Theory 2a

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PDA EU00144
Freeze-Drying in Practice
9 – 13 September 2024

Martin Christ
Osterode am Harz, Germany

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PDA Parenteral Drug Association

PDA TRAINING

Theory 2a+b

- Basic principles of freeze drying processes
  - Physical understanding
  - Critical process parameters
- Development and composition of a (biological) formulation
- Development of a lyophilization cycle: Practical advice
  - How to approach it? What are the most important parameters?
  - How to choose them?
  - Development of cycles for practical work

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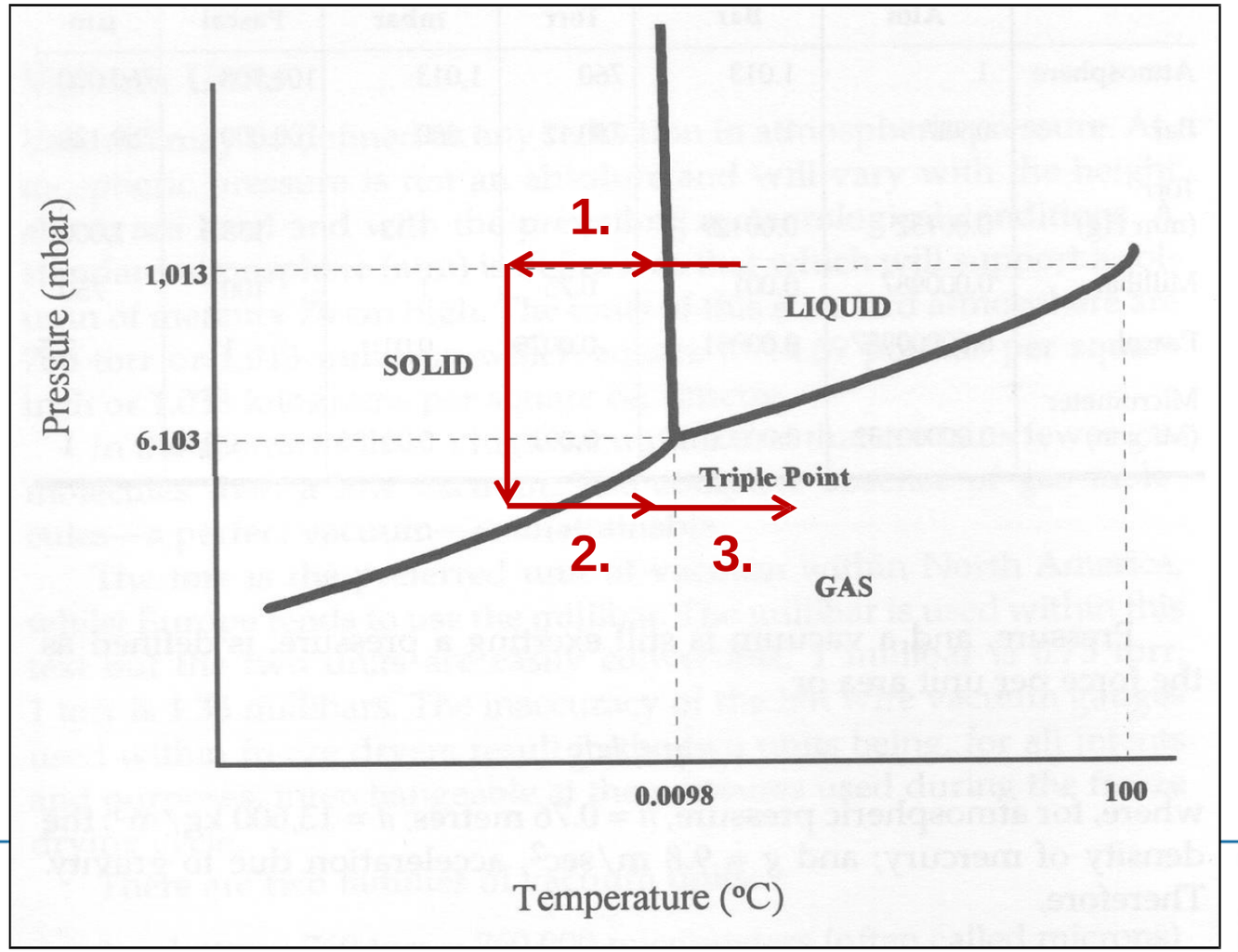
Basic principles

- Drying by sublimation of ice as well as desorption of adsorbed water
- **Phases:**
  - **1. Freezing phase**
    - approx. 2-10 h
  - **2. Primary drying**
    - approx. 5 h - 5 d
  - **3. Secondary drying**
    - < ~13h



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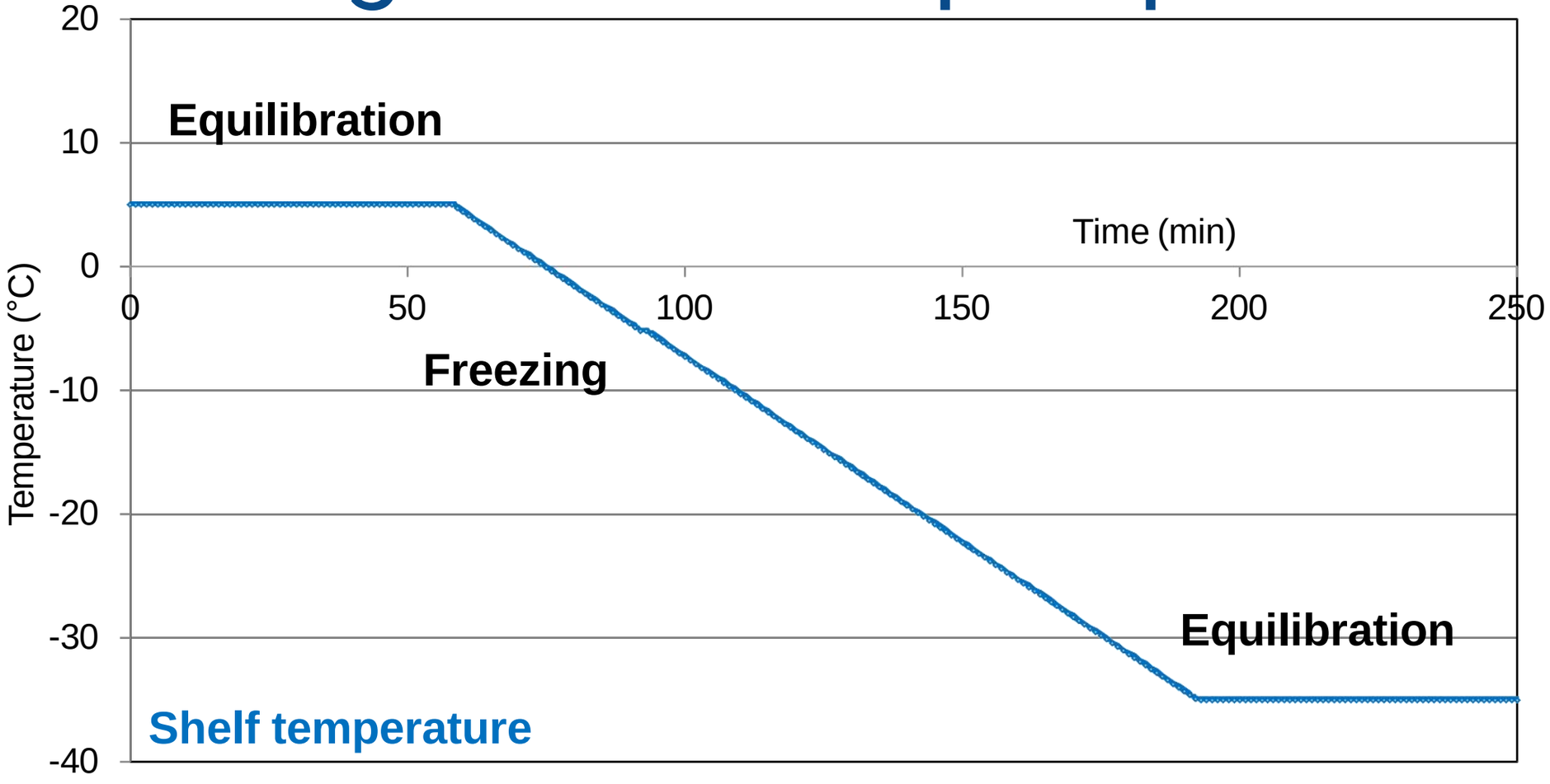
Freezing – Process perspective



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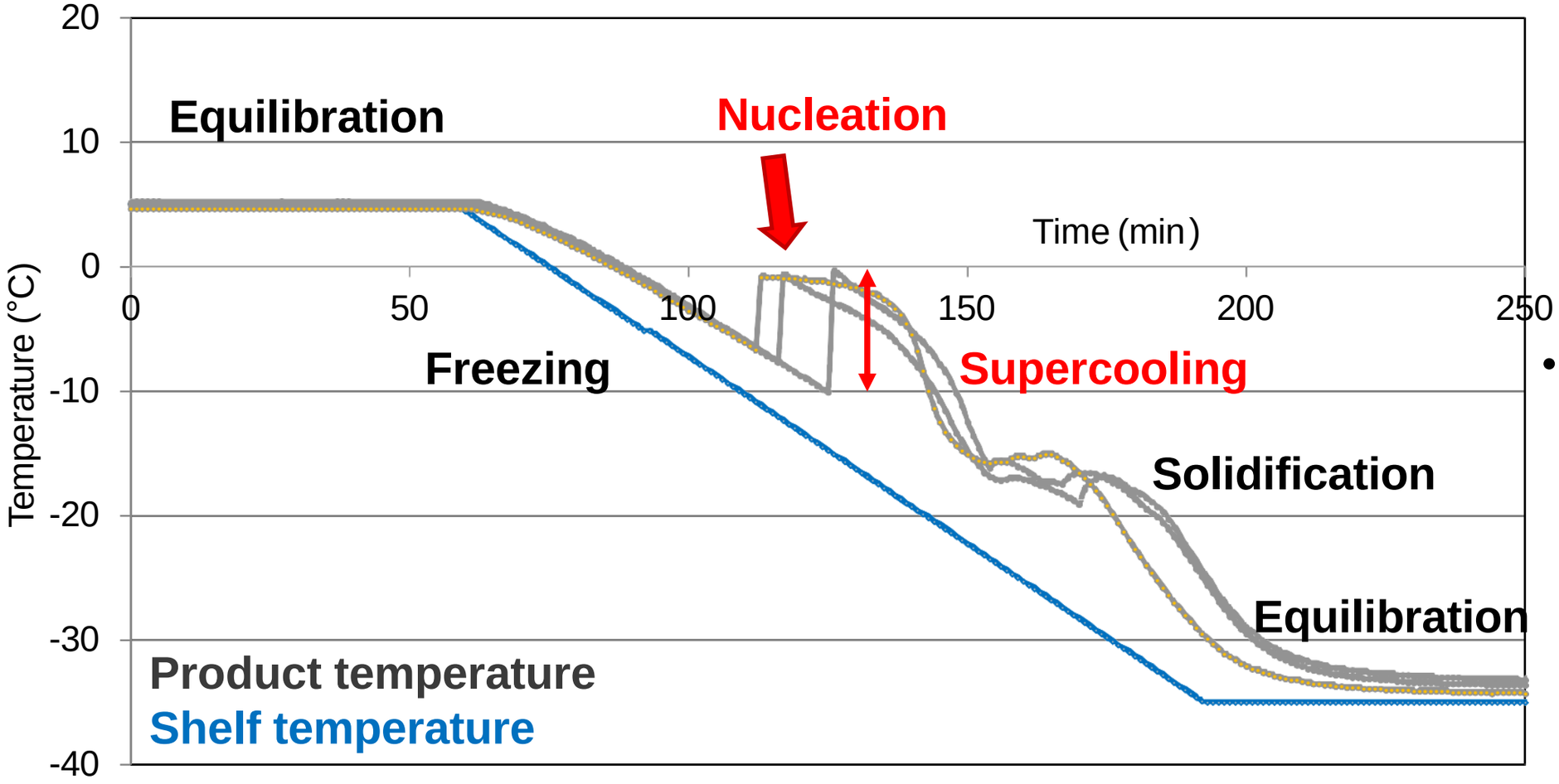
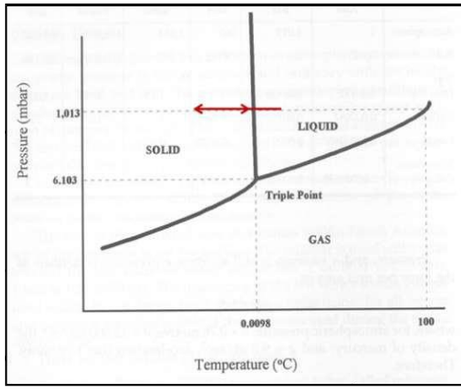
Freezing – Product perspective





- Recommendation: additional equilibration step pre-nucleation during cooling

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Freeze concentration

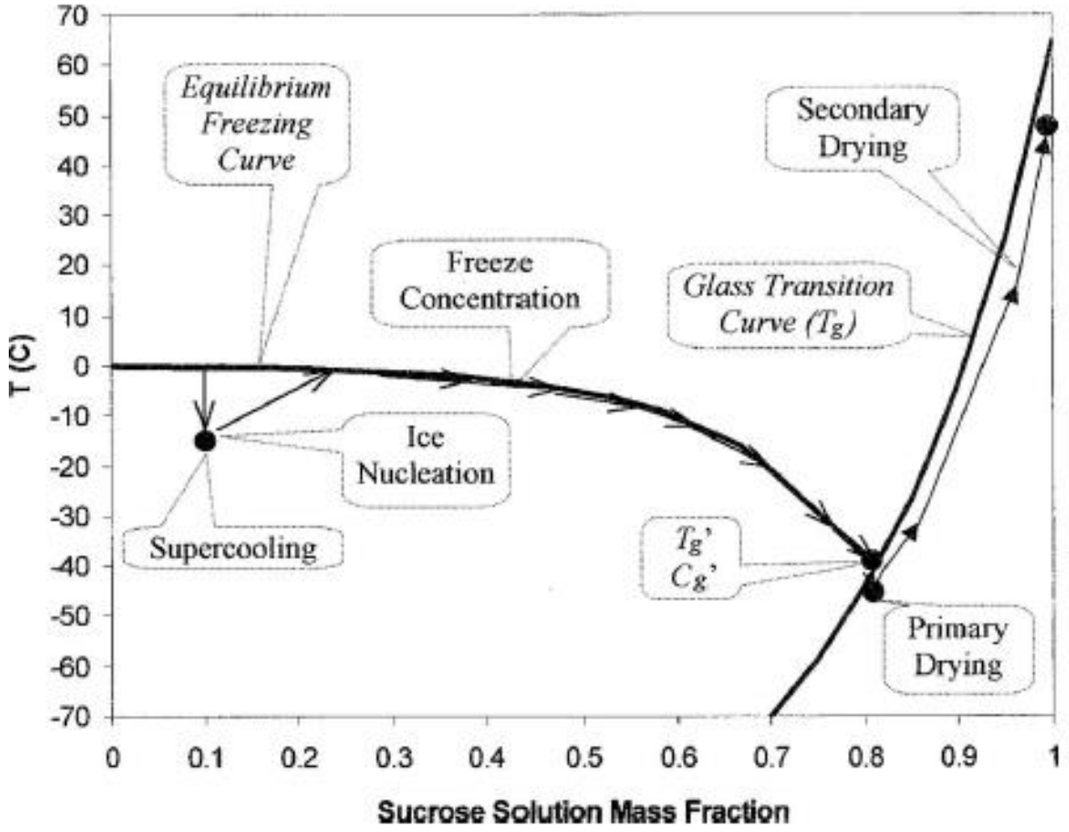

FIGURE 1 Supplemented phase diagram for sucrose. Arrows show freeze-drying process for a 10% sucrose solution.

