Theory 9

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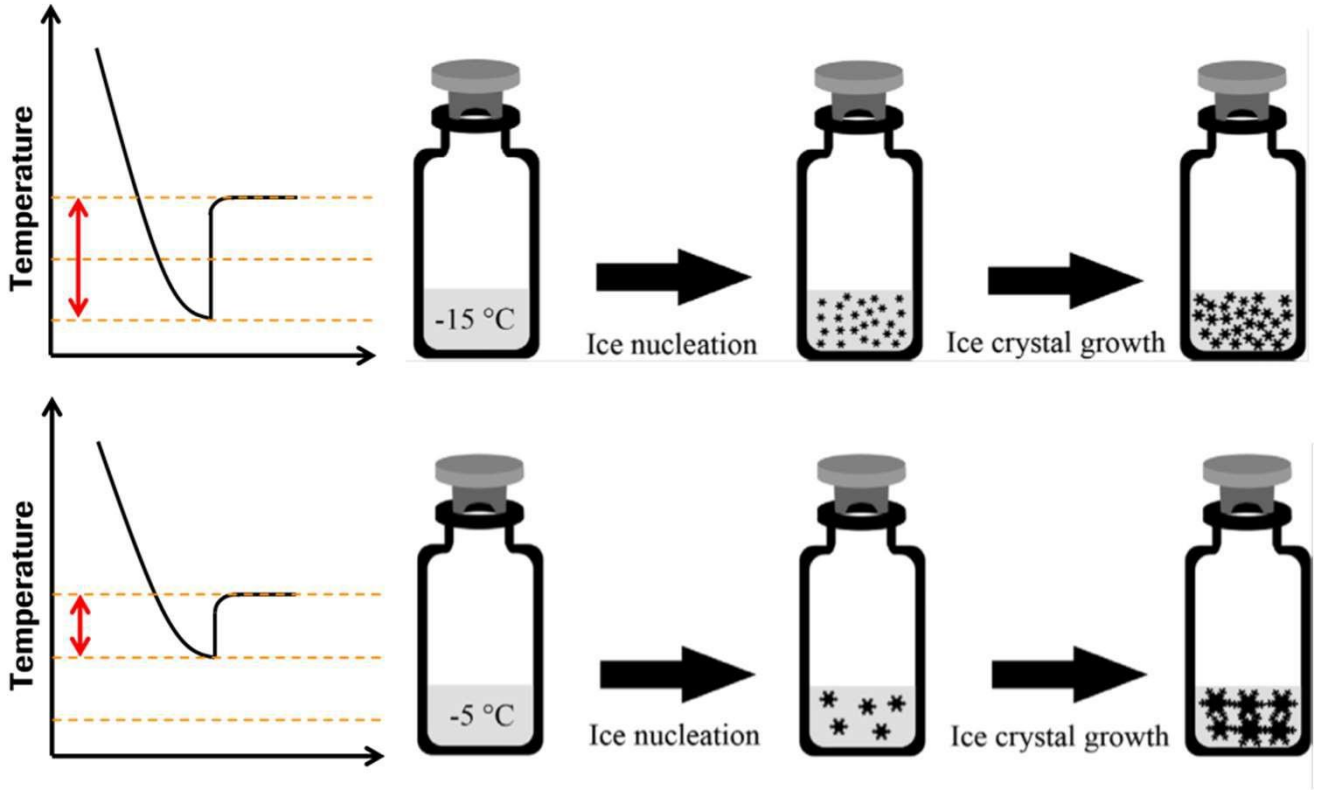
PDA EU
Freeze – Drying in Practice

12 – 16 June 2023
Martin Christ
Osterode am Harz, Germany

Adapted from slides originally created by and with courtesy of PD Dr. Andrea Allmendinger

Controlled nucleation



Low degree of supercooling

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Big dentritic ice crystals

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Morphology / Product resistance

↓

Drying time

- Increases inter-/intra-batch- and vial-to-vial homogeneity
- Shorter primary drying
- Better stability (?)

