Welcome to PDA Europe
Post Conference Training Course

Development of a Freeze Drying Process

- From Formulation to a Robust Process -

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Agenda:

First Day – Physics, Thermodynamics and Scientifics

- *Accomodation & Introduction*
- *Nucleation (Freezing Process)*
- *Sublimation (Drying Process)*
- *Desorption (Setting of Residual Moisture)*

(Scientific Basics, Sensoring and PAT, Exercises)

Agenda:

Second Day – Engineering and Practice

- *Repetition of Previous Day / Wake-Up questions*
- *Module Structure of a Freeze Dryer*
- *Qualification & Validation – Hints for the SAT*
- *Qualification, Validation and Cleaning of freeze dryers*
- *Chilling End*

CV Georg Frinke:

→ Oct 2001 Graduation *Mechanical engineer/ Thermodynamics* ***(UAS Cologne)***

→ Apr 2004 *Modularization of Lyophilizers* ***(GEA Lyophil)***

→ May 2006 *Development of a DV-VHP-Process for Lyophilizers (Patent)*

→ Dec 2007 *Implementation of a BTM-Procedure/PAT*

→ June 2010 *System & Process Engineer for a double-Lyo near Basel* ***(Optima)***

→ April 2012 *Process Engineer for international Lyo-Projects (China / Russia)*

→ April 2012 – *Aug 2016 Process & Site Engineer for a clinical production site of Janssen R&D Schaffhausen / Switzerland*

Since September 2016 Site Engineer for Bayer Pharma Wuppertal

Since 2007 ***Voluntary support for the valuable PDA Europe***

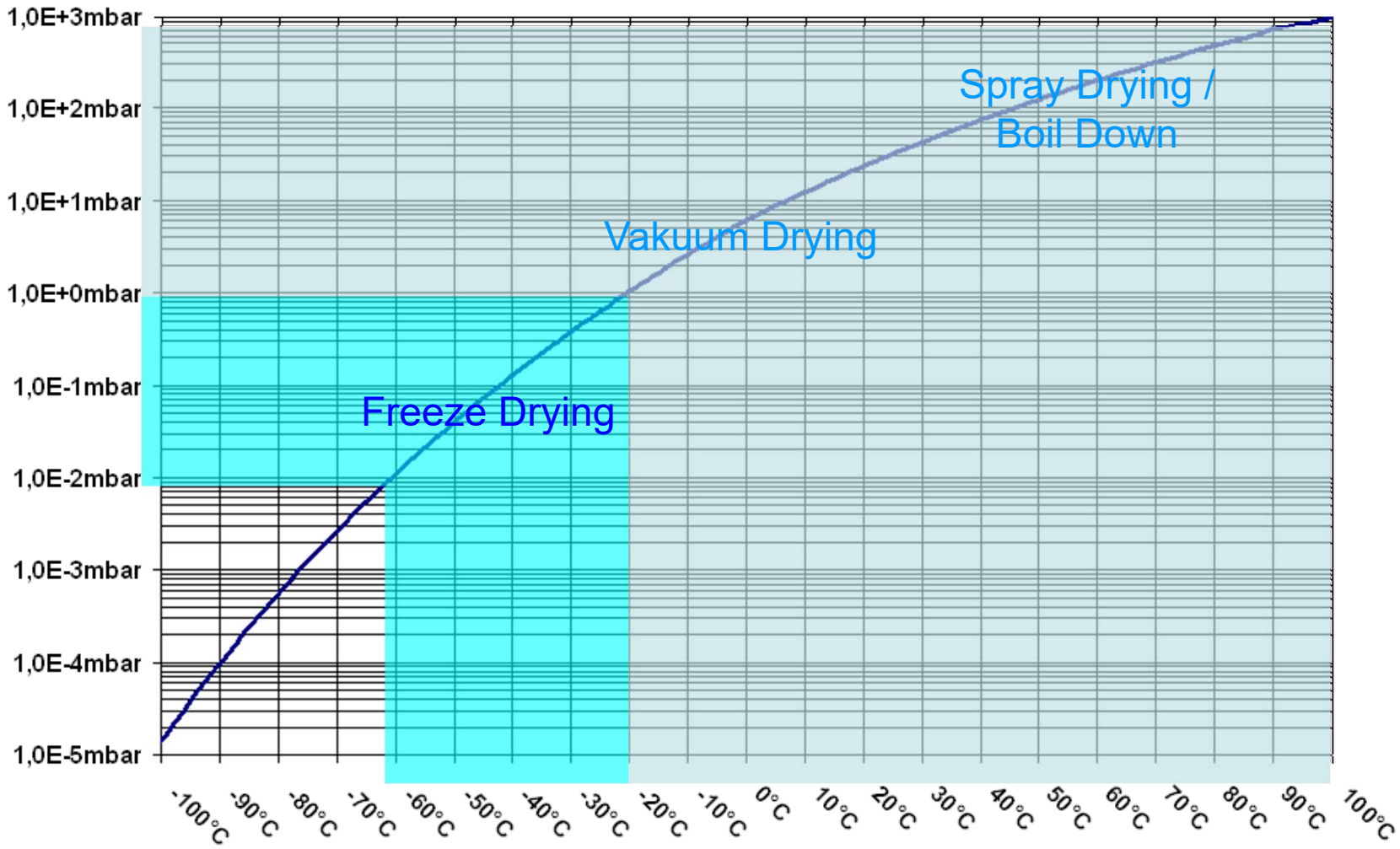
First Approach to drying:

- Drying Technologies – an Overview
- Advantages of Freeze Drying
- History of Freeze Drying
- Schematic of a freeze drying process

General aspects of drying:

- Separation and removal of liquid / solid (frozen) water by evaporation
- The different methods mainly differentiate by evaporation temperature and corresponding pressure
- Higher temperatures increase risk of chemical side reactions
- The higher level of energy allows higher process performance

Drying Technologies – an Overview



Drying Technologies – an Overview

	Through-put Index	Continuous Process	Physical conditions	Side Effects / Disadvantages
Spray Drying	10.000	Yes	Liquid (Aerosol), Evaporation at high temperature, Dry output at high temperatue	Chemical reactivity needs to be considered at process development
Vacuum Drying	10	Not realized	Liquid, Evaporation at low temperature, Dry output at low temperatue	Interaction of concentration effects with drying effects, molecules are not immobilized during Drying
Freeze Drying	1	Not pharma-ceutically realized	Solid, Evaporation at low temperature, Dry output at low temperature	Concentration effects during freezing phase needs to be considered

Freeze Drying:

- The basic idea is to completely remove water from some material while leaving the basic structure and composition of the material intact
- Since the process is carried out at low temperature, it is most suitable for heat-sensitive compounds
- Therefore freeze drying is particularly suitable for the production of parenterals whenever other drying or stabilization methods are not applicable

Principle Advantages of Freeze Drying:

- With regard to physico-chemical and microbiological decomposition the removal of water leads to a much better stability
- Product is immobilized during Drying
- No change of concentration during Drying
- Lowest molecular energetic level -> important for temperature sensitive products (e.g. proteins)

Principle Advantages of Freeze Drying:

- Product temperature can be easily tuned very accurate everytime in the cycle
- Everything dessicable can be lyophilized
- Everything freezable can be lyophilized
- Removal of solvent at frozen conditions allows easy reconstitution

=> When you can freeze, but not thaw a product, lyophilize it

Generals

- Lyophilization derived from Greek:

  “lyo” + “phil”: well solutable, easy to solute

- Freeze Drying means the removal of water under frozen/solid conditions
- Freeze Drying and Lyophilization are synonyms

Further Advantages of Freeze Drying:

- Lyophilization allows drying at the final product container
- High Accuracy of dosage possible
- Product handling in inertial atmosphere with standard equipment possible

History of Freeze Drying (I):

- Drying of frozen vegetables at air below freezing point (Highlands of south american mountains)
- There is no known specific inventor of freeze drying as it seemed to be more of an evolutionary process
- First industrial production at world war II in 1940 (Blood Plasma, antibiotics)

History of Freeze Drying (II):

- Neumann introduces method for detection of ice temperature by pressure measurements in 1958 (barometric/manometric ice temperature measurement
- Freeze drying really took off in the 1960‘s
- Current general design of industrial Freeze Dryers introduced first time to market at early 70ies (batch based)

Freeze dried products

- ✓ **Food**
- ✓ **Pharmaceuticals**
- ✓ **Chemicals**
- ✓ **Further application**
  - Archaeology
  - Freez dried flowers
  - Taxidermy
  - Restauration (e.g. water-damaged documents)

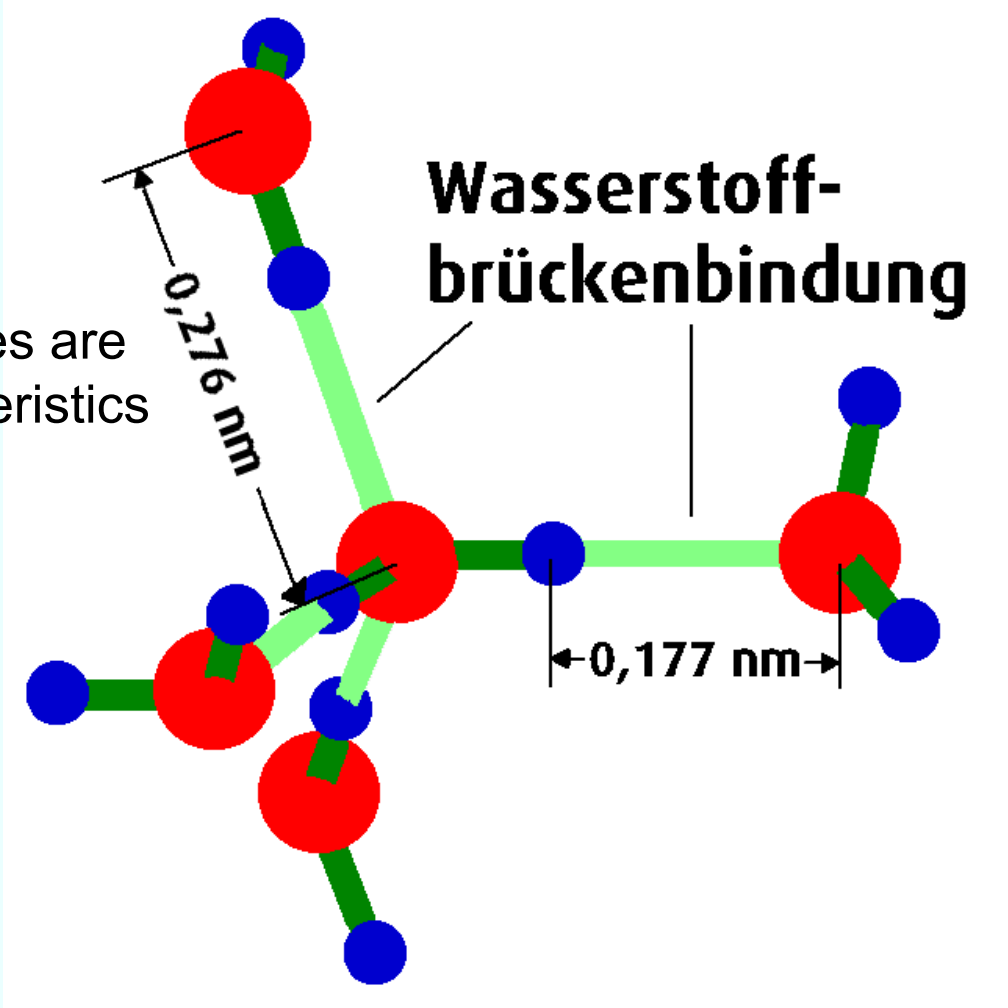
Components of Formulation

- Solvent (mostly water, sometimes organic solvents e.g. ethanol, tBA)
- Buffer / (Isotonic / pH)
- Stabilizers (e.g. Sucrose, Trehalose) / Structure building ingredients (e.g. Mannitol)
- Tensids
- Further adjuvants
- API

The final formulation is a specific composition with respect to the requirements for long term storage of the API.