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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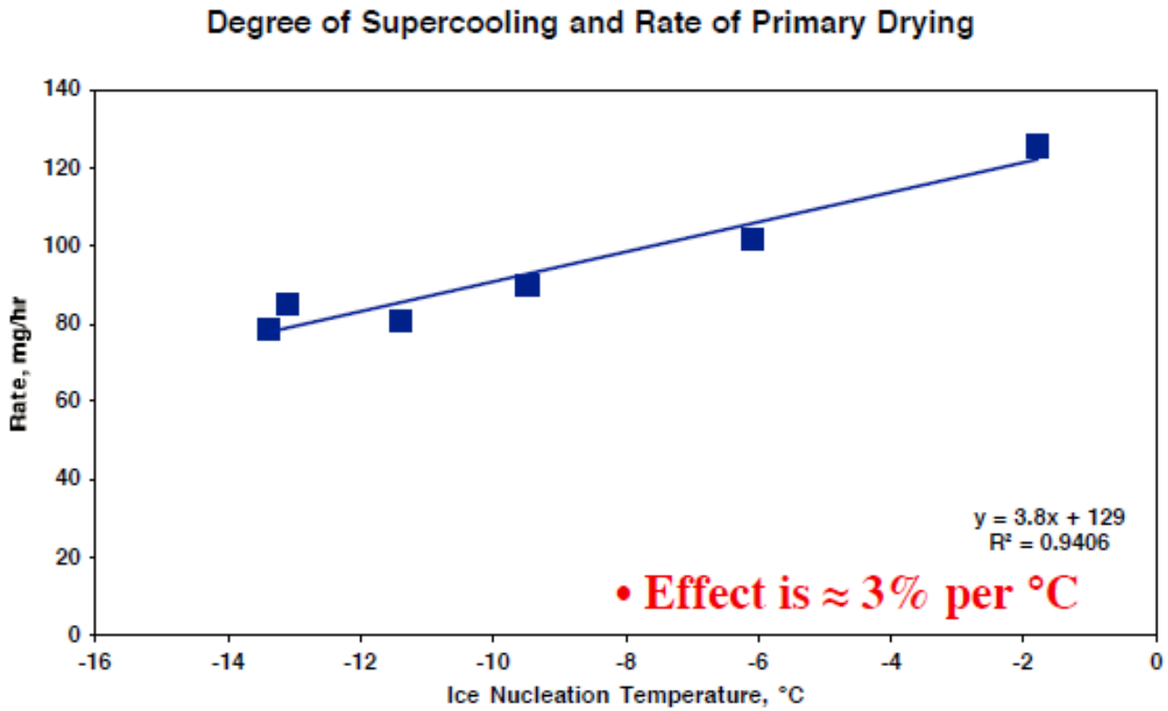
Freezing – Impact of degree of supercooling

More Supercooling Means Slower Drying

Data From: Searles, et. al., J. Pharm. Sci., 90(7), 2001



- For every 1°C increase in nucleation temperature, drying time is estimated to decrease by 1 to 3%[a]
- Typical degrees of supercooling:
  - (Clean) Lab environment: supercooling down to -20 °C
  - cGMP environment: supercooling down to -30 °C or less

[a] "The Ice Nucleation Temperature Determines the Primary Drying Rate of Lyophilisation for Samples Frozen on a Temperature-Controlled Shelf", Searles J.A. et al., 2001, J. Pharm. Sci., *90:7, pp. 860-871.*

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[b] "Controlled Nucleation in Freeze-Drying: Effects on Pore Size in the Dried Product Layer, Mass Transfer Resistance, and Primary Drying Rate". Konstantinidis et al. J. Pharm. Sci. 2011, 100 (8), 3453–3470

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Freezing – advice for process design

- Decide if thermal treatment (annealing or controlled ice nucleation) shall be implemented → Theory 9
- Define loading temperature (usually: room temperature)
- Define process:
  - Equilibration step: decide temperature (above eq. freezing point) + hold time (min. 30min)
  - Coolin ramp rate (0.2 – 2 °C/min) → for scalability reasons: 0.3 – 0.7 °C/min
  - Target temperature: min. 5°C below Tg'
  - Hold time dependent on fill depth: ≤ 1cm: 1h, 1-2 cm: 2h, >2h: 4h

Based on: 1) "Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update." Tchessalov et al. Pharm Res 40, 2433–2455 (2023)., 2) "Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice". Tang, X., Pikal, M.J. Pharm Res 21, 191–200 (2004).

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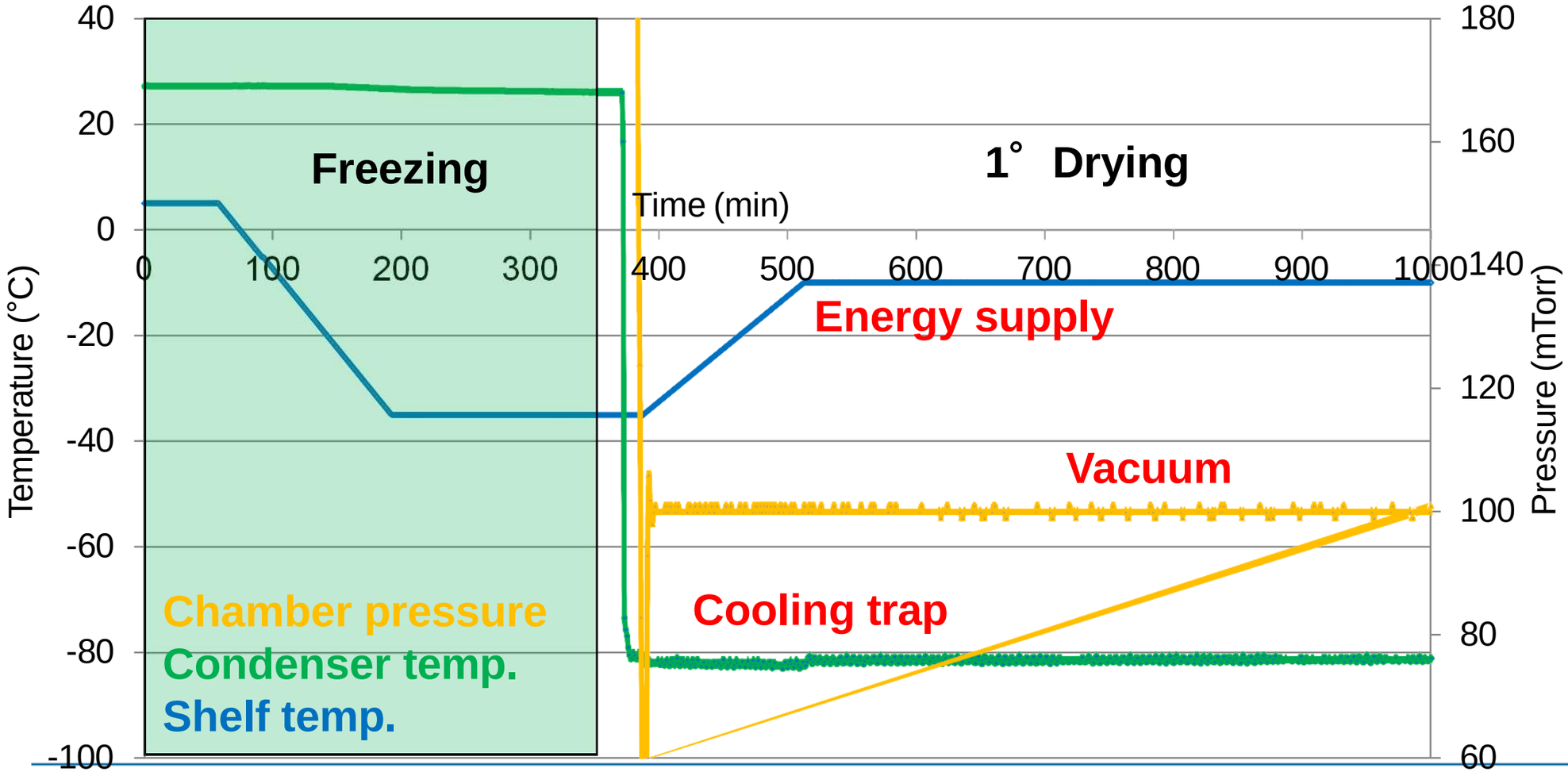
Primary Drying



Vacuum typically:
50 – 200 mTorr
(67 – 267 µbar)

Shelf temp.:
- Depends on formulation properties (T_c, T_{eu}, → T_p)
- Total solid content
- Fill height
- Vial and equipment properties

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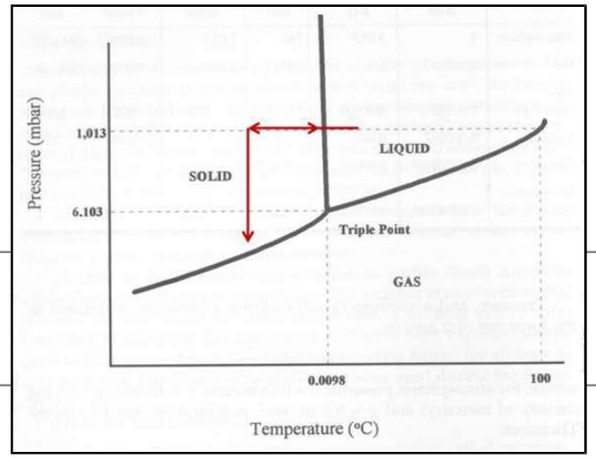
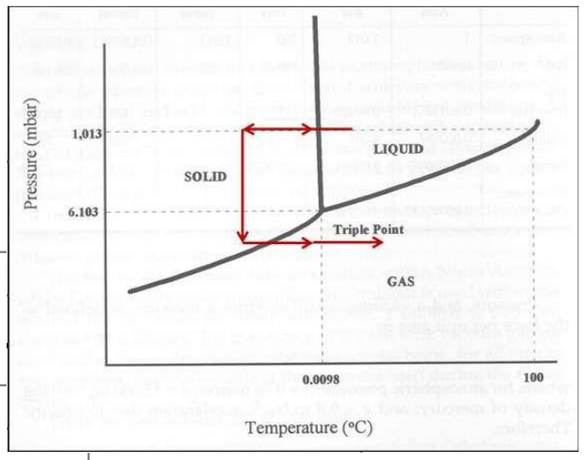
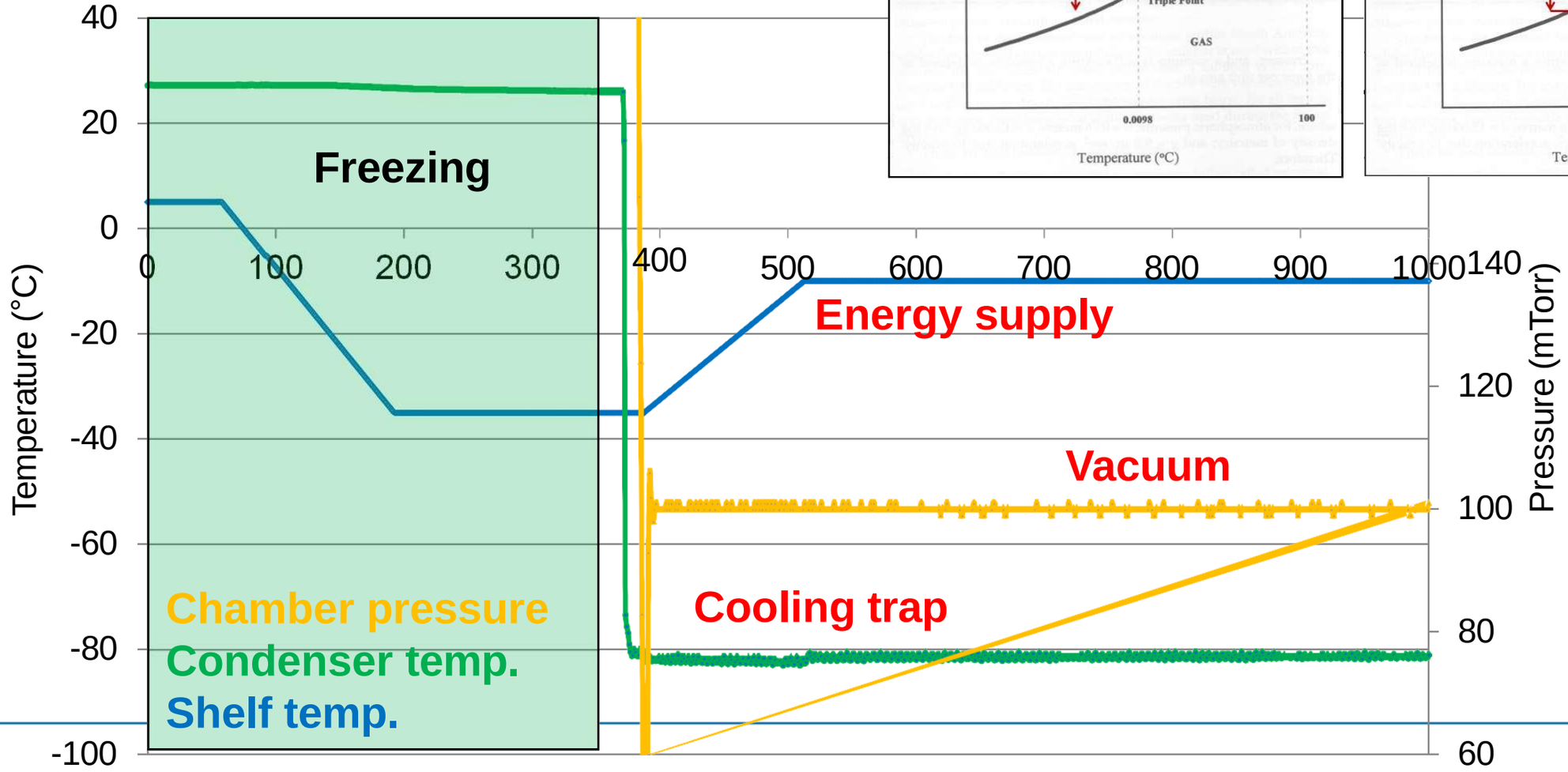
Primary Drying