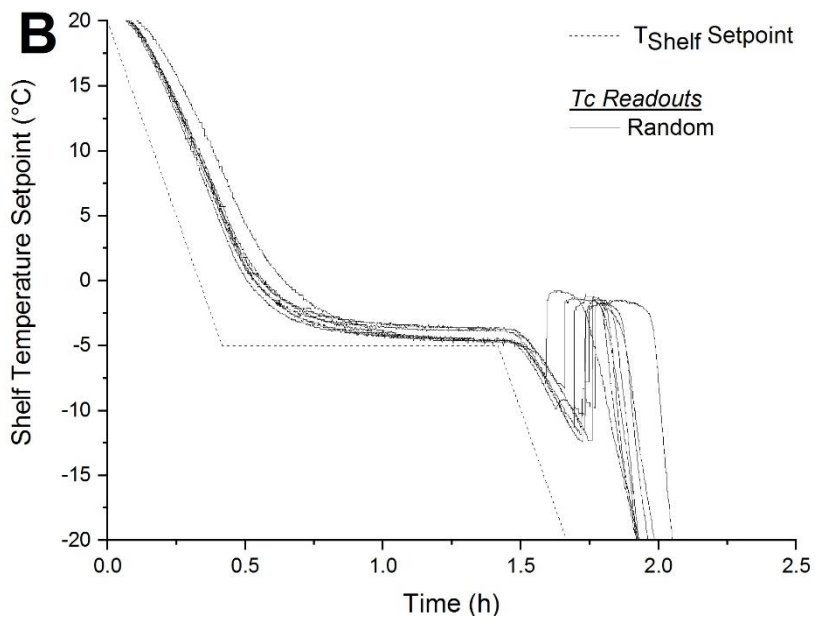
Review: Geidobler R, Winter G. Eur J Pharm Biopharm. 2013 Oct;85(2):214-22

Video

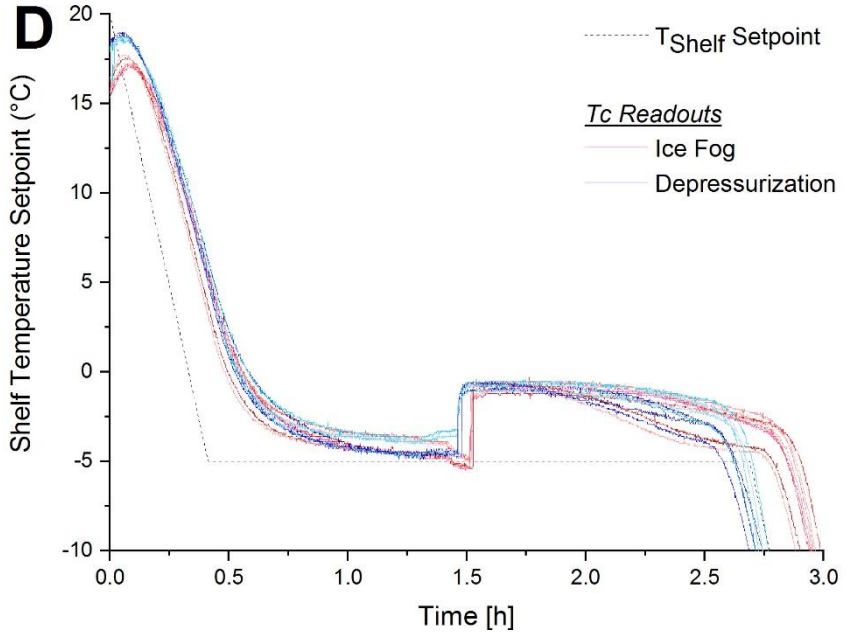
Video1_IceFog.wmv

Com1ecting People, Science and Regulation

Monitoring



Uncontrolled ice nucleation



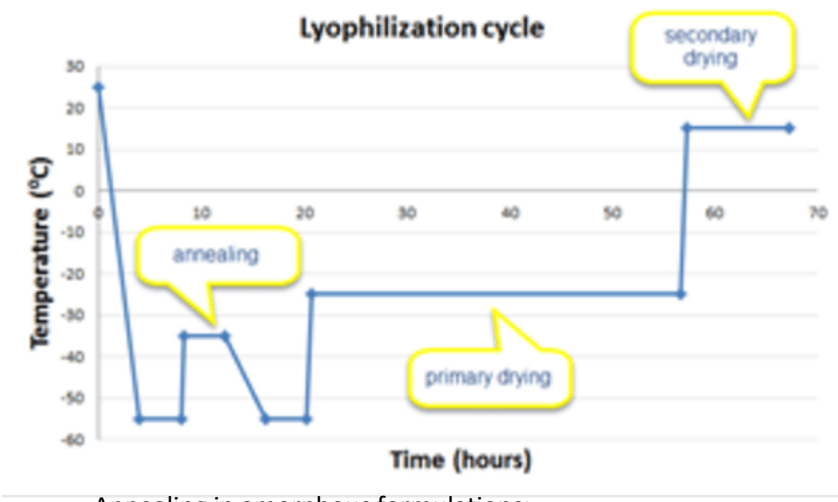
Controlled ice nucleation

Gitter JH, Geidobler R, Presser I, Winter G. A Comparison of Controlled Ice Nucleation Techniques for Freeze-Drying of a Therapeutic Antibody. *J Pharm Sci*. **2018**;107(11):2748–54.