Properties of Pure Water

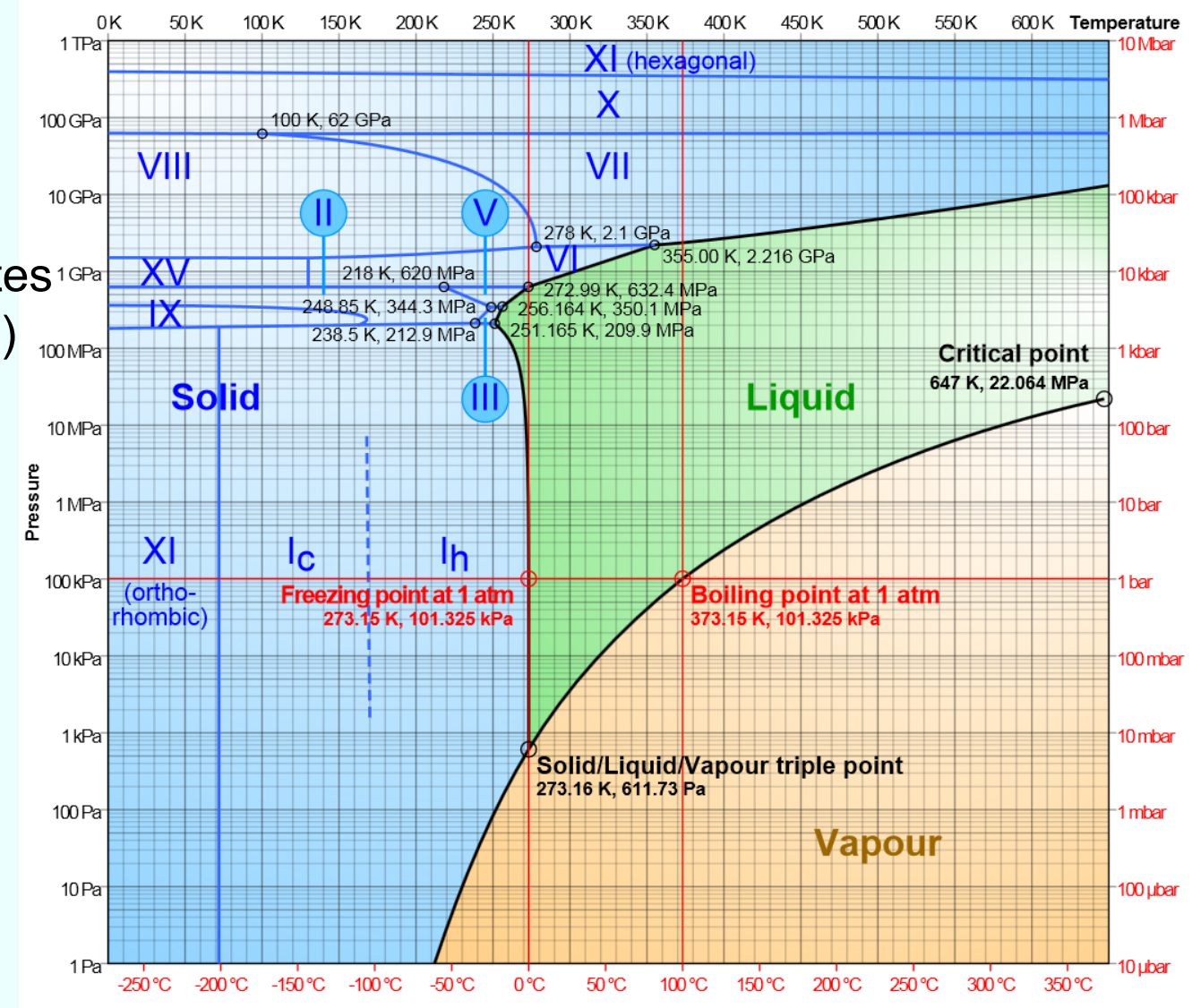
- Molecular weight: 18,02g/mol
- Physical and chemical properties are given by molecular dipol characteristics
- Basis for acid-base reactions



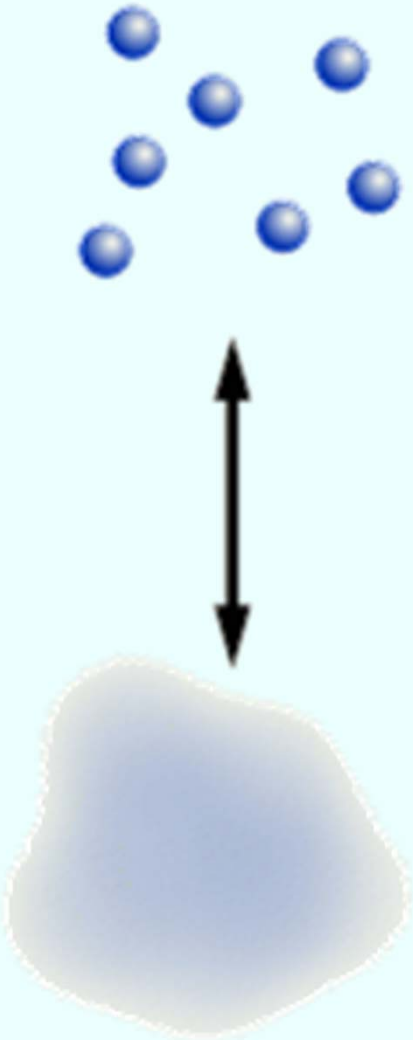
Triple Point

- All three aggregates (steam, water & ice) coexist at same pressure and temperature

