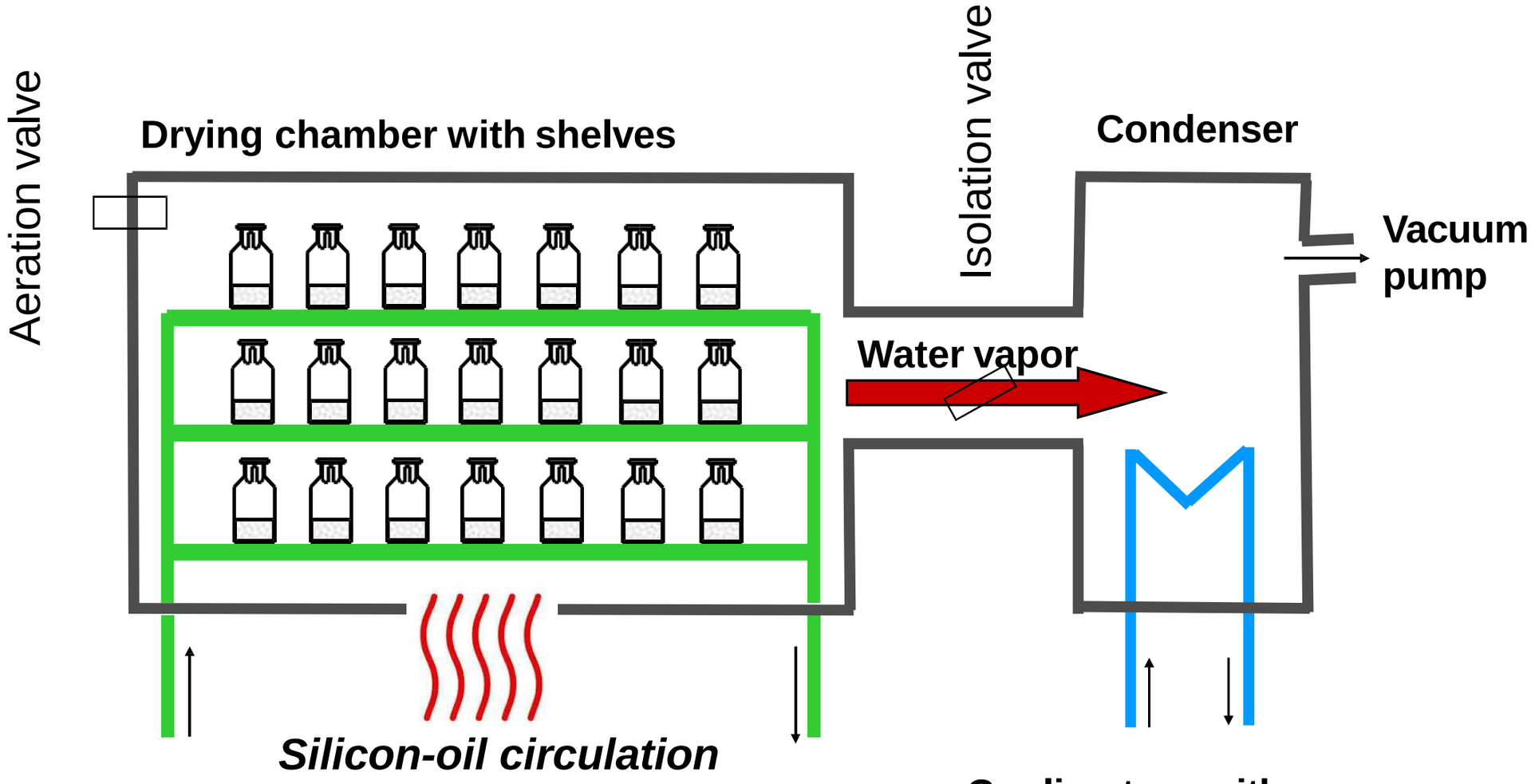
Freeze drying equipment