Freezing – Annealing/Thermal treatment

Annealing = hold step at $\mathbf{T_s > T_g'}$ to allow for (complete) crystallization of potentially crystalline components

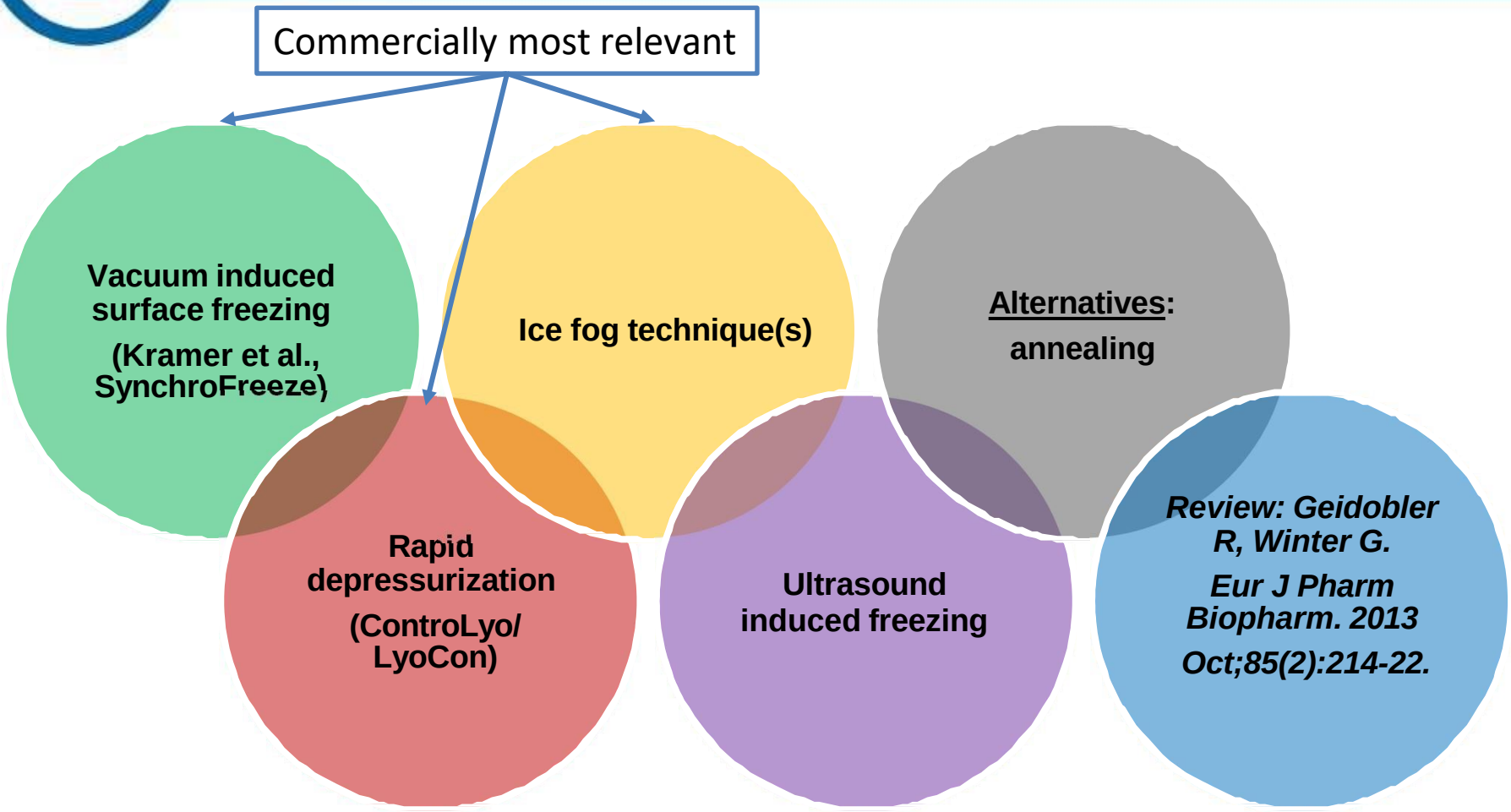
- Mainly used in formulations with crystalline bulking agents (e.g., Mannitol or Glycine)
- Allows for crystallization of potentially crystalline excipients in the freezing step and prevents crystallization during (primary) drying and has been shown to increase chemical stability
- Only partial crystallization of potentially crystalline excipients may impair product stability after lyo
- Literature recommendation (Tang, Pikal, Pharm. Res., 2004):
  - Apply regular freezing procedure
  - Allow for complete solidifaction by hold times of 1-2h
  - Bring product temperature to 10 °C – 20 °C above T_g', but well below T_{eu}
  - Allow for complete solidifcation afterwards again before starting with primary drying
    - Example annealing step for Mannitol/Glycine: T_s = - 20 °C or -15 °C for >= 2h