ϑ_{Tr}: 0,01°C
p_{Tr}: 6,12mbar



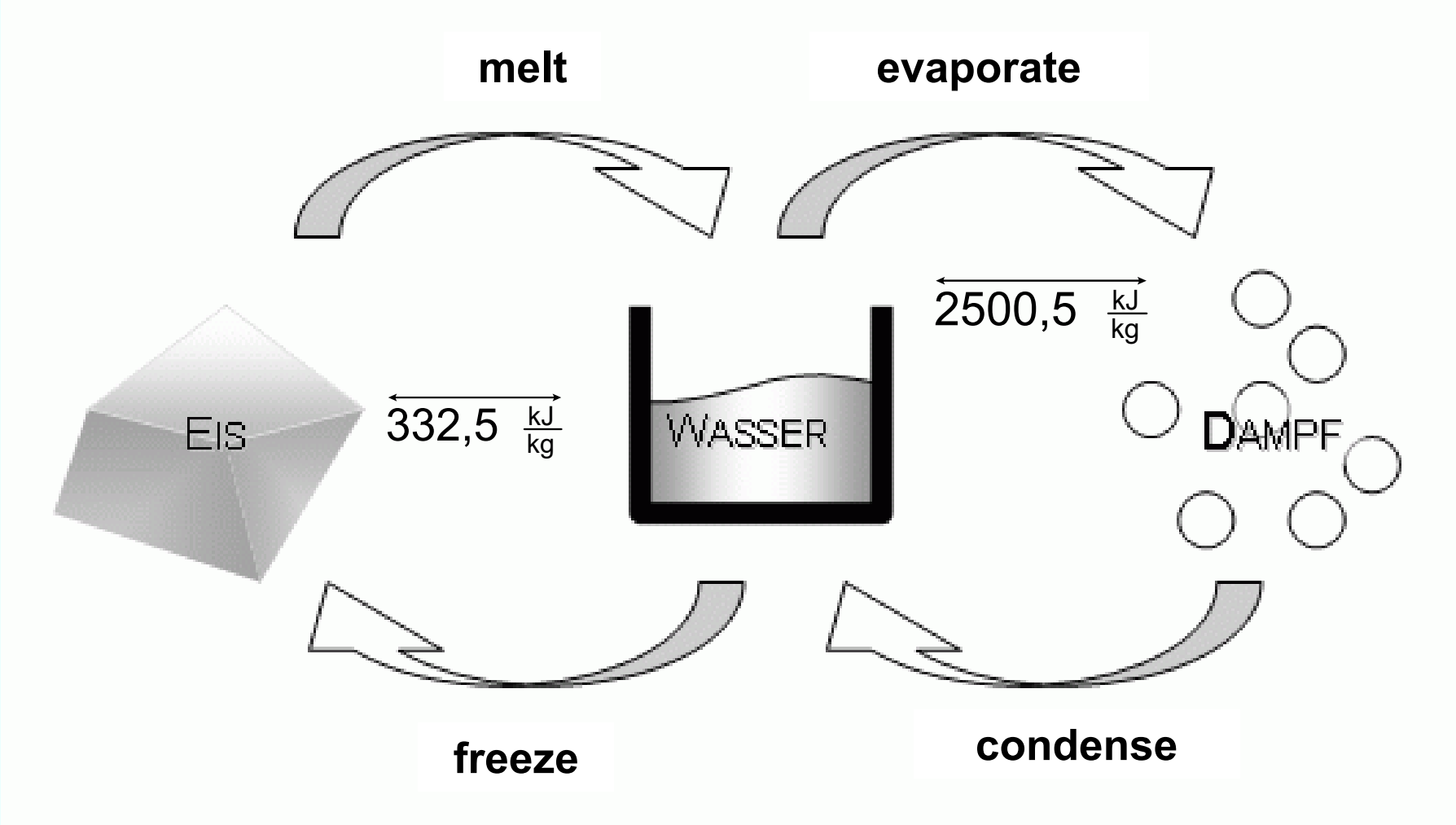
Equilibrium by mass law equation



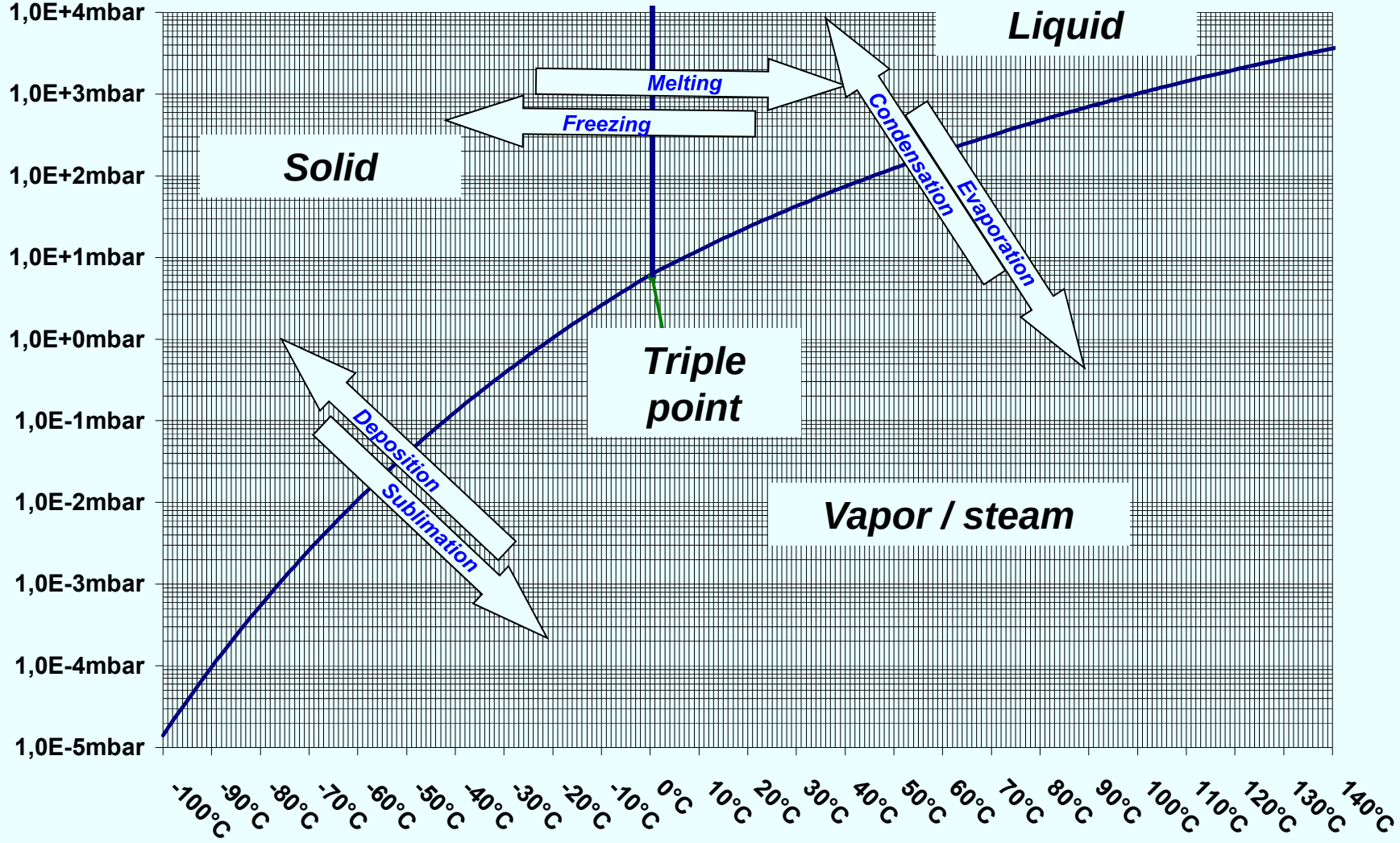
- Kinetic balance at phase border of two or more aggregates
- Vapor pressure and vapor temperature are explicitly related => ***saturated vapor curve***
- Below triple point ice evaporates directly => ***sublimation***
- Equal heat flux between two phases