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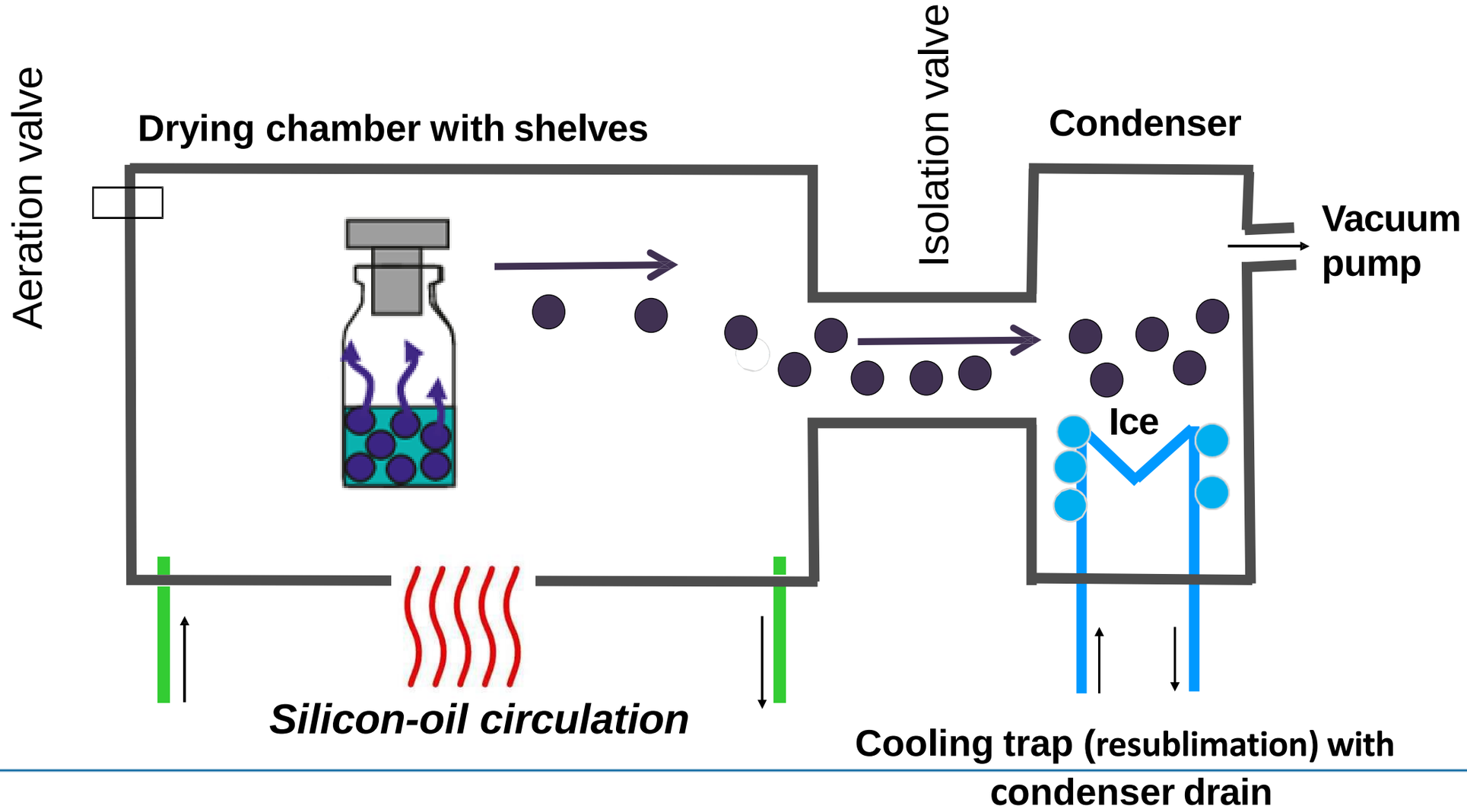
Freeze drying equipment