Annealing in amorphous formulations:
Jim A. Searles. Freezing and Annealing Phenomena in Lyophilization published in Freeze Drying/Lyophilization of Pharmaceutical and Biological Products. Vol. 206, 3rd edition.
T. Kharatyan et al. Quantitative Analysis of Glassy Relaxation and Ostwald Ripening during Annealing Using Freeze-Drying Microscopy. Pharmaceutics. 2022;14(6), 1176.

Literature recommendation for design of DSC mesaurements: Pansare SK, Patel SM. Practical Considerations for Determination of Glass Transition Temperature of a Maximally Freeze Concentrated Solution. AAPS PharmSciTech. 2016;17(4):805–19.

Methods for controlled nucleation



Literature recommendation:

processes

MDPI

Article

Comparison of Techniques to Control Ice Nucleation during Lyophilization

Jacob Luoma [1,†], Erika Ingham [1], Carmen Lema Martinez [2] and Andrea Allmendinger [2,3,*,†]

Roche

Controlled Ice Nucleation during Lyophilization

- Comparison of Nucleation Techniques and their Impact on Protein Stability

Andrea Allmendinger and Jake Luoma

Pharmaceutical Development
Roche/Genentech, Basel/San Francisco

Conference Freeze-Drying of Pharmaceuticals and Biologics
Garmisch-Patenkirchen, September 2018

Reprint of slides originally created by and with courtesy of PD Dr. Andrea Allmendinger

Outline

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Background to controlling ice nucleation (CIN)

- Benefits
- Technologies

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Case-study:

Comparison of nucleation techniques

- Solid state
- Stability
- Challenges

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Summary and take-home messages