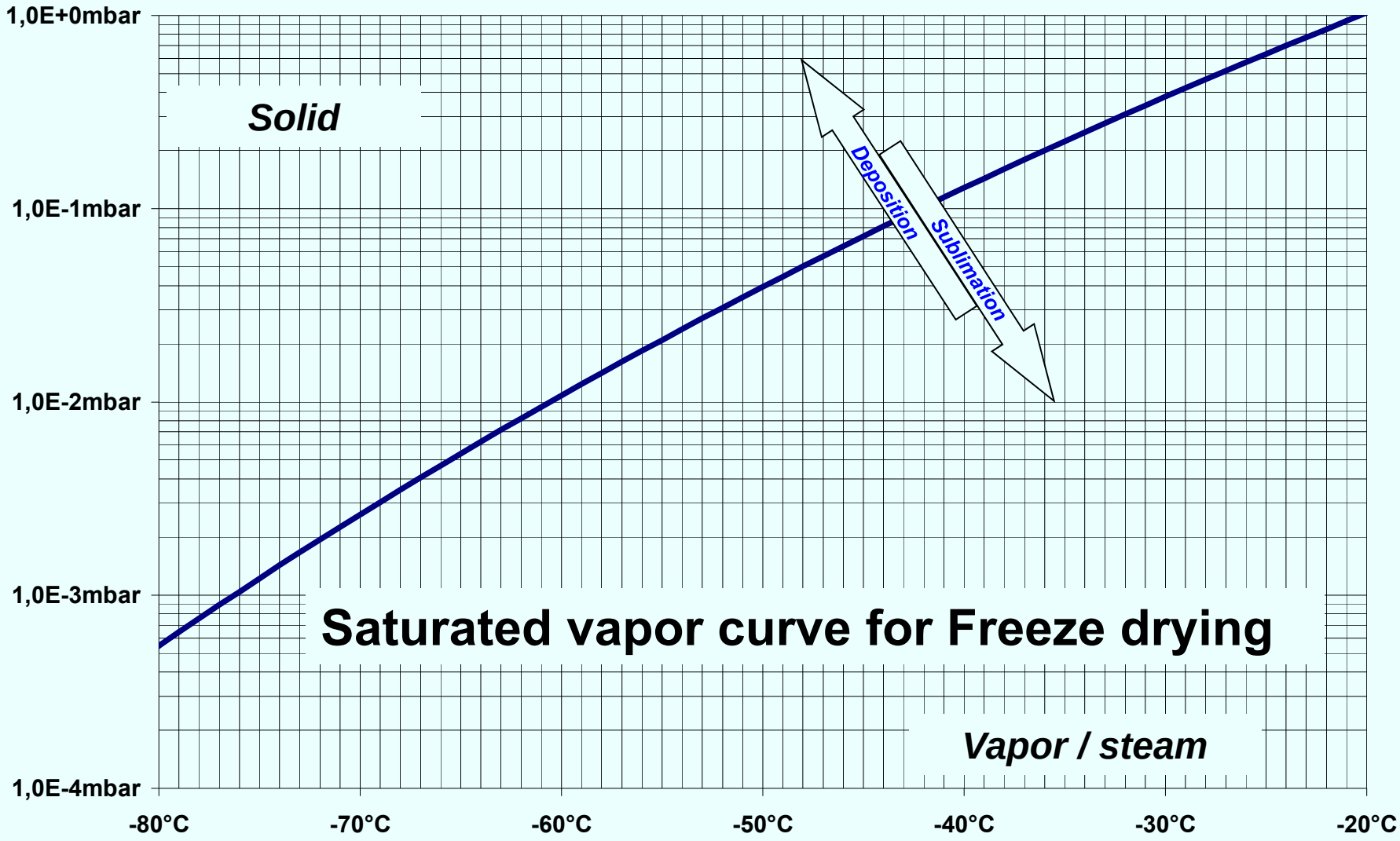
$$\text{Gas} \underset{-\Delta G}{\overset{+\Delta G}{\Leftrightarrow}} \text{Liquid} \underset{-\Delta G}{\overset{+\Delta G}{\Leftrightarrow}} \text{Solid}$$

Energy flux at phase changes



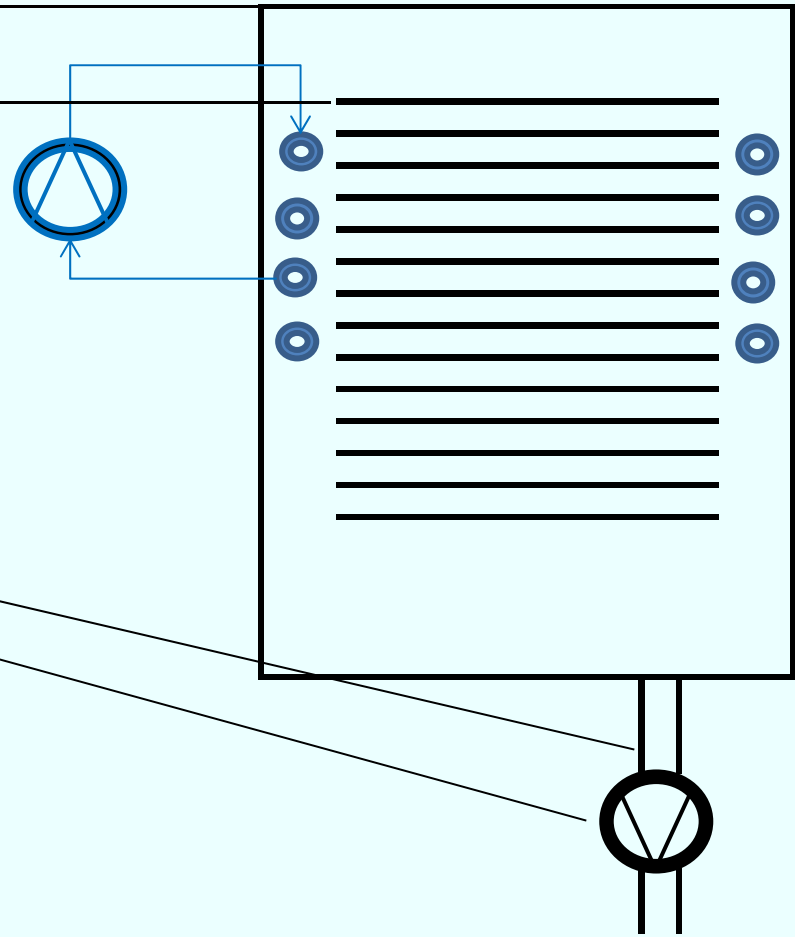
Saturated vapor curve




1,0E+0mbar
1,0E-1mbar
1,0E-2mbar
1,0E-3mbar
1,0E-4mbar
-80°C
-70°C
-60°C
-50°C
-40°C
-30°C
-20°C
Solid
Deposition
Sublimation
Saturated vapor curve for Freeze drying
Vapor / steam