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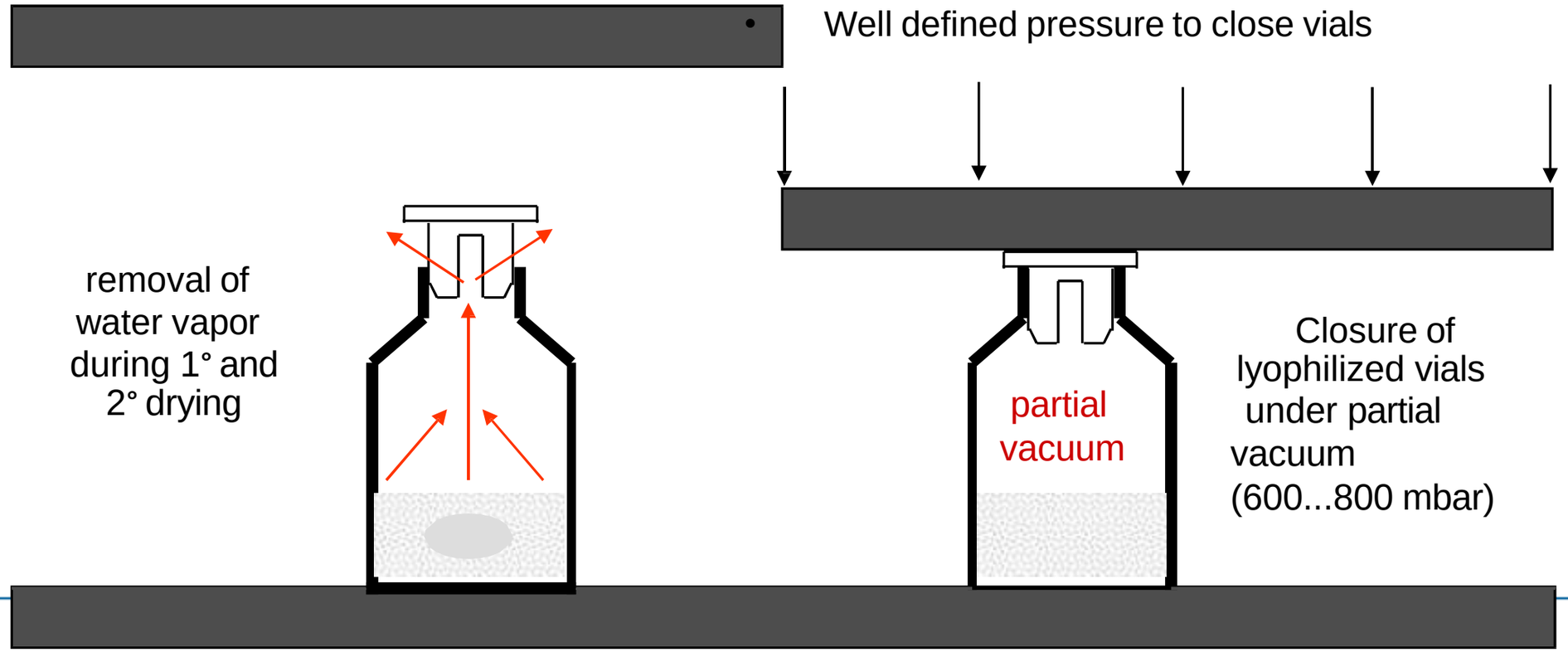
Stopper position

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

- Upper shelf to close vials
- Well defined pressure to close vials



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The Freeze drying process

Freezing

- Supercooling
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1° drying

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2° drying

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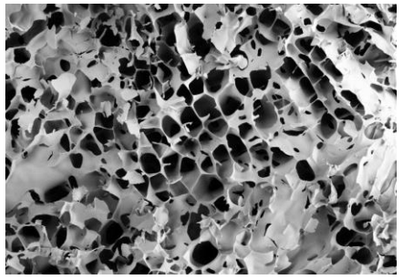
Pore structure