Outline

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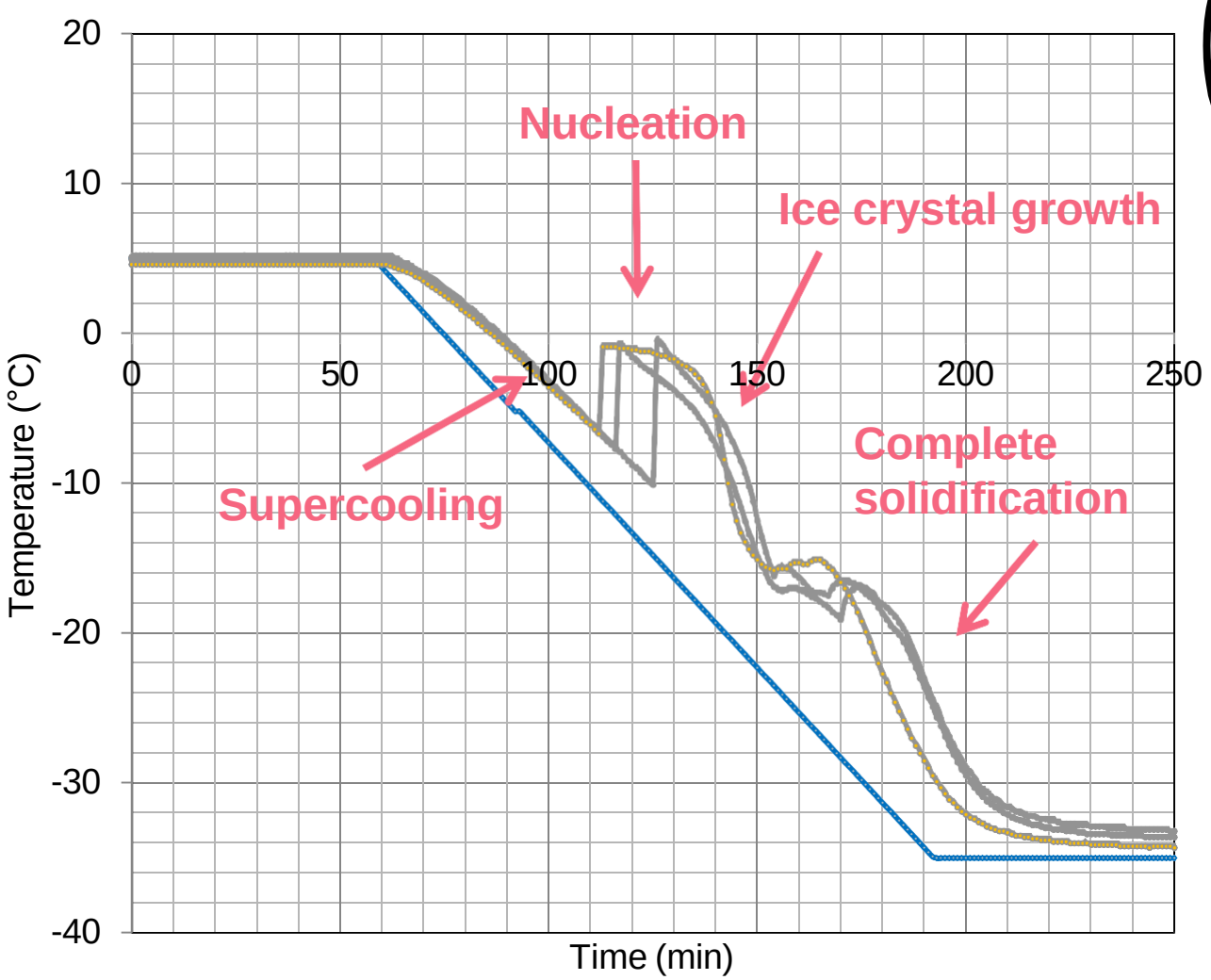
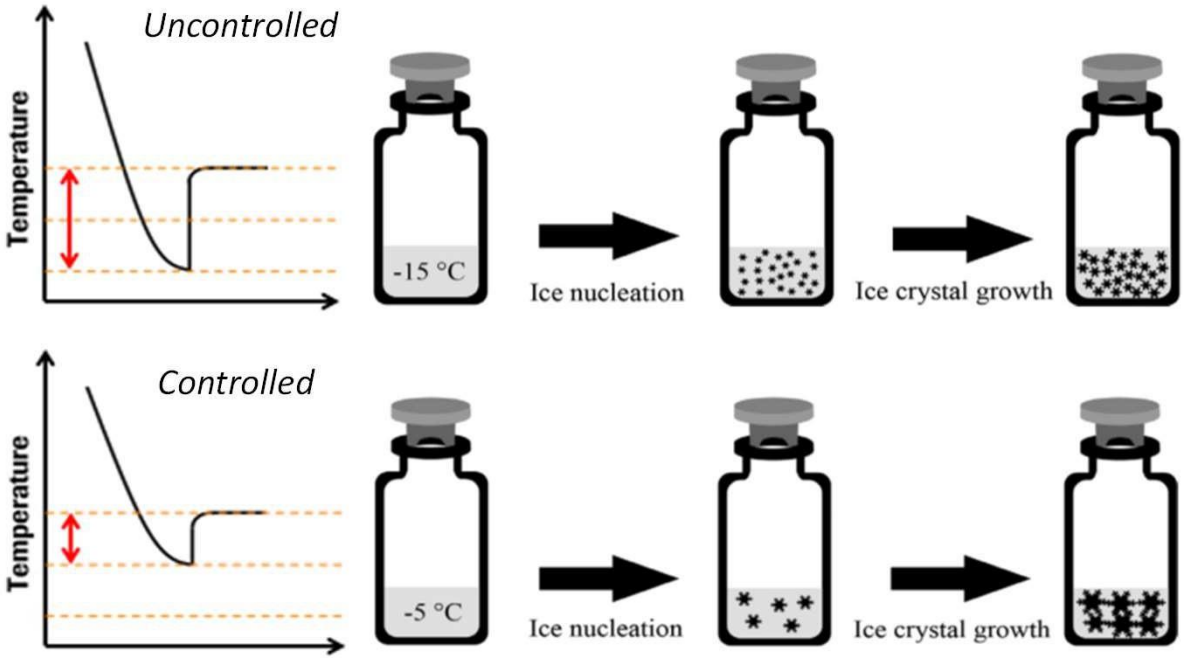
Summary and take-home messages