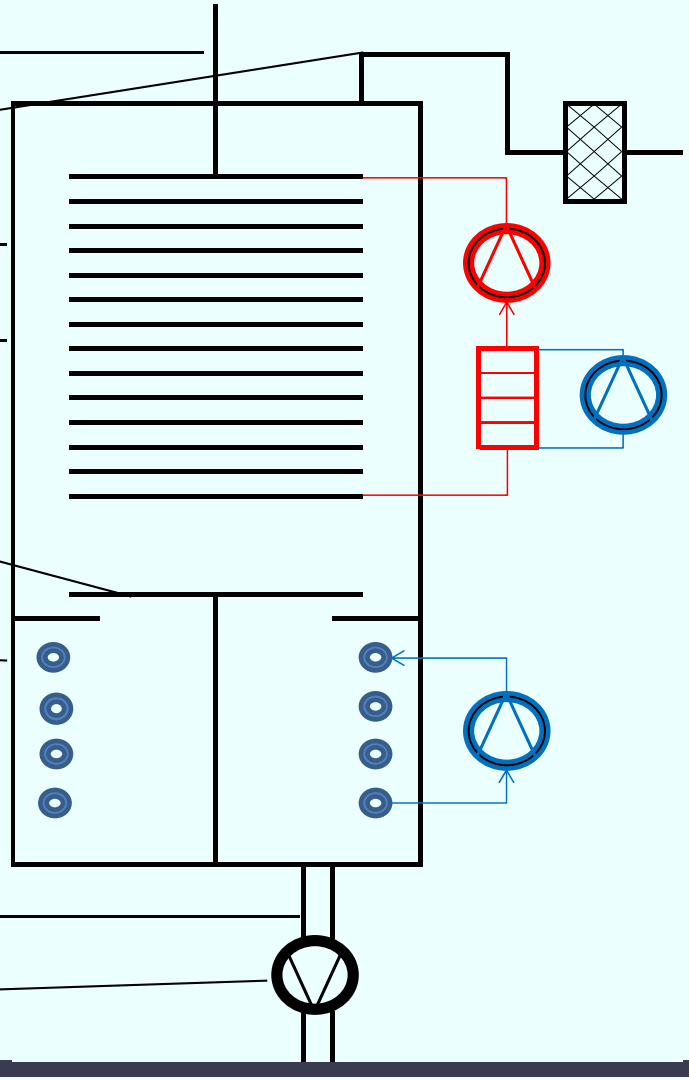
Functional Overview one-chamber Lyophilizer *(simplified)*

- Chamber
- Shelf system (electrically heated)
- Condenser coils / surface
- Refrigeration
- Drain
- Vacuum system



Functional Overview of a pharmaceutical Lyophilizer

- Hydraulic unit
- Aeration System with filter system
- Chamber
- Shelf system
- Intermediate / Main valve
- Condenser coils / surface
- Ice Condenser
- Heat transfer system
- Refrigeration
- Drain
- Vacuum system



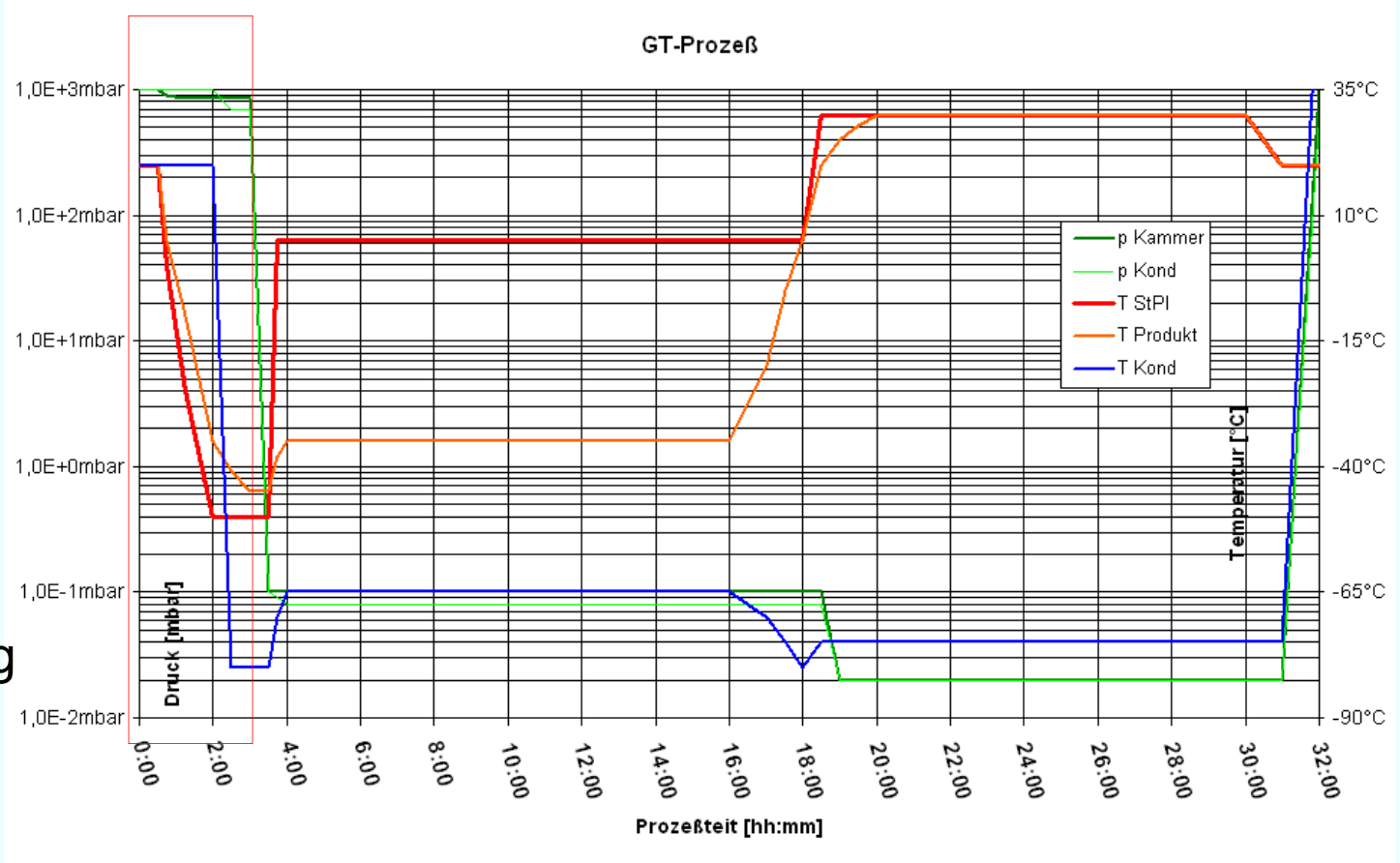
The Process – Freezing Pase:

- The product becomes immobilized by freezing
- The batch will homogenized (by further measurements)
- The product will be conditioned for ice removal

The temperature is changed from loading temperature to freezing temperature (not lower than -60°C), the pressure remains atmospheric/ambient

Freeze Drying Cycle

- Freezing
- Evacuation with condenser cooling
- Sublimation
- Desorption
- Defrosting (during unloading, Start of Turn-Around)



The Process – Drying Phase:

- The ice is removed by sublimation (evaporation)
- If you did something wrong during freezing phase, you will suffer now for it
- The process step ends with the removal of ice (no sharp edge to desorption)

The temperature is below critical temperature, the pressure is controlled to vacuum

Freeze Drying Cycle

- Freezing
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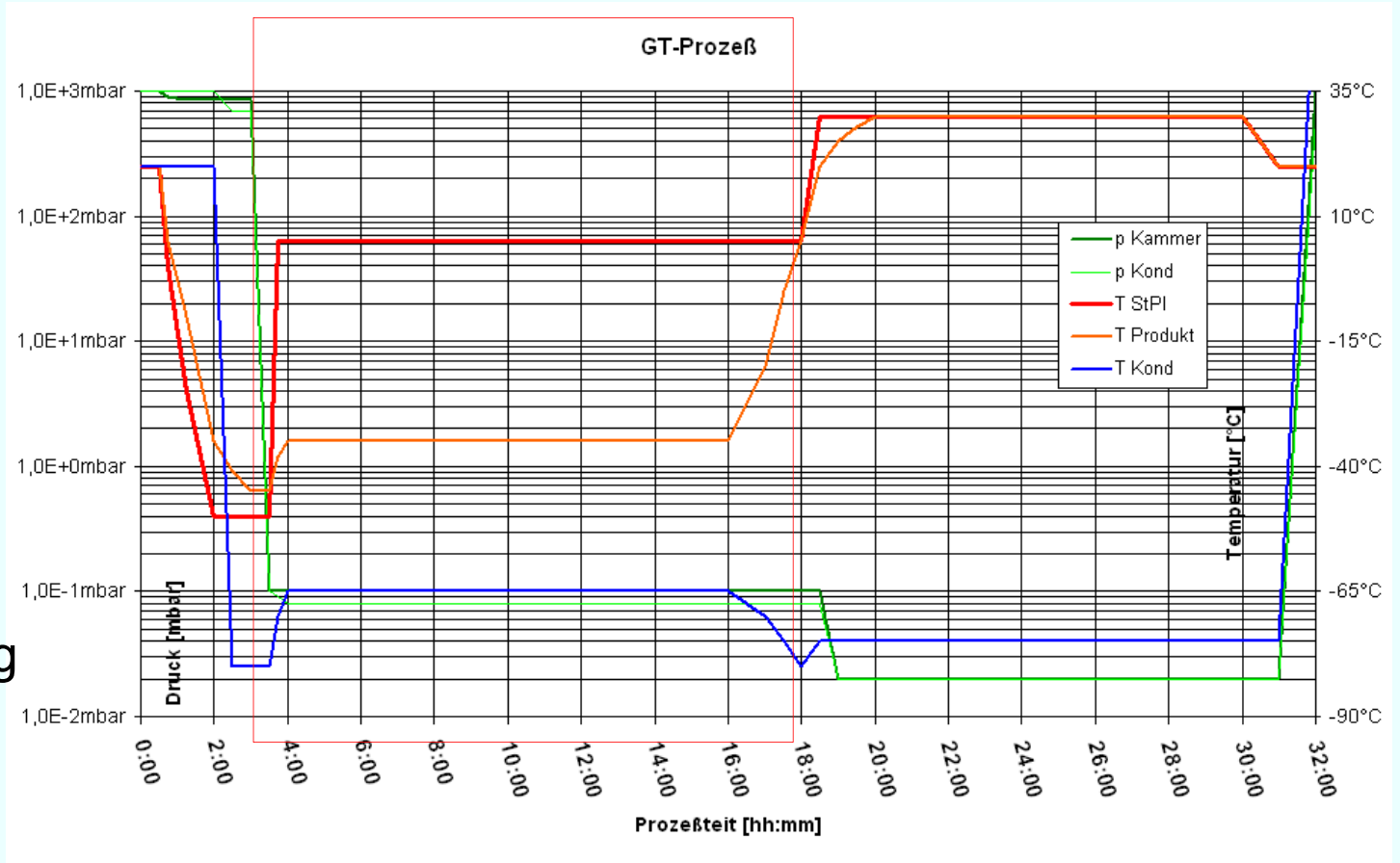
- Sublimation
- Desorption
- Defrosting (during unloading, Start of Turn-Around)