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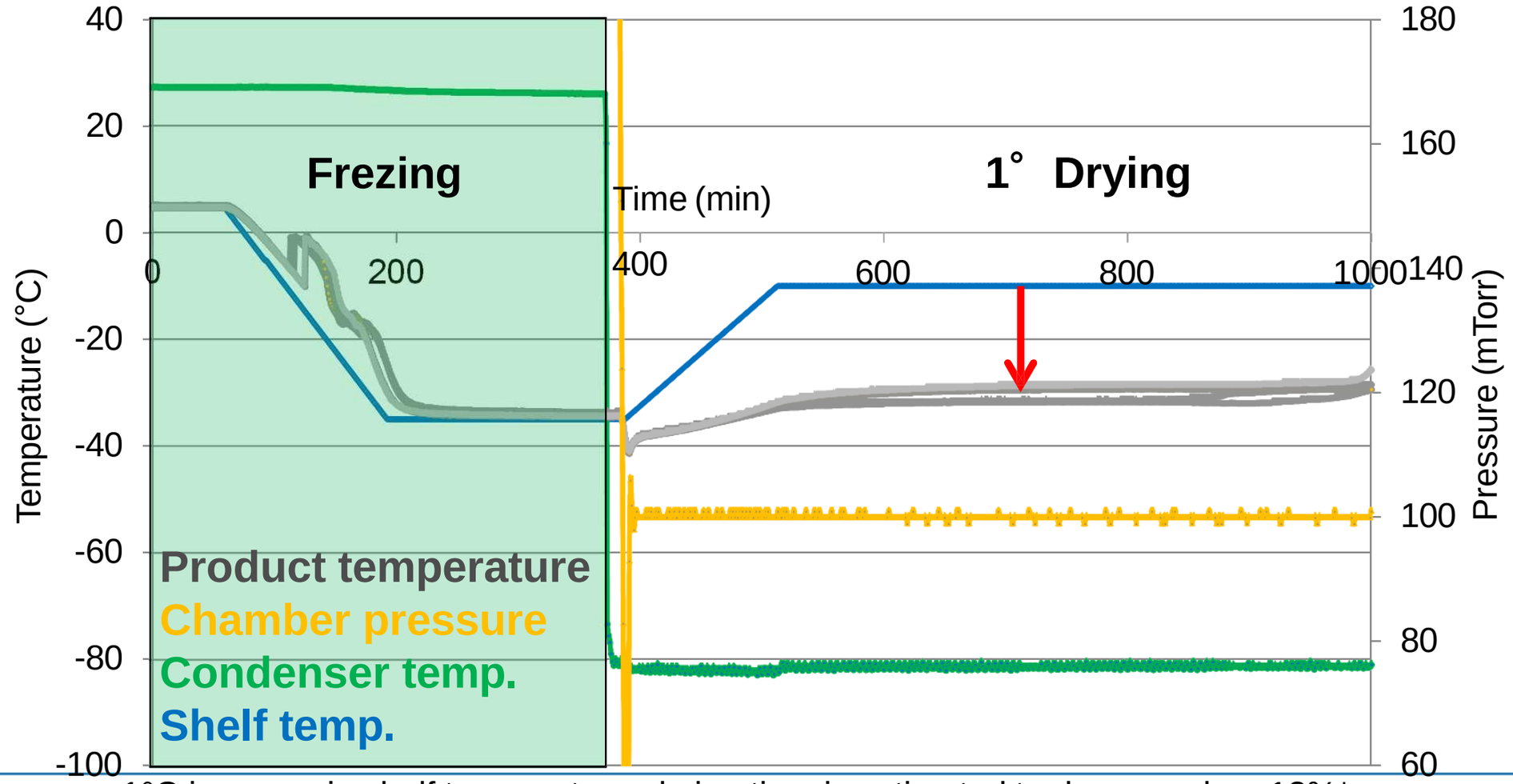
Primary Drying - Sublimation



Side note: for every 1°C increase in shelf temperature, drying time is estimated to decrease by ~13%*

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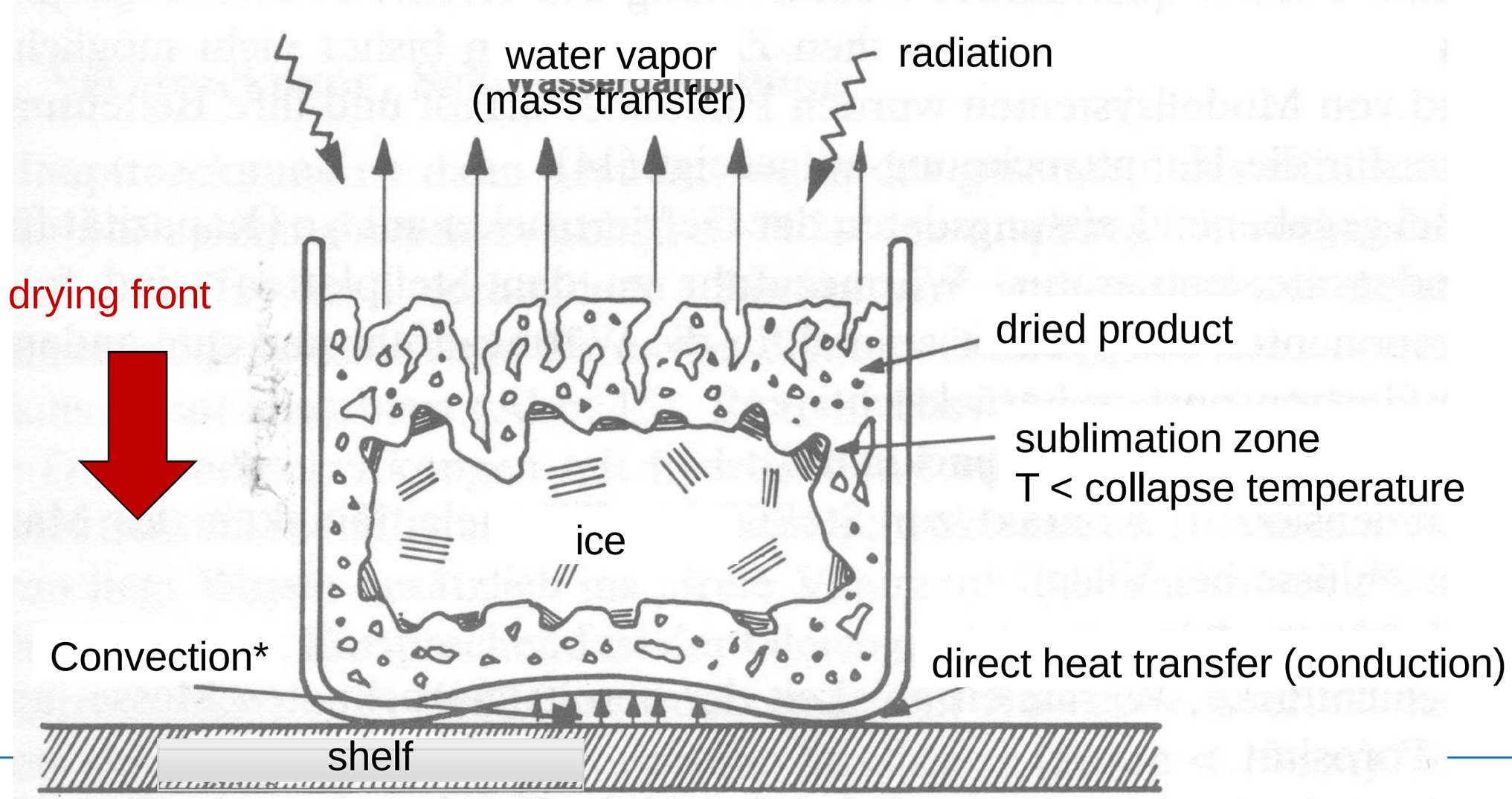
Primary Drying - Sublimation



*sometimes referred to as gas conduction

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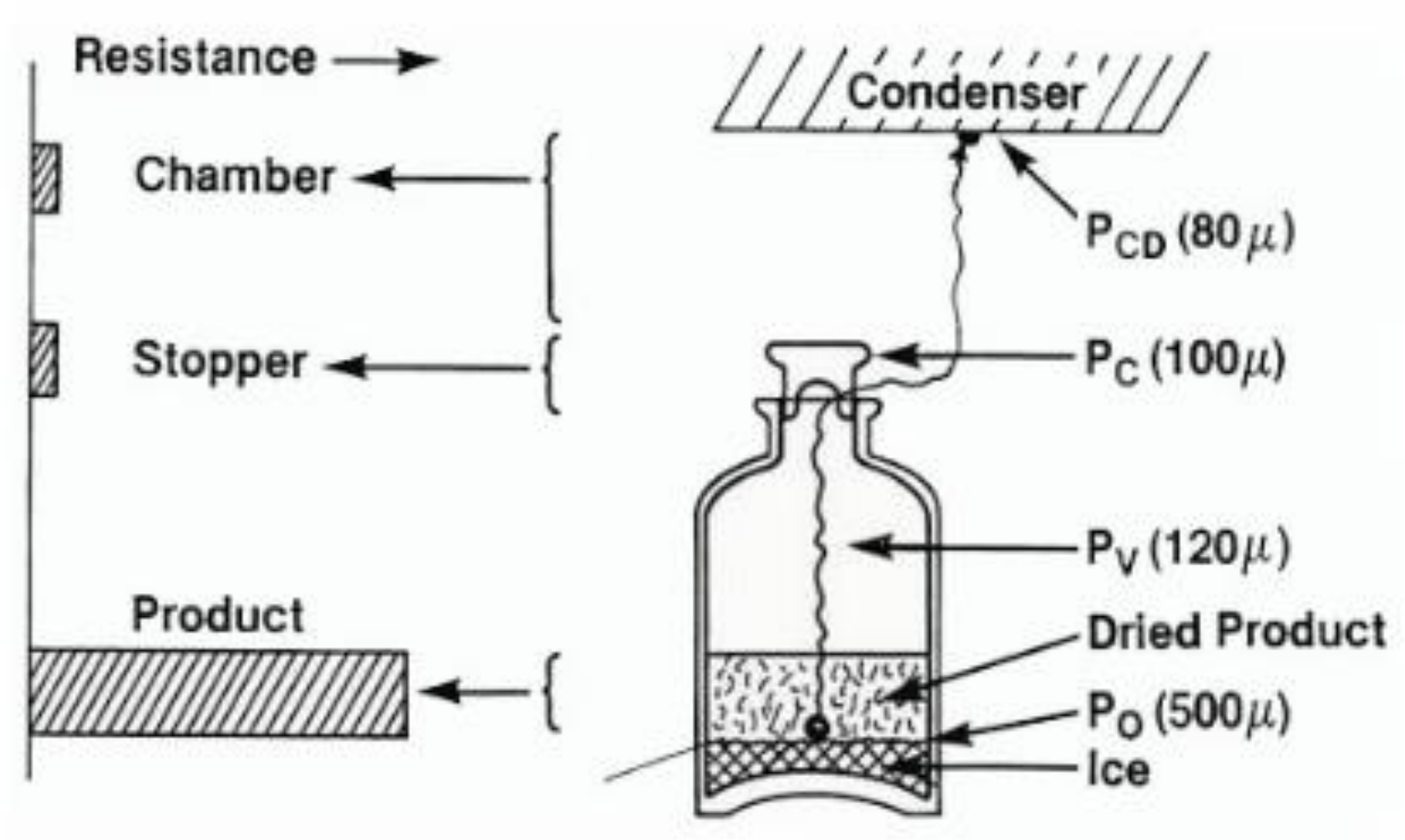
Primary Drying- Barriers to mass transfer



Mass transfer in primary drying. Schematic of resistances (pressure in μm Hg).
100 μg Hg = 100 mTorr = 133 μbar
P_0 – equilibrium vapor pressure of ice at sublimation interface
P_V – pressure in the vial
P_C – chamber pressure
P_{CD} – condenser pressure

Reprinted from “Use of laboratory data in freeze drying process design: Heat and mass transfer coefficients and the computer simulation of freeze drying,” by MJ. Pikal, 1985, J. Parenter. Sci. Technol., *39:3, pp. 115-138.* Copyright [1985] © Parenteral Drug Association.