Standard freezing step



Nucleation temperature impacts cake structure, CQAs, and cycle time



Geidobler et al.: Controlled ice nucleation in the field of freeze drying: Fundamentals and technology review. Eur J Pharm Biopharm. 85(2):214-22. (2013).

Pros of CIN

+ **Increase inter-vial homogeneity**
+ Shorter primary drying
+ Improved cake appearance

Cons of CIN

- Higher residual moisture
- Intra-vial homogeneity
- Additional process step

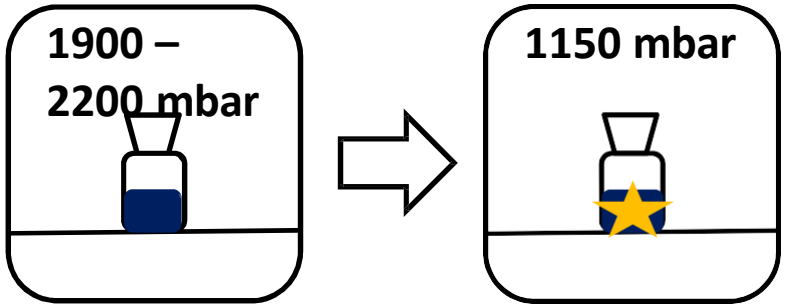
→ Lower vial-to-vial variability reduces scale differences and improves confidence in technical transfers especially for products which are difficult to lyophilize like molecules which are sensitive to moisture or surface area