Cake structure

Residual moisture

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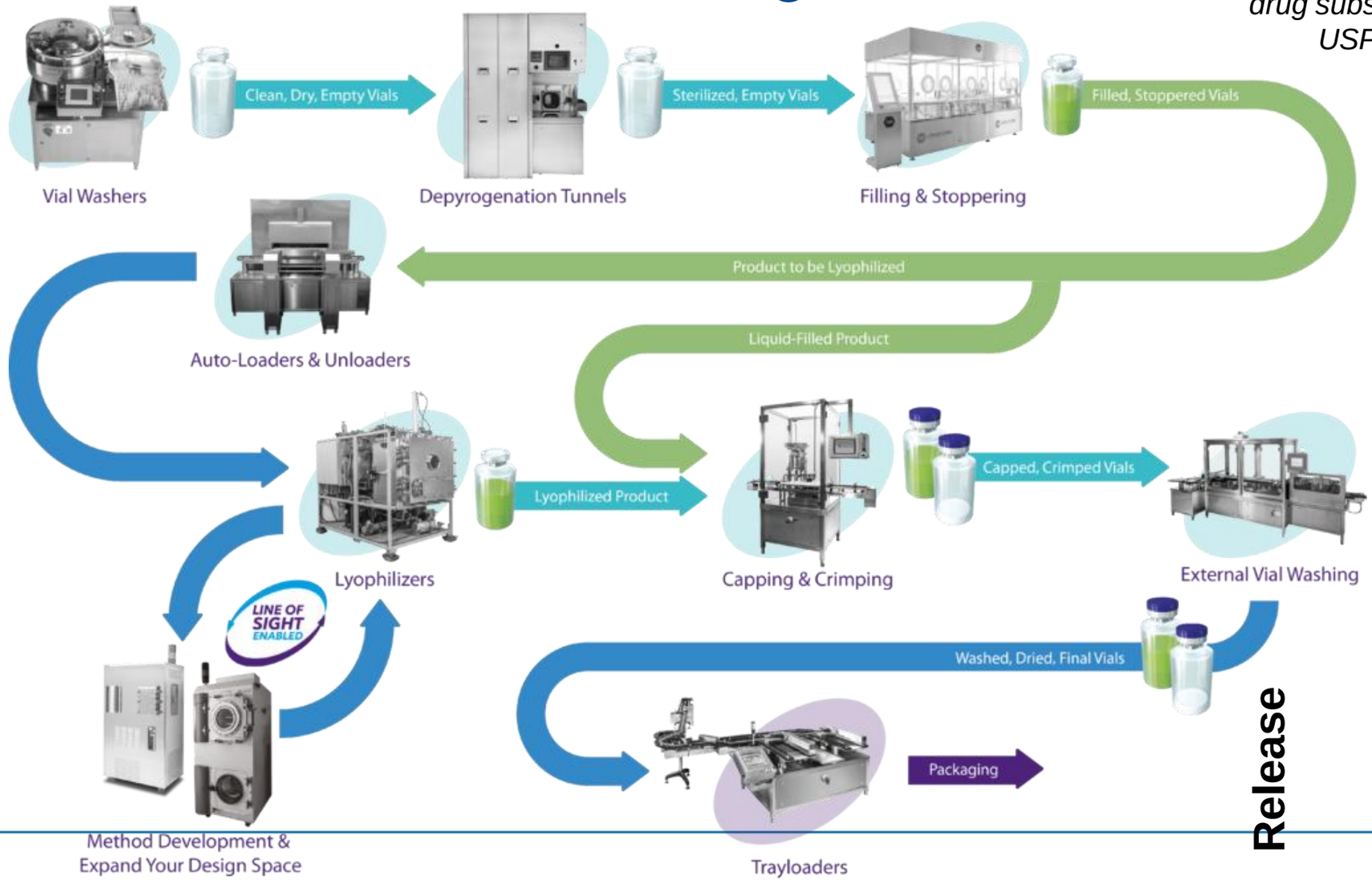
Fill-Finish Manufacturing DP

drug substance from USP/DSP



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Pros and Cons for Lyophilization

- **Pro**
  - (in most cases) better stability of e.g. proteins in comparison to liquid formulations
  - „platform“ technology to enable higher speed to FiM study
  - might become a game changer for overcoming deep temperature storage challenges with new delivery systems like LNPs, VLP, …
- **Con**
  - Additional process step/ unit operation
  - Time consuming (several days)
  - Energy intensive (>90% of constituent are removed) → $$$ 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 product (hygroscopic)
  - Handling: Reconstitution step required → Liquid formulations are more convenient/ easier to handle and can be combined w/ different injection devices

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