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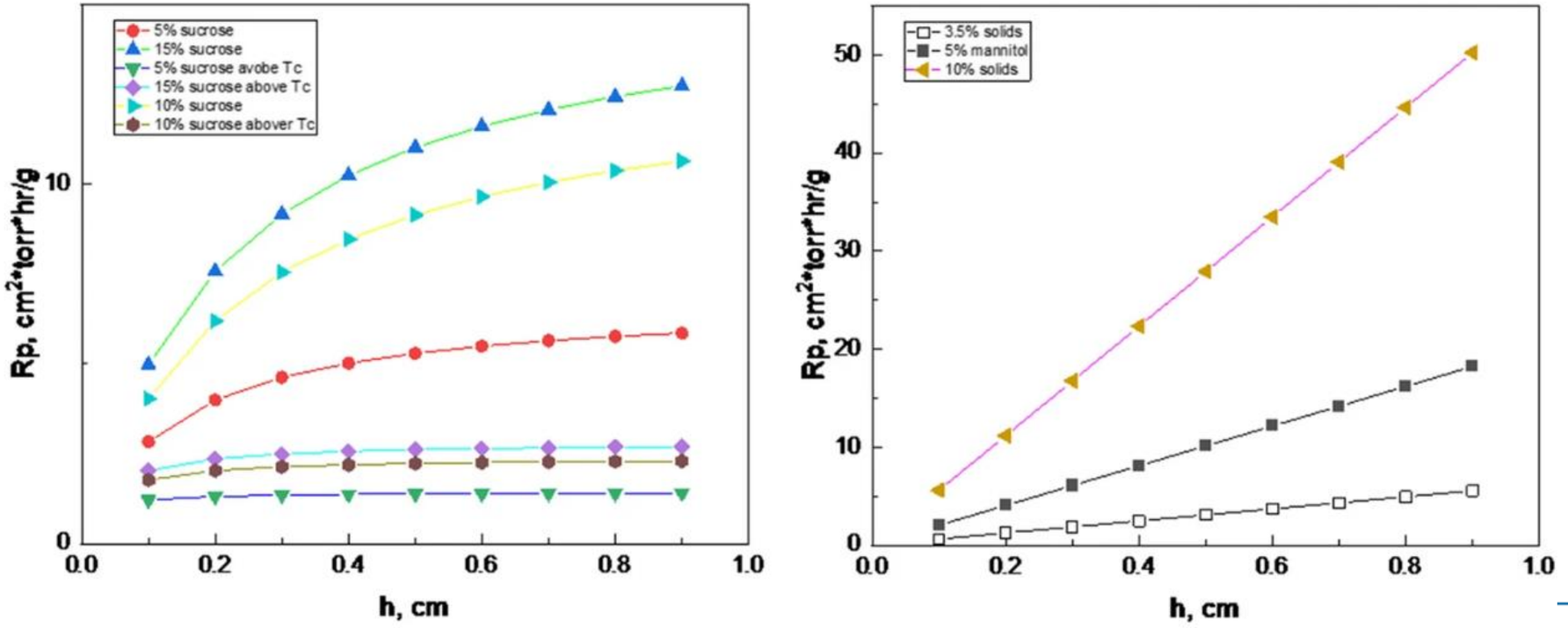
Primary drying – product resistance to mass transfer

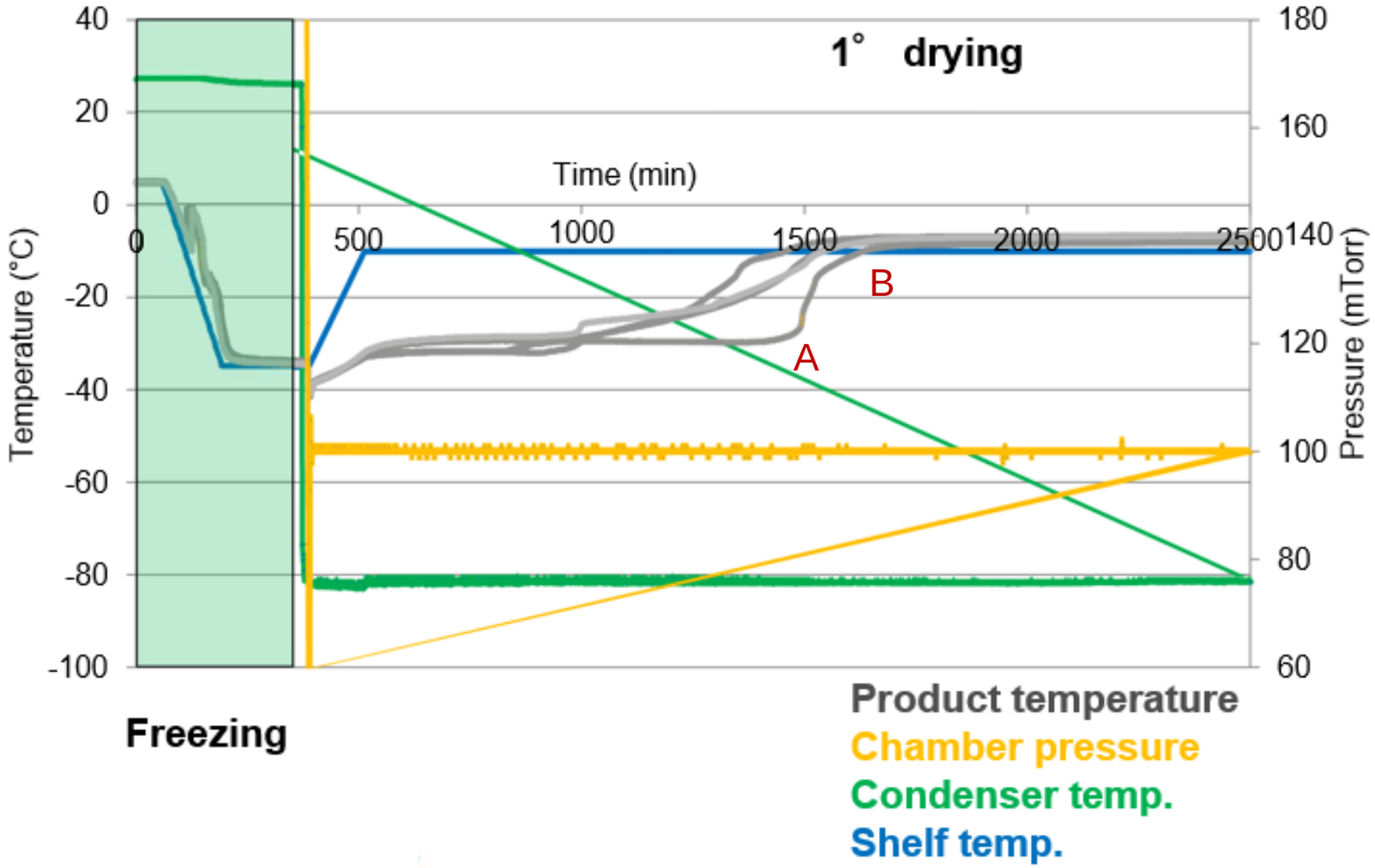
- Dry layer resistance to water vapor = biggest barrier to mass transfer during sublimation!
- Different behavior comparing amorphous (left) and (semi-)crystalline (right)
- Total solid content main driver for degree of resistance within one composition



R_p for amorphous (left) and crystalline (right) formulations.

Reprinted from “Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update.” Tchessalov et al. Pharm Res 40, 2433–2455 (2023). Copyright [2023] © Springer Nature

End of primary drying: product temperature



- If stoppers are correctly placed, A indicates the end of sublimation in that probed vial
- Delay time to reach shelf temperature (B) due to
  - Cooling by heat exchange with nearest neighbors
  - heat capacity of product+container
  - Self-cooling due to beginning of desorption

Biggest bias: Tc-vials see lower degree of supercooling (Tc = nucleation site)
→ Representativeness for rest of batch?

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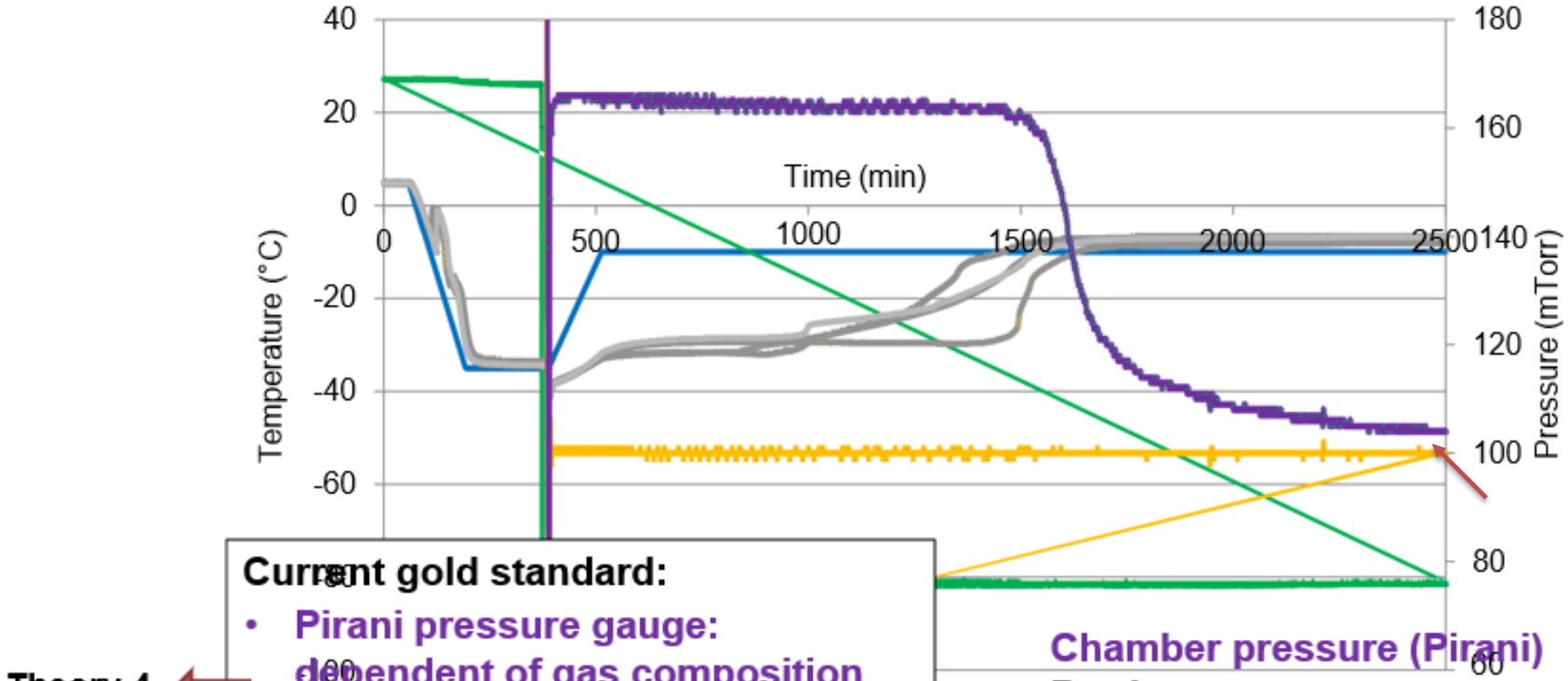
Further read: “Process Control in Freeze Drying: Determination of the End Point of Sublimation Drying by an Electronic Moisture Sensor”, M. Roy, MJ. Pikal, 1989, PDA J. Pharm. Sci. Technol,43(2).

End of primary drying: comparative pressure measurement



Current gold standard:

- **Pirani pressure gauge: dependent of gas composition (in the chamber)**
- **MKS pressure gauge: independent of gas composition**

Theory 4

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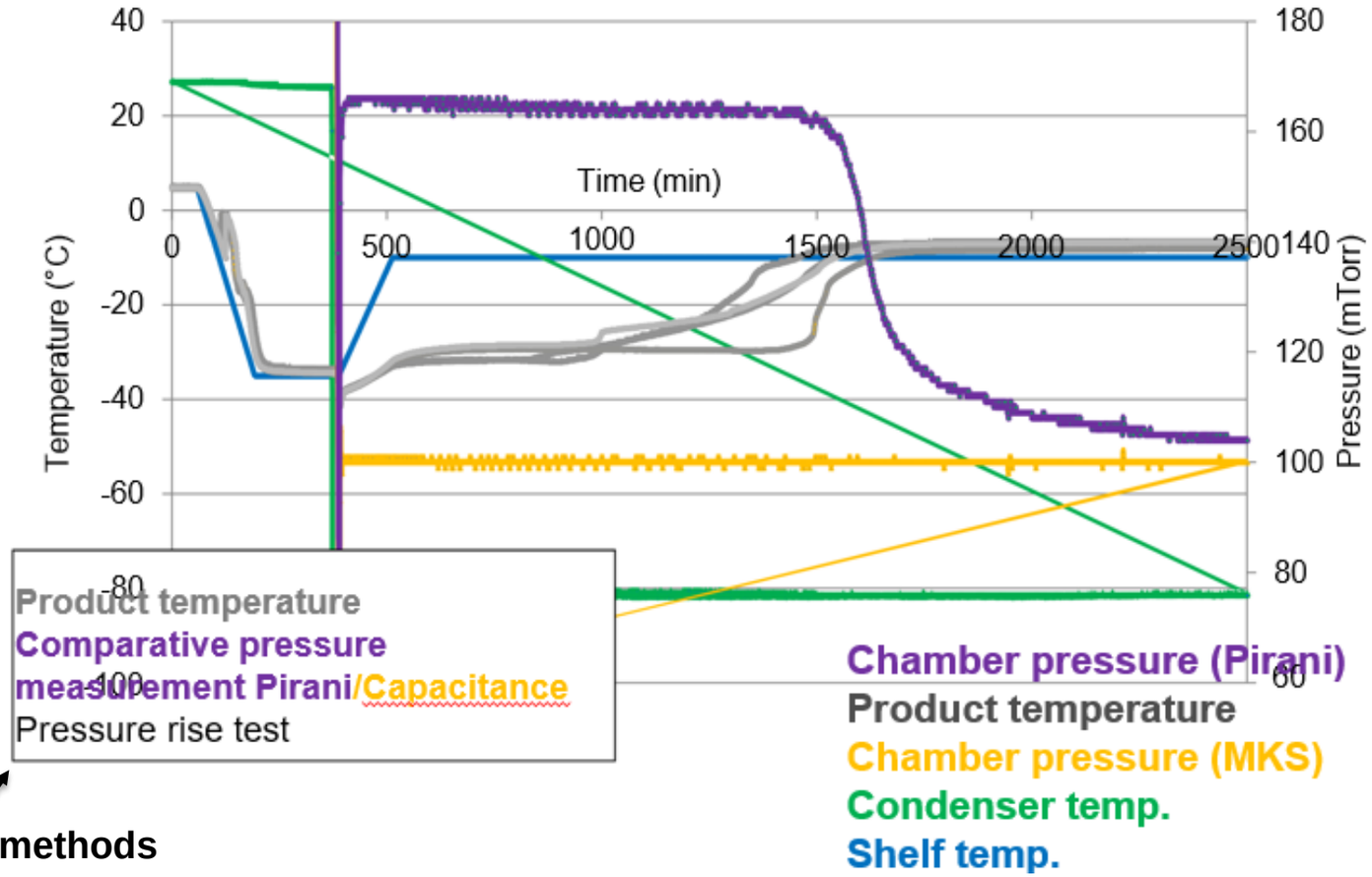
End of primary drying: summary



Standard methods

- Further methods:
  - TDLAS
  - Mass Spectrometry (H_20)
  - NIR
  - microbalance
  - Heat Flux Sensor
  - Vial impedance
  - Dew point sensors

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Further read: “Determination of end point of primary drying in freeze-drying process control”. Patel et al. AAPS PharmSciTech. 2010;11(1):73-84. & “Automatic control of a freeze-drying process: Detection of the end point of primary drying.” Pisano, R. (2020). Drying Technology, 40(1), 140–157

Primary Drying – advice for process design

- Determine the **target product temperature (T_p)**: amorphous formulations
  - For drying times >2d: $T_{collapse}$/$T_{eutectic}$ minus 2°C
  - For drying times <10h: $T_{collapse}$ minus 5°C
  - For drying times 10 ≤ t ≤ 2d: $T_{collapse}$ minus 3°C
  - Safety margin can also be calculated*
  - For (semi-)crystalline products: depending on equipment capabilities, a T_p of ~-10°C to -15°C is recommended (dependent on T_{eu} of the crystalline solute)
- Next, either use a simple heat/mass transfer model like 1) SP Scientific LyoCalculator or 2) LyoPRONTO or determine **$p_{chamber}$** and **T_{shelf}** „by hand“
- **Ramp rate** typically: 0.5 – 1 °C/min; **1° drying time** can be estimated[2]

*”Impact of natural variations in freeze-drying parameters on product temperature history: application of quasi steady-state heat and mass transfer and simple statistics.” Pikal et al. AAPS PharmSciTech. 2018;19(7):2828–42.