Technologies for controlling ice nucleation

- Techniques used in the following case study

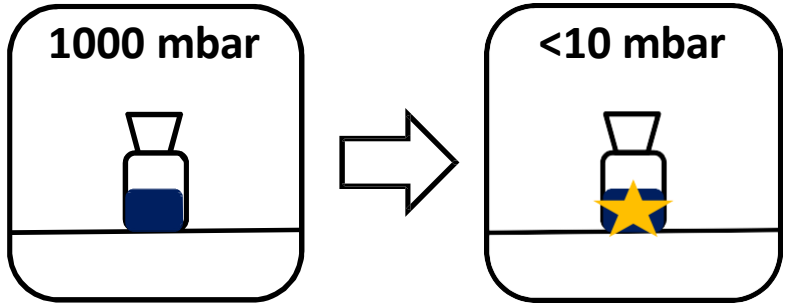
Depressurization

SP Scientific ControLyo®



Partial Vacuum

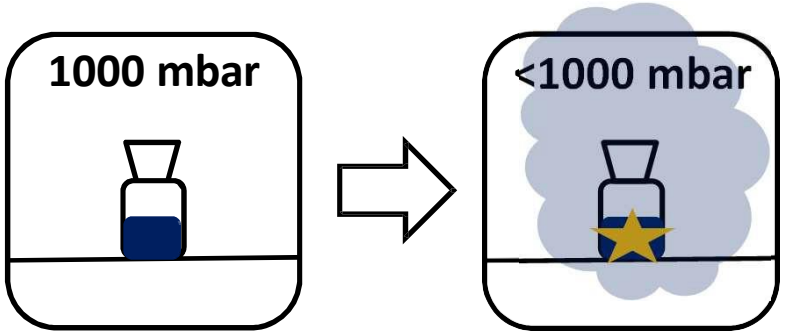
HOF SynchroFreeze™



Ice Fog

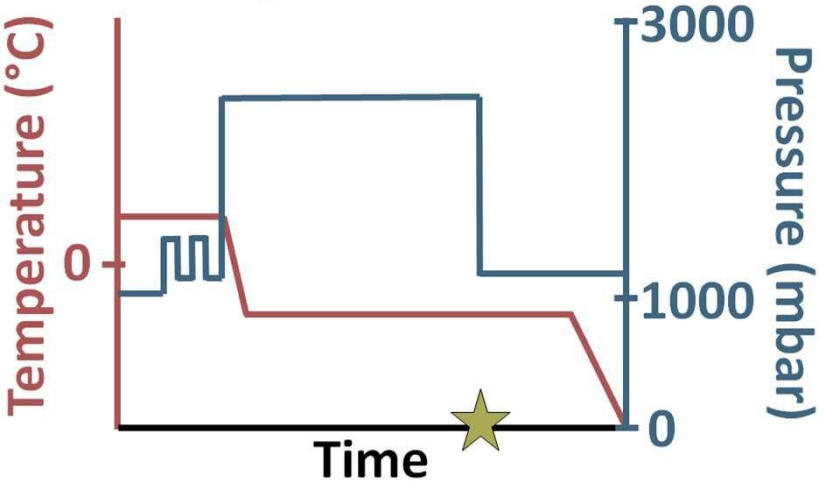
Linde/IMA VERISEQ®

Martin Christ LyoCoN,...

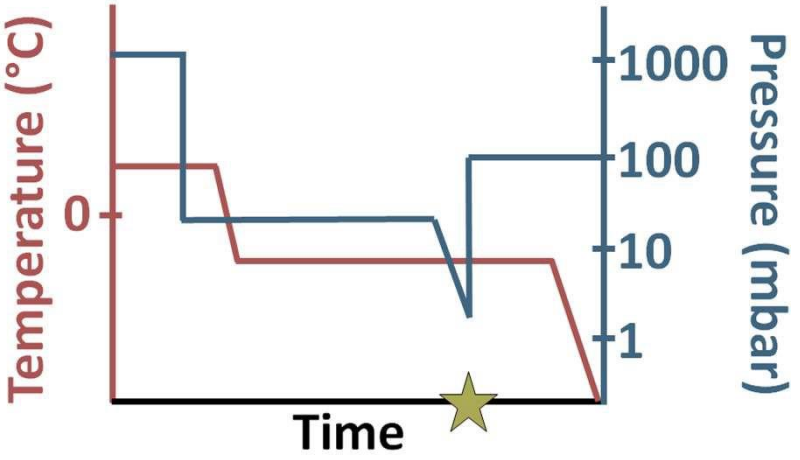


Controlled ice nucleation - Modes of operation

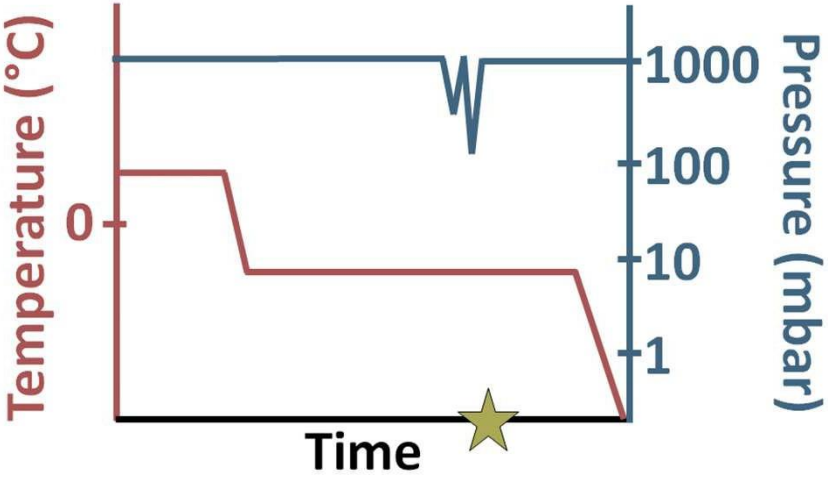
Depressurization



Partial Vacuum



Ice Fog



Nucleation event

Outline

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Summary and take-home messages

Nucleation temperatures achieved

Overview of nucleation temperatures for different formulations.