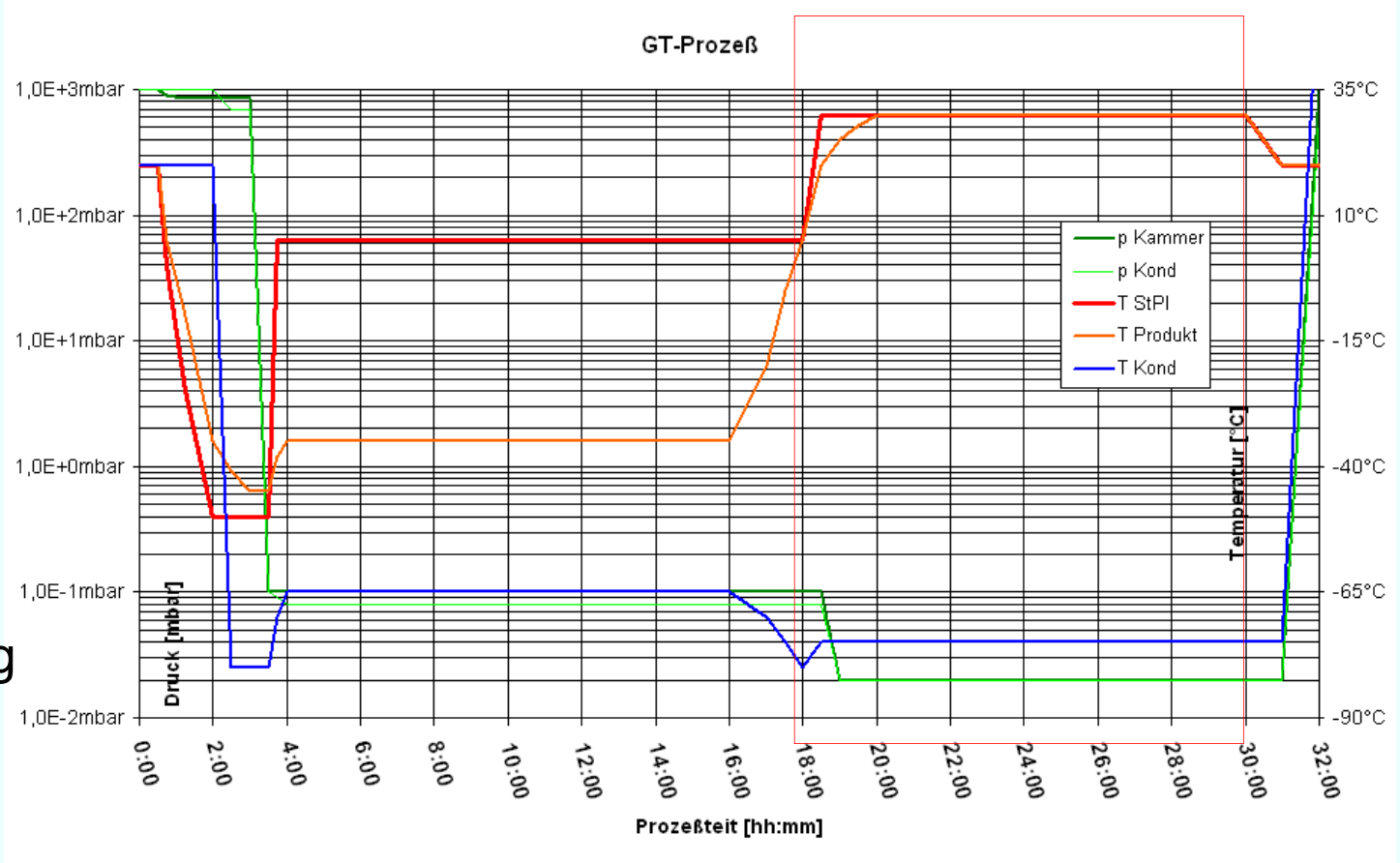
The Process – Secondary Drying:

- moisture level now adjusted by desorption (evaporation)
- If you did something wrong during freezing phase, you will suffer now for it
- If you did something wrong during drying phase, you will suffer now for it

The Temperature is high to maintain good desorption, the pressure is controlled to vacuum

Freeze Drying Cycle

- Freezing
- Evacuation with condenser cooling
- Sublimation
- Desorption
- Defrosting (during unloading, Start of Turn-Around)



General Equation for Mass and Heat balance of the vial

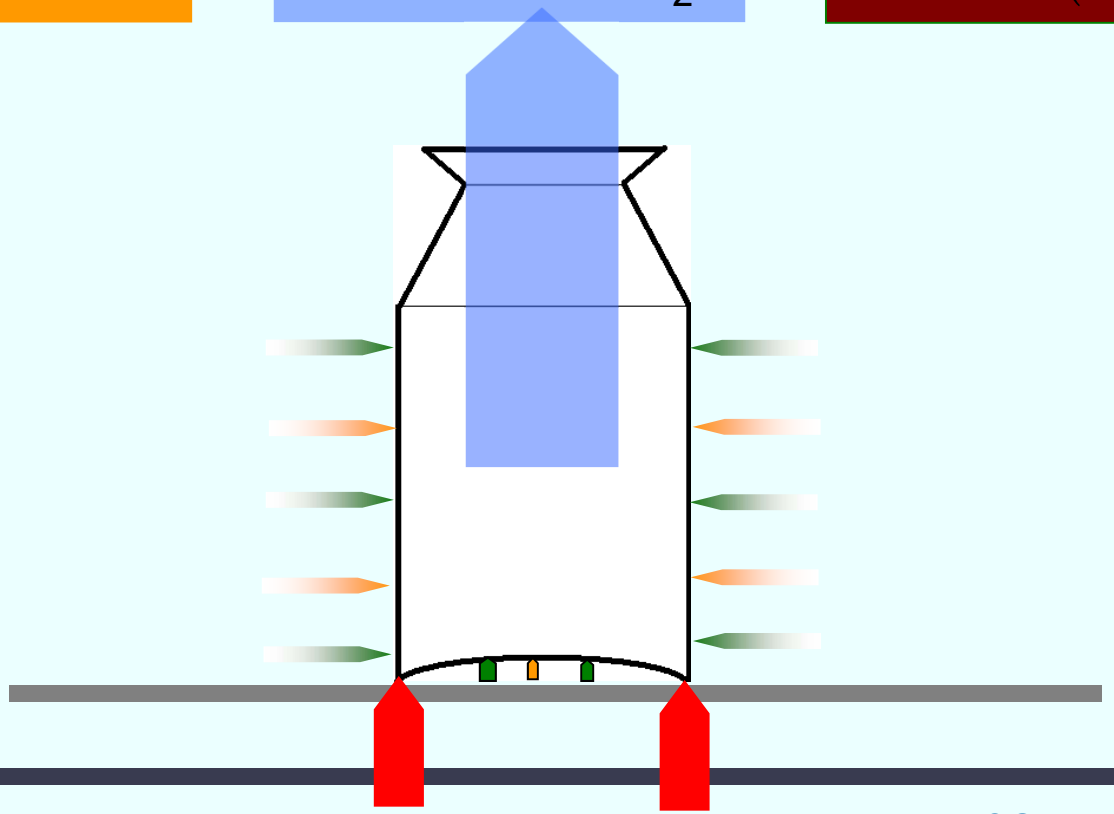
$$dQ_{Cond} + dQ_{Rad} + dQ_{Conv} = h_{Subl} \cdot dm_{H_2O} + d\vartheta \cdot C_{(\vartheta)}$$

Heat conduction

Heat radiation

Heat convection

Sublimation



General Equation for Heat Transfer

$$dQ_{Cond} + dQ_{Rad} + dQ_{Conv} = dQ_{comp}$$

$$\frac{dQ_{comp}}{dt} = k_V \cdot A_H \cdot [T_{Siliconeoil} - T_{Product}]$$

k_V	Very simplified Heat Transfer Coefficient
A_H	Vial Bottom Area
$T_{Product}$	Product at the Sublimation front

Thank you for your attention!

Questions?

R&D Equipment

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