Based on: 1) “Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update.” Tchessalov et al. Pharm Res 40, 2433–2455 (2023)., 2) “Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice”. Tang, X., Pikal, M.J. Pharm Res 21, 191–200 (2004).

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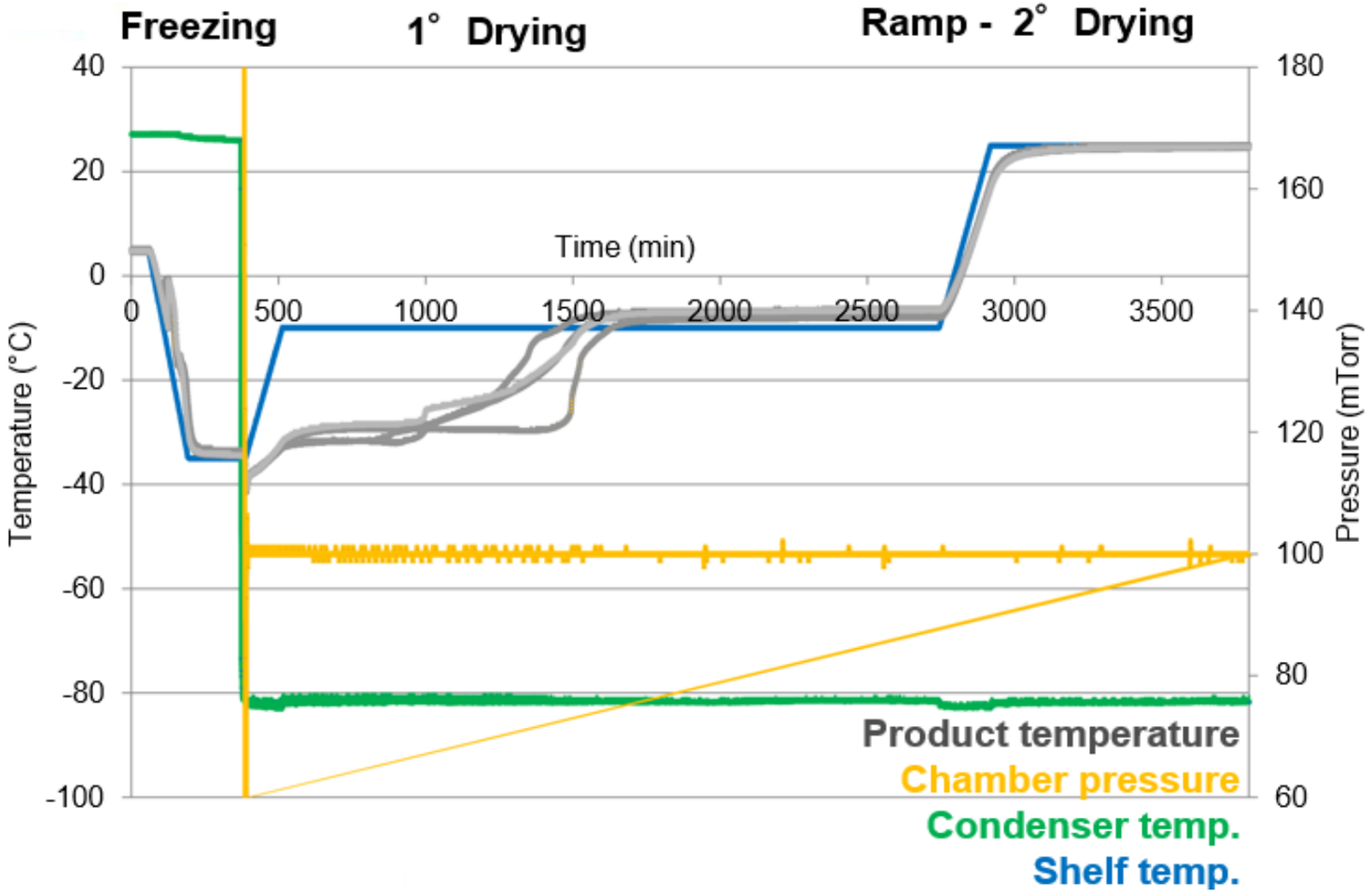
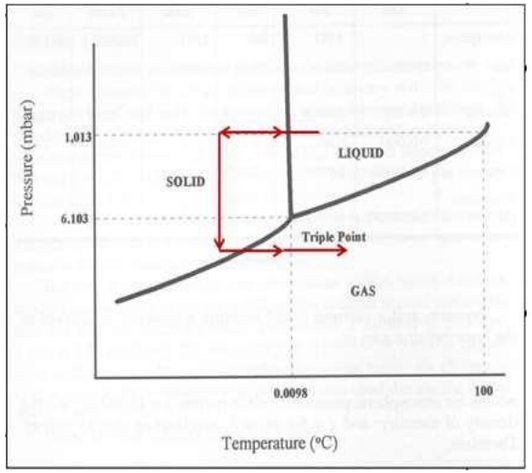
Secondary drying - Desorption





- Comprises ramp + isothermal hold
- Ramp is critical for preventing collapse (amorphous products)
  - 0.1 to 0.2 °C/min amorphous
  - 0.3 to 0.4 °C/min (semi-)crystalline
- Target shelf temperature for SD and time are driving factors for obtained residual moisture content (RMC) in product
- Often, 3-6h at 40-50 °C suffice to reach < 0.5% (*w/w*) RMC
- Chamber pressure below 0.267 mbar*

* Pc has almost no impact on drying rate, if kept below 0.267 mbar; for further details refer to: "The secondary drying stage of freeze drying: drying kinetics as a function of temperature and chamber pressure". Pikal et al. Int. J. Pharm. 60:3 (1990)

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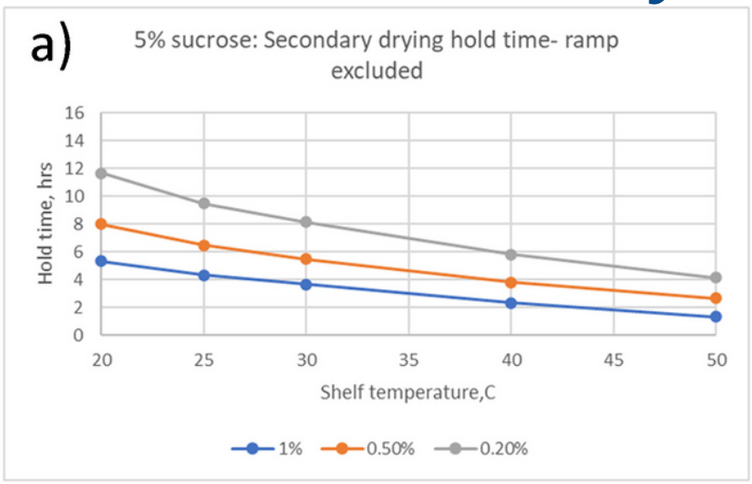
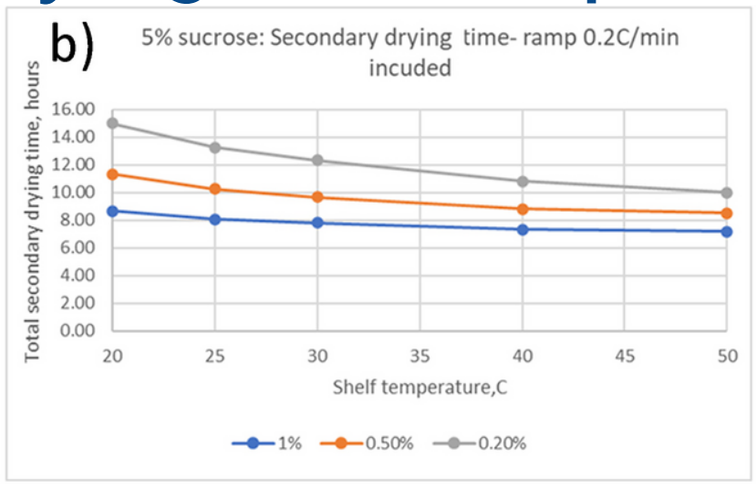
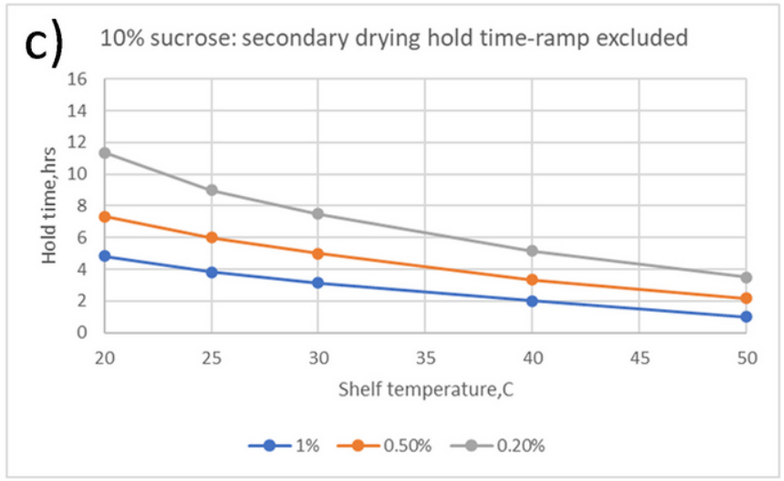
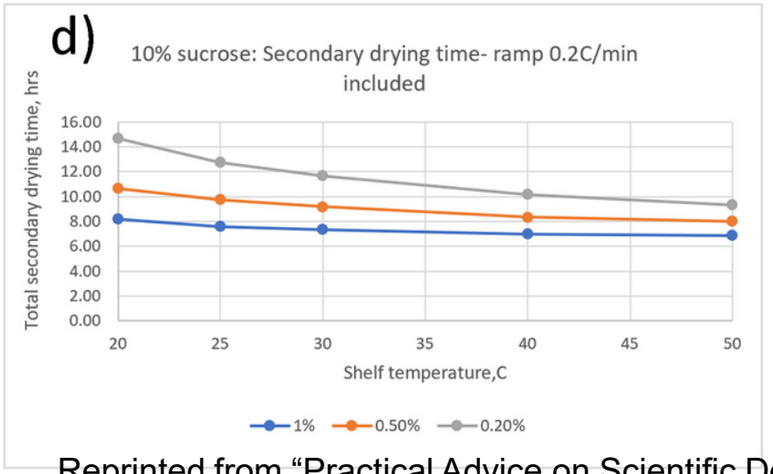
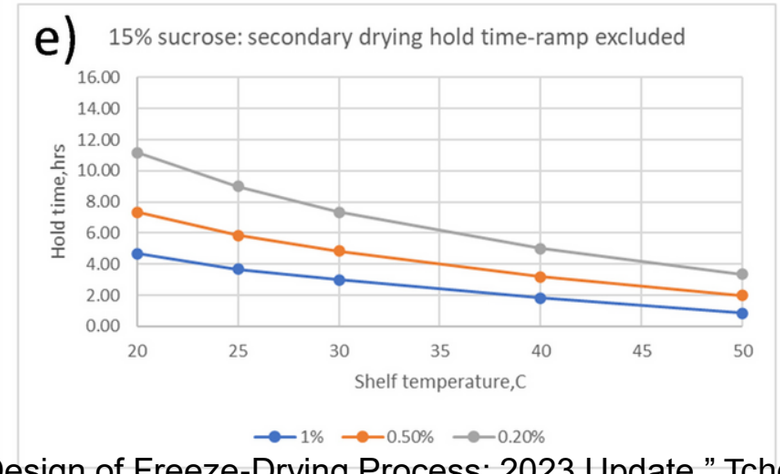
Secondary drying – Desorption of sucrose

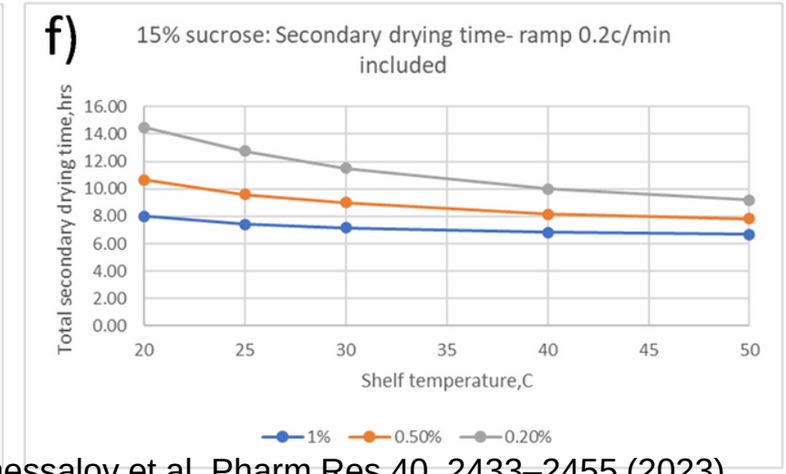












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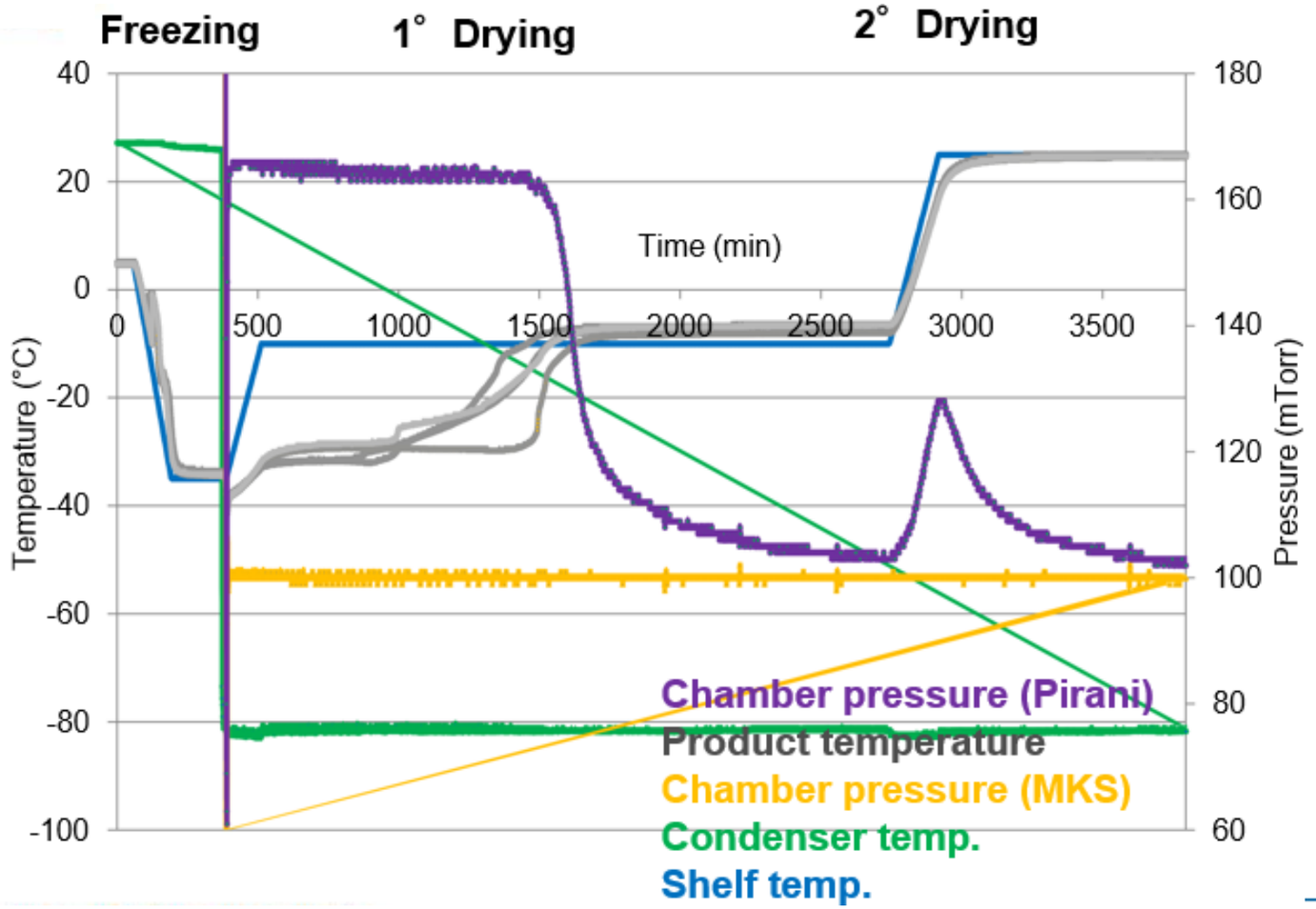
Or estimation via an excel-based model: Ekneet K. Sahni, Michael J. Pikal, Journal of Pharmaceutical Sciences, 106:3, 2017

Secondary Drying – Pressure gauges



- Determination of 2° drying endpoint not accurate enough via comparative pressure measurement
- But in dependence of formulation properties and drying conditions, an increase in Pirani can be observed

- For advanced process developer: establishing an excel-based model* can be helpful

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*Reference: Ekneet K. Sahni, Michael J. Pikal, Journal of Pharmaceutical Sciences, 106:3, 2017

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Secondary drying – advice for process design

- Define ramp and target shelf temperature; p_c not too important*
- Ramp is critical for preventing collapse (amorphous products)
  - 0.1 to 0.2 °C/min amorphous
  - 0.3 to 0.4 °C/min (semi-)crystalline
- Define isothermal hold at target shelf temperature
  - Often, 3-6h at 40-50 °C suffice to reach < 0.5% (w/w) RMC (see theory 2a, slide 19 for sucrose 5-15%)

* Pc has almost no impact on drying rate, if kept below 0.267 mbar; for further details refer to: "The secondary drying stage of freeze drying: drying kinetics as a function of temperature and chamber pressure". Pikal et al. Int. J. Pharm. 60:3 (1990),

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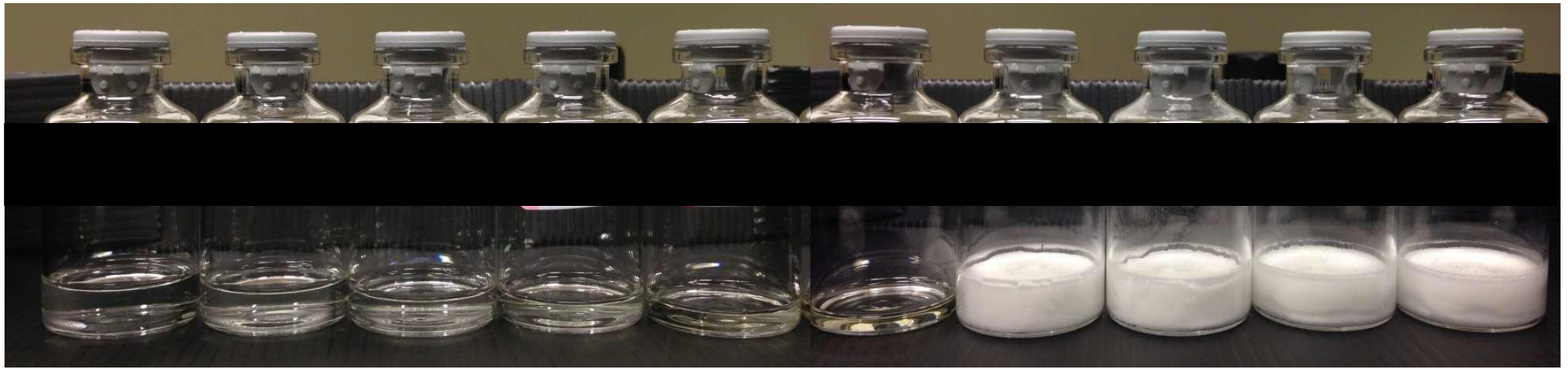
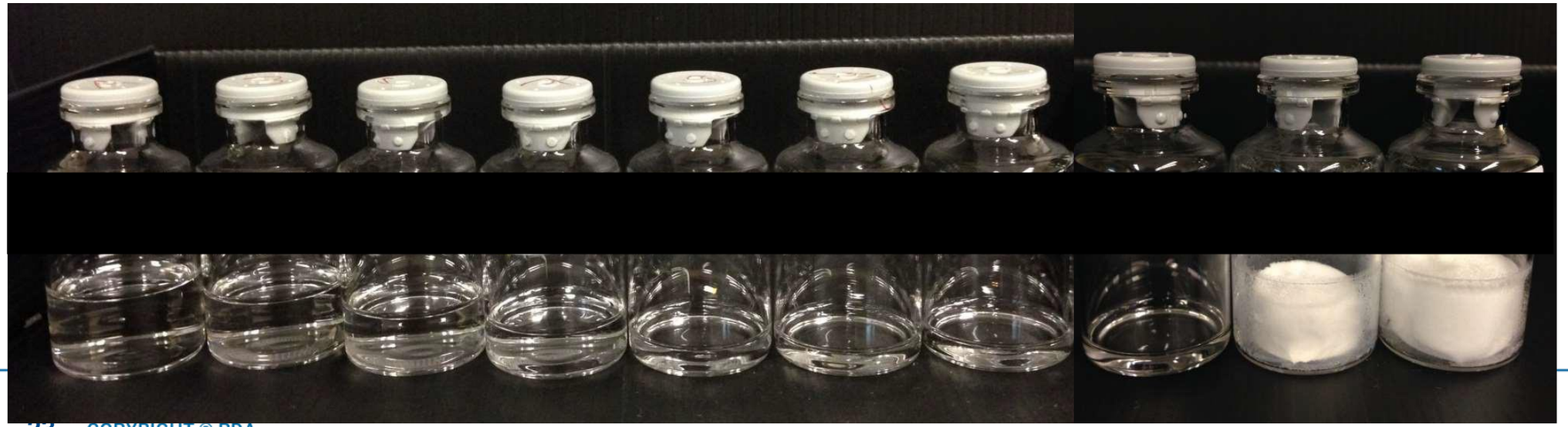
Progress of drying





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Development and composition of a (biological) formulation

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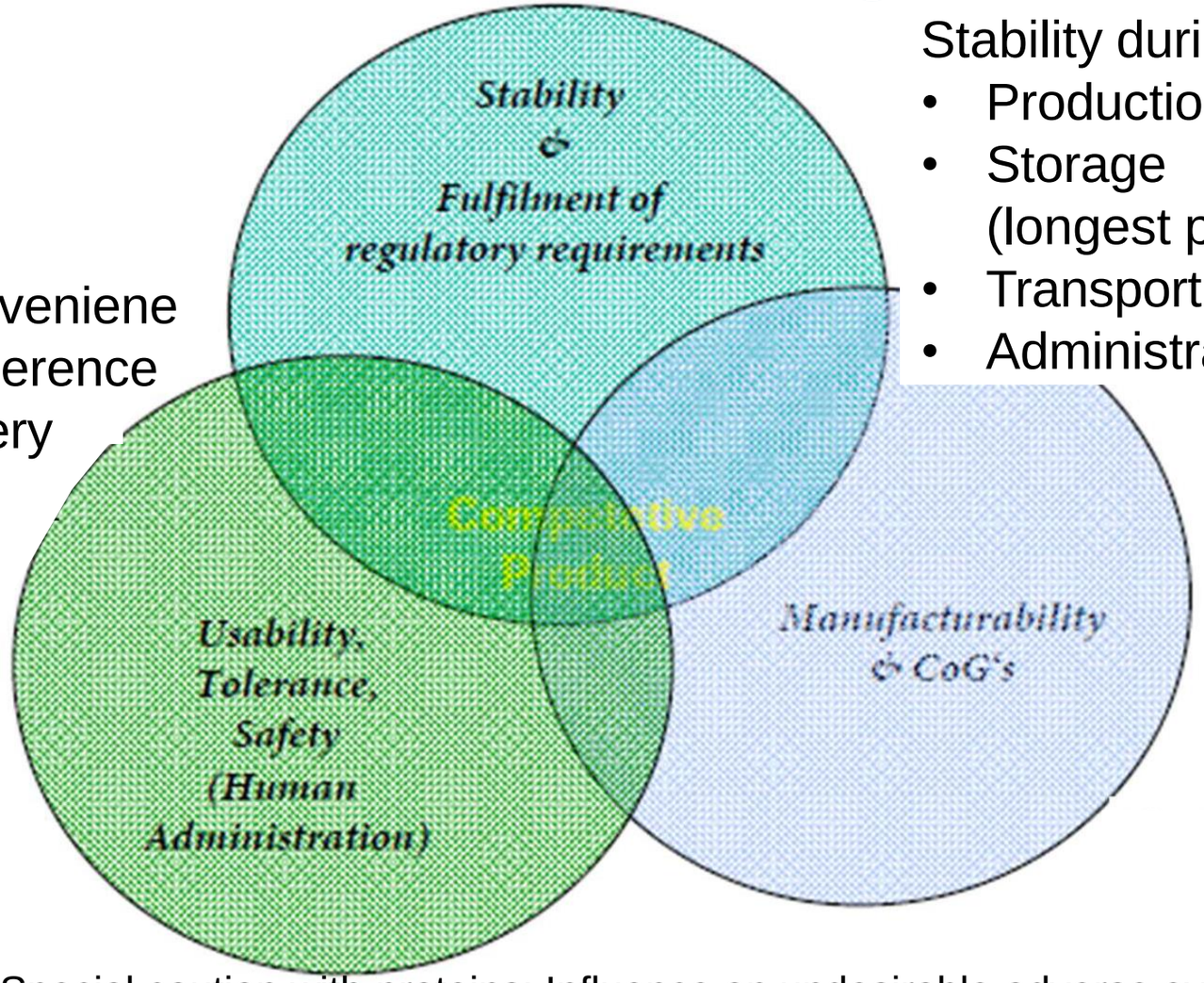
Requirements of a Drug Product

- Patient conveniene
- Patient adherence
- Dose delivery



Stability during:

- Production
- Storage
  (longest possible)
- Transport and
- Administration

Special caution with proteins: Influence on undesirable adverse events and clinical efficacy, immunogenicity and pharmacokinetic profile through product specific degradation products.

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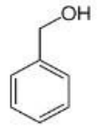
Design of a (protein) formulation

Antioxidant (Methionine)

Preservatives (Multi-does-vials)

Benzylalcohol

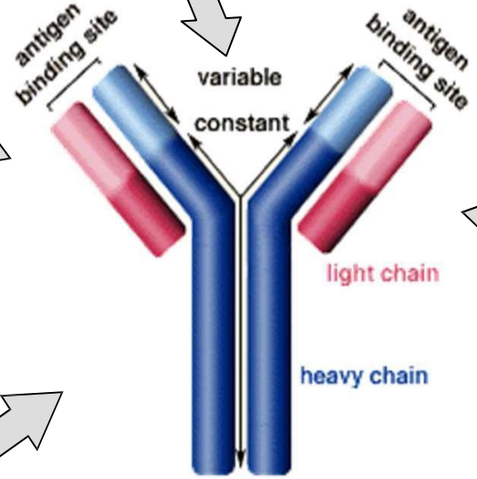


Buffer system

(His/HisHCl, Citrate,Tris)

~~**Acetate**~~

~~**Phosphate**~~



Lyo/cryoprotectants and bulking agents (Sucrose, Trehalose, Mannitol,…)

Stabilizers during freezing/ thawing (Sucrose, Trehalose)

- tonicity adjusting agents at the same time

Surfactants (Polysorbate 20/80, Poloxamer 188)

Liquid vs. Lyo IV vs. SC

Viscosity reduction e.g. Arginine-HCl

Literature recommendation: Marketed products in EU: Gervasi V, et al. Eur J Pharm Biopharm. 2018;131 (2017):8–24.
Stability of protein pharmaceuticals: Manning MC et al. Pharm Res. 2010;27(4):544–75.
A review of Formulations of Commercially Available Antibodies: Strickley R et al., J.Pharm.Sci. 2021;110(7):2590-2608

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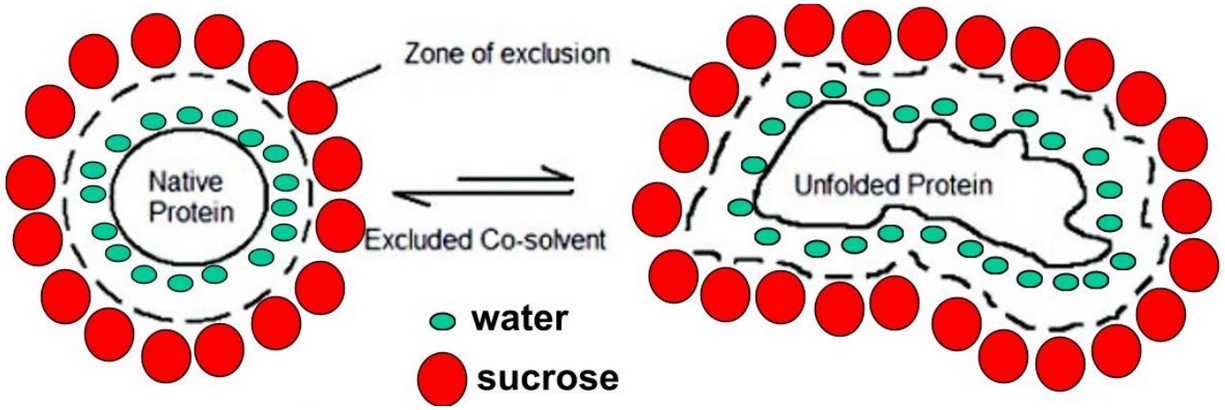
Lyo/cryo-protective excipients

Cryoprotectant

Stabilizes during the freezing process

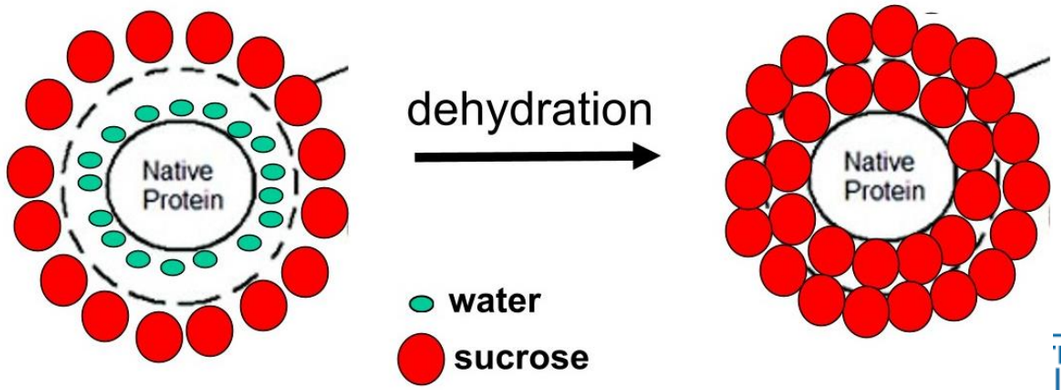
- Non-specific stabilization by preferentially excluded excipients/solutes from protein surface (e.g., disaccharides)
- Protein chemical potential of native and denatured state is increased, but magnitude of exclusion varies directly with protein surface area → greater for denatured than native state
- Thus, free energy of unfolding (ΔG) is increased (Timasheff 1988; Arakawa, Timasheff 1985).



Lyoprotectant

Stabilizes during the drying process

- Water stablizes a protein in liquid solution by hydrogen bonding. The excipient replaces the hydrogen bonds of water during drying and thus stabilizes the protein (water replacement) & forms a glass.



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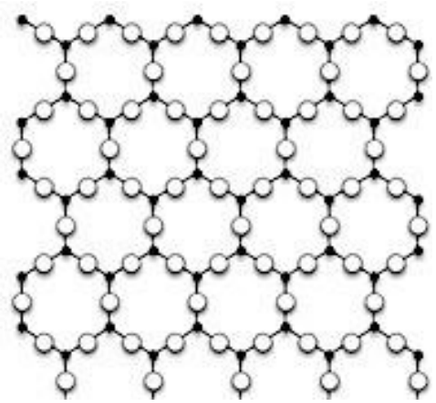
Lyo/cryoprotective excipients

Crystalline excipients

Ordered crystal structure



Eutectic temperature
(defined melting point)

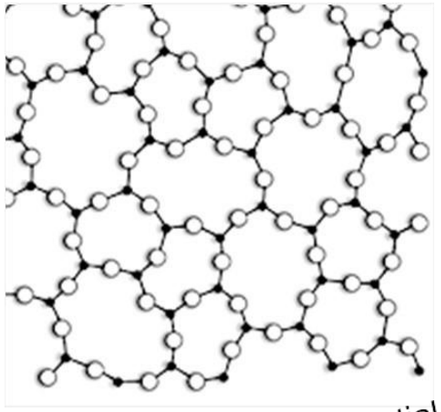
- Bulking agent
- High eutectic temperature :
  - Elegant cake appearance
  - Fast drying

- In many cases no stabilization (e.g. for most proteins)
- Different morphologies dependent on excipient (Mannitol→ Annealing)
- Glass breakage (Mannitol at high fill)

Glycine, Mannitol, NaCl, …

Amorphous excipients

Glassy state



Characterization by differential scanning calorimetry

Glas transition temperature

- Stabilzation of e.g. proteins
- Acceptable bulking agent at the same time

- Low M_w excipients: Low glass transition temperatures → Cake structure?
- High M_w excipients: Higher glass transition temperatures → poorer stabilization?

Sucrose, Trehalose, HPβCD, PVP, Dextran, …

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Examples

Kadcyla 100 / 160mg

20 mg/mL ado-trastuzumab emtansine
10 mM succinate pH 5.0
60 mg/mL D-Sucrose
0.02% Polysorbate

Herceptin 150 / 400 mg

21 mg/mL Trastuzumab
4 mM L-Histidine/-HCl, pH 6.0
20 mg/mL D-Trehalose
0.008 mg/mL Polysorbate 20

Source: A review of Formulations of Commercially Available Antibodies: Strickley R et al., J.Pharm.Sci. 2021;110(7):2590-2608

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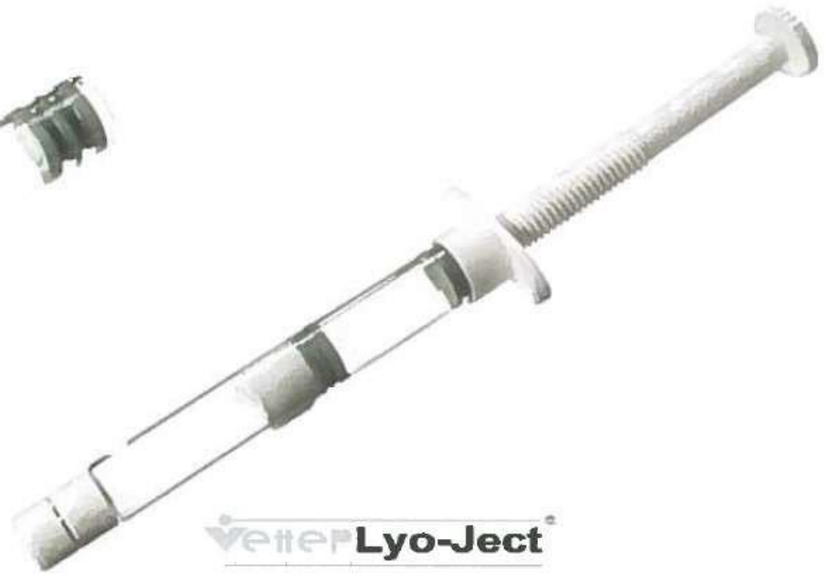
Primary packaging

Vial &
Elastomer
stoppers
(different coatings)

Dual
chamber
Cartridge



Syringe
(Dual chamber syringe)

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Theory 2b

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Freeze-Drying in Practice
9 – 13 September 2024

Martin Christ
Osterode am Harz, Germany

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PDA TRAINING

Development of a lyophilization cycle: Practical advice

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Where to find guidance?

- Pretty good starting point:

Pharmaceutical Research, Vol. 21, No. 2, February 2004 (© 2004)

Review

Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice

Xiaolin (Charlie) Tang[1] and Michael J. Pikal[1,2]

https://doi.org/10.1023/B:PHAM.0000016234.73023.75

Pharmaceutical Research (2023) 40:2433–2455
https://doi.org/10.1007/s11095-023-03607-9

ORIGINAL RESEARCH ARTICLE

Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update

Serguei Tchessalov[1] · Vito Maglio[1] · Petr Kazarin[2] · Alina Alexeenko[2] · Bakul Bhatnagar[1] · Ekneet Sahni[3] · Evgenyi Shalaev[4]

- https://doi.org/10.1007/s11095-023-03607-9

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How to approach it?

- Identify the maximum allowable/target product temperature during 1° drying
- Process design
  - Determine an adequate freezing procedure (annealing? Controlled nucleation?)
  - Ramps, equilibration steps, target freezing temperature, hold times
- 1°drying (simulation models or “paper-based”)
  - Determine combination of chamber pressure and shelf temperature
  - Ramp
  - Drying time (isothermal hold)
  - PAT for endpoint determination
- 2° drying
  - Ramp
  - Target shelf temperature and isothermal hold time

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Freezing – advice for process design

- Decide if thermal treatment (annealing or controlled ice nucleation) shall be implemented → Theory 9
- Define loading temperature (usually: room temperature)
- Define process:
  - Equilibration step: decide temperature (above eq. freezing point) + hold time (min. 30min)
  - Coolin ramp rate (0.2 – 2 °C/min) → for scalability reasons: 0.3 – 0.7 °C/min
  - Target temperature: min. 5°C below Tg'
  - Hold time dependent on fill depth: ≤ 1cm: 1h, 1-2 cm: 2h, >2h: 4h

Based on: 1) "Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update." Tchessalov et al. Pharm Res 40, 2433–2455 (2023)., 2) "Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice". Tang, X., Pikal, M.J. Pharm Res 21, 191–200 (2004).

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Primary Drying – advice for process design

- Determine the **target product temperature (T_p)**: amorphous formulations
  - For drying times >2d: $T_{collapse}$/$T_{eutectic}$ minus 2°C
  - For drying times <10h: $T_{collapse}$ minus 5°C
  - For drying times 10 ≤ t ≤ 2d: $T_{collapse}$ minus 3°C
  - Safety margin can also be calculated*
  - For (semi-)crystalline products: depending on equipment capabilities, a T_p of ~-10°C to -15°C is recommended (dependent on T_{eu} of the crystalline solute)
- Next, either use a simple heat/mass transfer model like 1) SP Scientific LyoCalculator or 2) LyoPRONTO or determine **$p_{chamber}$** and **T_{shelf}** „by hand“
- **Ramp rate** typically: 0.5 – 1 °C/min; **1° drying time** can be estimated[2]

*”Impact of natural variations in freeze-drying parameters on product temperature history: application of quasi steady-state heat and mass transfer and simple statistics.” Pikal et al. AAPS PharmSciTech. 2018;19(7):2828–42.

Based on: 1) “Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update.” Tchessalov et al. Pharm Res 40, 2433–2455 (2023)., 2) “Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice”. Tang, X., Pikal, M.J. Pharm Res 21, 191–200 (2004).

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Side note: Online calculators (heat/mass transfer simulations)

- **SP Scientific LyoCalculator (based on Pikal et al. model)**
  - Not officially available anymore, but still can be accessed here:
  - http://web.archive.org/web/20200924004836/http:/www.spscientific.com/LyoCalc/Lyocalculator.html
- **LyoPRONTO (Shivkumar et al.)**
  - Open source, theoretical assumptions in journal article
  - Tutorial available as book chapter
  - extended features like freezing calc, primary drying calc, design space calc, primary drying optimizer, but needs more advanced knowledge
  - Can be accessed here: https://lyopronto.geddes.rcac.purdue.edu/

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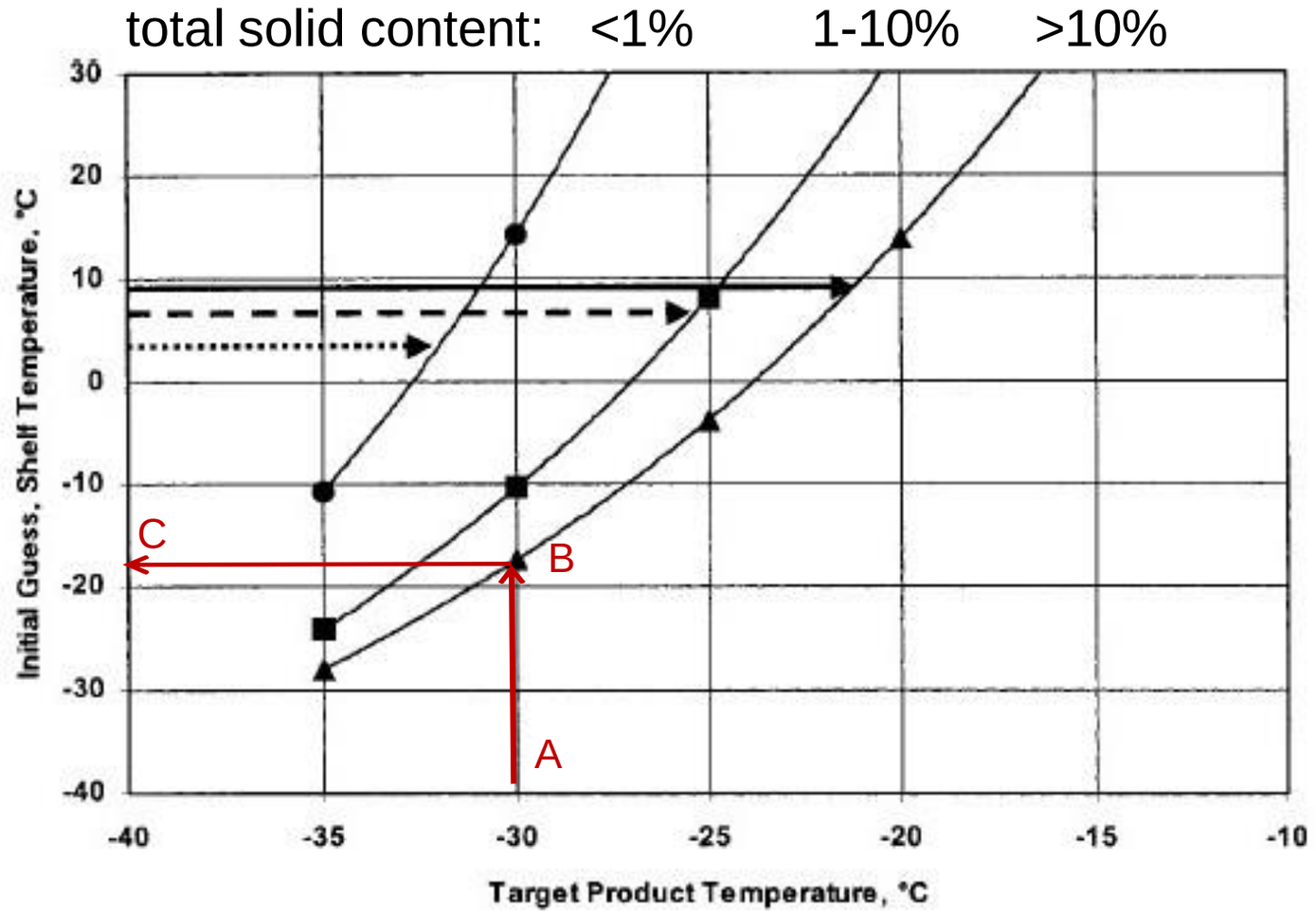
Primary Drying – shelf temperature estimation



The total solid content defines the product resistance.

Initial shelf temperature estimation:
T_c = -27°C

T_p 2-3°C below of T_c
→ For instance T_p = -30°C [A]

Setting of T(shelf) depends on product resistance and thus on total solid content (sc); Example: 11% solid content [B]

Readout is shelf temperature setpoint on y-axis: ~ -18 °C [C]

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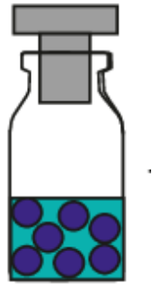
Primary Drying - Chamber pressure (p_c) estimation

Chamber pressure **>** Vapor pressure of ice at sublimation interface

p_c: 500 mTorr (0.67 mbar)



T_s = -30°C

Δp (chamber, ice) = driving force for sublimation!

Chamber pressure **<** Vapor pressure of ice at sublimation interface

p_c: 100 mTorr (0.13 mbar)

T_s = -30°C

- Vapor pressure of ice at -30°C → 0.31 mbar = 290 mTorr
- **Empiric equation:** $P_c = 0.29 \cdot 10^{(0.019 \cdot T_P)}$ p_c given in [Torr]; T_p = target product temp.
- For instance: **p_c** (Torr) = 0.29*10^(0.019*(-30)) = 0.078 Torr = **78 mTorr**

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Vapor pressure of ice

Source: https://www.lyotechnology.com/assets/vpoi-chart-101915.pdf

Vapor Pressure of Ice

In contact with its own vapor

Temp	Vapor Pressure			Temp	Vapor Pressure		
°C	Pa	µmHg	µbar	°C	Pa	µmHg	µbar
0	611.1	4584.4	6111	-42	10.22	76.6	102
-2	517.7	3883.6	5177	-44	8.10	60.8	81
-4	437.4	3281.6	4374	-46	6.39	48.0	64
-6	368.7	2765.9	3687	-48	5.03	37.7	50
-8	309.9	2325.1	3099	-50	3.94	29.5	39
-10	259.9	1949.4	2599	-52	3.07	23.0	31
-12	217.3	1630.0	2173	-54	2.38	17.9	24
-14	181.2	1359.1	1812	-56	1.84	13.8	18
-16	150.6	1130.1	1506	-58	1.41	10.6	14
-18	124.9	936.9	1249	-60	1.08	8.1	11
-20	103.2	774.4	1032	-62	0.82	6.2	8.2
-22	85.07	638.2	851	-64	0.62	4.7	6.2
-24	69.88	524.3	699	-66	0.47	3.5	4.7
-26	57.23	429.3	572	-68	0.35	2.6	3.5
-28	46.71	350.4	467	-70	0.26	2.0	2.6
-30	38.00	285.1	380	-72	0.19	1.5	1.9
-32	30.81	231.1	308	-74	0.14	1.1	1.4
-34	24.89	186.7	249	-76	0.10	0.8	1.0
-36	20.03	150.3	200	-78	0.08	0.6	0.8
-38	16.07	120.5	161	-80	0.05	0.4	0.5
-40	12.84	96.3	128	-82	0.04	0.3	0.4

mbar = 750.1 microns | 1 micron = 0.1333 Pa | 1 Pa = 7.5006 microns

1 mbar = 100 Pa | 1 micron = 0.0013 mbar | 1 Pa = 0.01 mbar

mbar (cgs units) = millibar (10 E3 dyns/cm sq)
microns = micrometers of mercury
Pa (SI units) = Pascals (N/m^2)
micron = µmHg = mTorr

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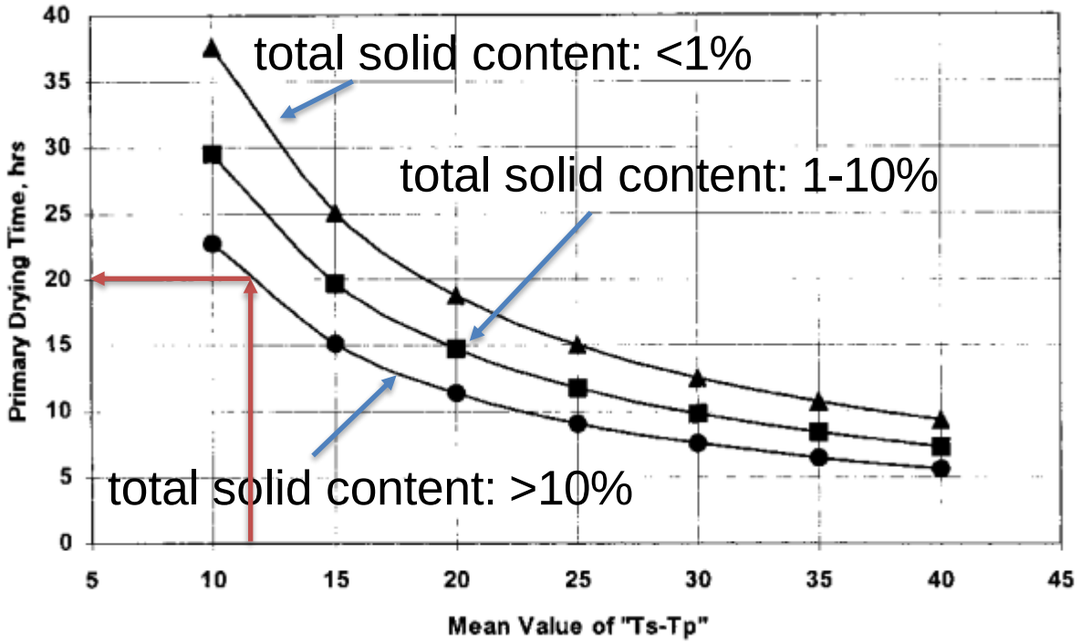
Primary Drying – rough(!) drying time estimation



Limitation: This figure is assuming a 1-cm-thick frozen cake(!)

- For our example:
  - T_s = -18 °C, T_p = -30 °C, total solid content: 11%
  - Calc. $T_s - T_p$ = -18°C – (-30 °C) = **12 °C**
  - Comparing the values with the graph yielding an roughly estimated drying time of ~20h for 1° drying

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Simulations (assuming: 20R vial, 10 mL fill, 11% total solid content, Tp=-30°C, amorphous)

Simulations for „by hand“ estimates:

User Inputs

Shelf Temperature	-18	[°C]
Chamber Pressure	0.104	[mBar]
Fill Volume	10	[mL]
Solute Concentration	11	[%]
Vial Outer Diameter	3.0	[cm]
Resistance Parameters R_o	2.3	
A_1	5.3	
A_2	0.7	

CLEAR VALUES | MATERIAL DATABASE | CALCULATE

Ts = -18 °C
p_c = 0.1 mbar

Report

Primary Drying Time	42.9	[Hrs]
Average Sublimation Rate per Vial	0.199	[g/Hr]
Maximum Product Temperature	-30.7	[°C]

CALCULATE | DETAILED OUTPUT | DOWNLOAD DATA AS CSV

Simulations optimizing for T_p = -30°C:

User Inputs

Shelf Temperature	-14	[°C]
Chamber Pressure	0.07	[mBar]
Fill Volume	10	[mL]
Solute Concentration	11	[%]
Vial Outer Diameter	3.0	[cm]
Resistance Parameters R_o	2.3	
A_1	5.3	
A_2	0.7	

CLEAR VALUES | MATERIAL DATABASE | CALCULATE

Ts = -14 °C
p_c = 0.07 mbar

Report

Primary Drying Time	34.4	[Hrs]
Average Sublimation Rate per Vial	0.249	[g/Hr]
Maximum Product Temperature	-29.9	[°C]

DETAILED OUTPUT | DOWNLOAD DATA AS CSV

Material Database

	Materials	R_o	A_1	A_2
USE	Povidone, 5% (v/v)	1.1	5	0
USE	Sucrose, 5% (w/w) with ice nucleated at -5°C	1	2.4	0.7
USE	Sucrose, 5% (w/w) with ice nucleated at -10°C	1.5	3.4	0.7
USE	Sucrose, 5% (w/w) with ice nucleated at -15°C (note: values were extrapolated)	2.3	5.3	0.7

Calculations performed with SP Scientific LyoCalculator

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Secondary drying – advice for process design

- Define ramp and target shelf temperature; p_c not too important*
- Ramp is critical for preventing collapse (amorphous products)
  - 0.1 to 0.2 °C/min amorphous
  - 0.3 to 0.4 °C/min (semi-)crystalline
- Define isothermal hold at target shelf temperature
  - Often, 3-6h at 40-50 °C suffice to reach < 0.5% (w/w) RMC (see theory 2a, slide 19 for sucrose 5-15%)

* Pc has almost no impact on drying rate, if kept below 0.267 mbar; for further details refer to: "The secondary drying stage of freeze drying: drying kinetics as a function of temperature and chamber pressure". Pikal et al. Int. J. Pharm. 60:3 (1990),

- Based on: 1) "Practical Advice on Scientific Design of Freeze-Drying Process: 2023 Update." Tchessalov et al. Pharm Res 40, 2433–2455 (2023)., 2) "Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice". Tang, X., Pikal, M.J. Pharm Res 21, 191–200 (2004).

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Development of cycles for practical work

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Experimental overview

- 3 different lab freeze dryers are available for runs
- Five different model formulations will be prepared and freeze dried:

Composition of formulations

#	Formulation	BSA	Excipient	Solid content	Buffer system	Surfactant	T_g' / T_{eu}	Fill volume
1	Formulation 1	25 mg/mL	240 mM Sucrose	~105 mg/mL	20 mM HisHCl pH 6.0	0.02% (w/v) Polysorbat 20	~ -27	10 mL
2	Formulation 2/3	-	240 mM Sucrose	~80 mg/mL			~ -32	10 mL
3								5 mL
4	Formulation 4	-	120 mM Sucrose	~40 mg/mL			~ -32	10 mL
5	Formulation 5	-	220 mM Mannitol	~40 mg/mL			~-1	10 mL

- Suggestion: run three differently conservative/aggressive cycles to observe different process behaviors and product appearance

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Available freeze dryer equipment

PAT	Epsilon 2-6D Lyo I	Epsilon 2-6D Lyo II	Epsilon2-4 Lyo III
Pirani	X	X	X
MKS	X	X	-
Comparative pressure measurement	X X	X X	-
PT100 (TC)			
WTM+ (wireless TC)	X	X	X
LyoRx	X	X	X
LyoCam	X	X	X
Controlled nucleation	X	-	-
Mass spectrometry	-	X	-
$\Delta T_p/\Delta T_s$	X	X	-

working sheet
Conservative

Lyophilization Program

Product assumptions: **T_g' = -32 °C;**
drying safely **below** T_g'; **8%** solute conc.

Regulation of vacuum: □Pirani □ MKS Target T_p = -? °C

Process step	Manual mode: Loading (Pre-cooling)	Freezing	Freezing	Freezing	Freezing	1° drying	1° drying	1° drying	2° drying	2° drying	Manual mode: stoopering
Time (hh:mm)											
Shelf temp. (°C)	20										
Vacuum (mbar)	off	off	off	off	off						750
Safety pressure (mbar)	off	off	off	off	off	0.26	0.26	0.26	0.26	0.26	
Δ T shelf (°C)		off	off	off	off	off	off	off	off	off	
Δ T product (°C)		off	off	off	off	off	off		off	off	
LyoControl Rx (%)		off	off	off	off	off	off	off	off	off	
camera interval (min)		15	60	1	5	10	10	10	10	60	

working sheet
Regular

Lyophilization Program

Product assumptions: **T_c = -30°C**; drying **around/slightly above** T_c; **8%** solute conc.; Target T_p = -30 °C

Regulation of vacuum: □Pirani □ MKS

Process step	Manual mode: Loading (Pre-cooling)	Freezing	Freezing	Freezing	Freezing	1° drying	1° drying	1° drying	2° drying	2° drying	Manual mode: stoopering
Time (hh:mm)											
Shelf temp. (°C)	20										
Vacuum (mbar)	off	off	off	off	off						750
Safety pressure (mbar)	off	off	off	off	off	0.26	0.26	0.26	0.26	0.26	
Δ T shelf (°C)		off	off	off	off	off	off	off	off	off	
Δ T product (°C)		off	off	off	off	off	off		off	off	
LyoControl Rx (%)		off	off	off	off	off	off	off	off	off	
camera interval (min)		15	60	1	5	10	10	10	10	60	

working sheet
Aggressive

Lyophilization Program

Product assumptions: **T_g' = -27°C**; drying **above** T_g'; **8%** solute conc.
Target T_p = -?°C

Regulation of vacuum: □Pirani □MKS

Process step	Manual mode: Loading (Pre-cooling)	Freezing	Freezing	Freezing	Freezing	1° drying	1° drying	1° drying	2° drying	2° drying	Manual mode: stoopering
Time (hh:mm)											
Shelf temp. (°C)	20										
Vacuum (mbar)	off	off	off	off	off						750
Safety pressure (mbar)	off	off	off	off	off	0.26	0.26	0.26	0.26	0.26	
Δ T shelf (°C)		off	off	off	off	off	off	off	off	off	
Δ T product (°C)		off	off	off	off	off	off		off	off	
LyoControl Rx (%)		off	off	off	off	off	off	off	off	off	
camera interval (min)		15	60	1	5	10	10	10	10	60	