Formulation #	Protein conc.	Total solid content	Vial format (cc)	Nominal fill (mL)	Highest controlled nucleation temperature achieved		
					Depressurization	Partial vacuum	Ice fog
1	10 mg/mL mAb	9%	2	1	Failure to nucleate (UCN)	-5	-5
			20	10	-5	-5	-5
			50	20	-5	-5	-5
2	100 mg/mL mAb	18%	2	1	Failure to nucleate (UCN)	-15	n.p.
			20	10	-5	-15	-5
			50	20	-5	-15	n.p.
3	2.5 mg/mL enzyme	11%	6	0.9	-10	-5	n.p.
			20	10	-5	-5	n.p.
			50	20	-10	-15	-10

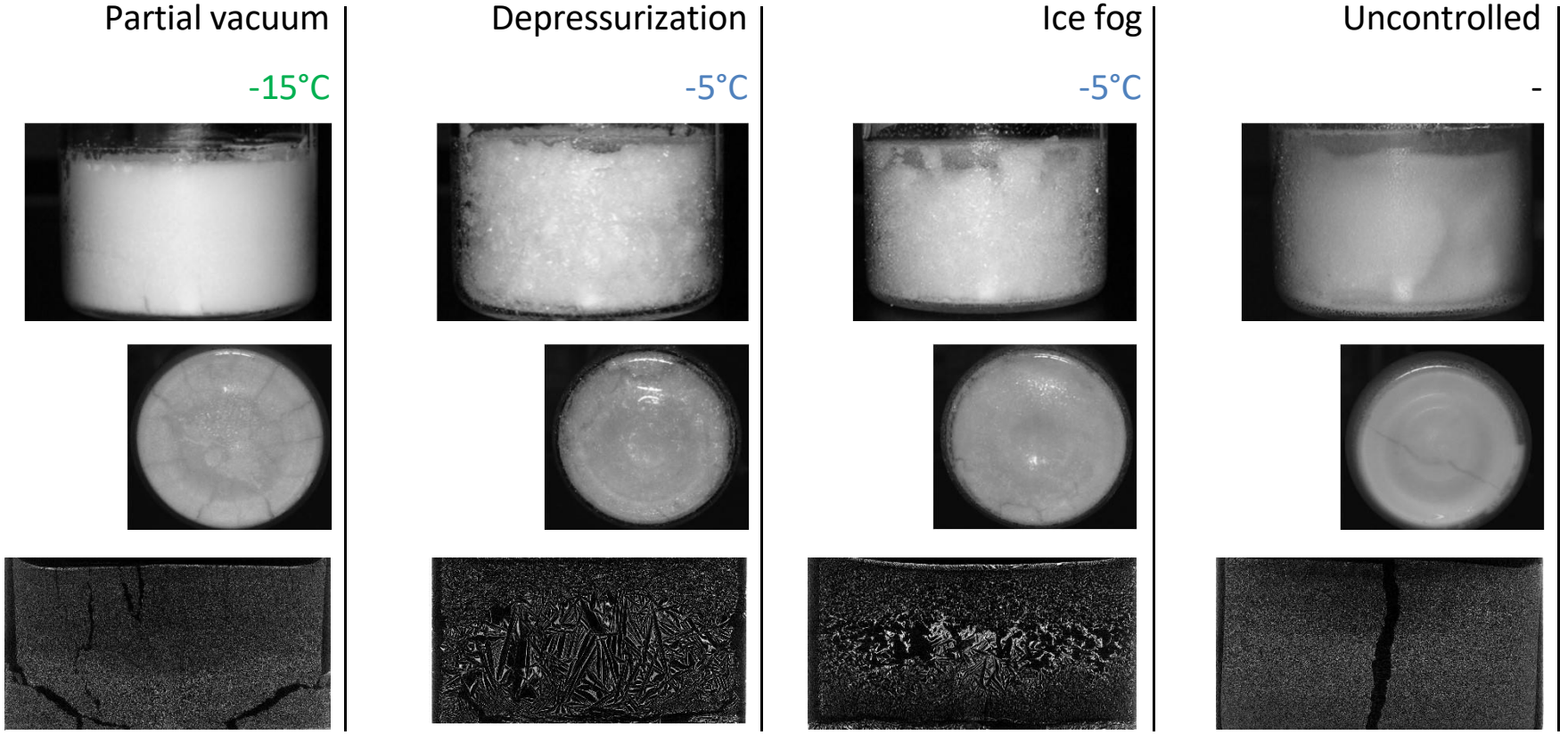
n.p. = not performed, UCN = uncontrolled nucleated

- Depressurization method struggled with 2cc vials
- Partial vacuum method struggled with Formulation 2/3 (high total solids)

Nucleation at different temperatures

– cake appearance and macroscopic cake structure

Formulation 2: 100 mg/mL mAb, nucleation temperature: **-5°C** and **-15°C**



- Nucleation ten degrees apart resulted in large changes in cake structure and macroscopic cake structure

Nucleation at different temperatures

– cake appearance and macroscopic cake structure

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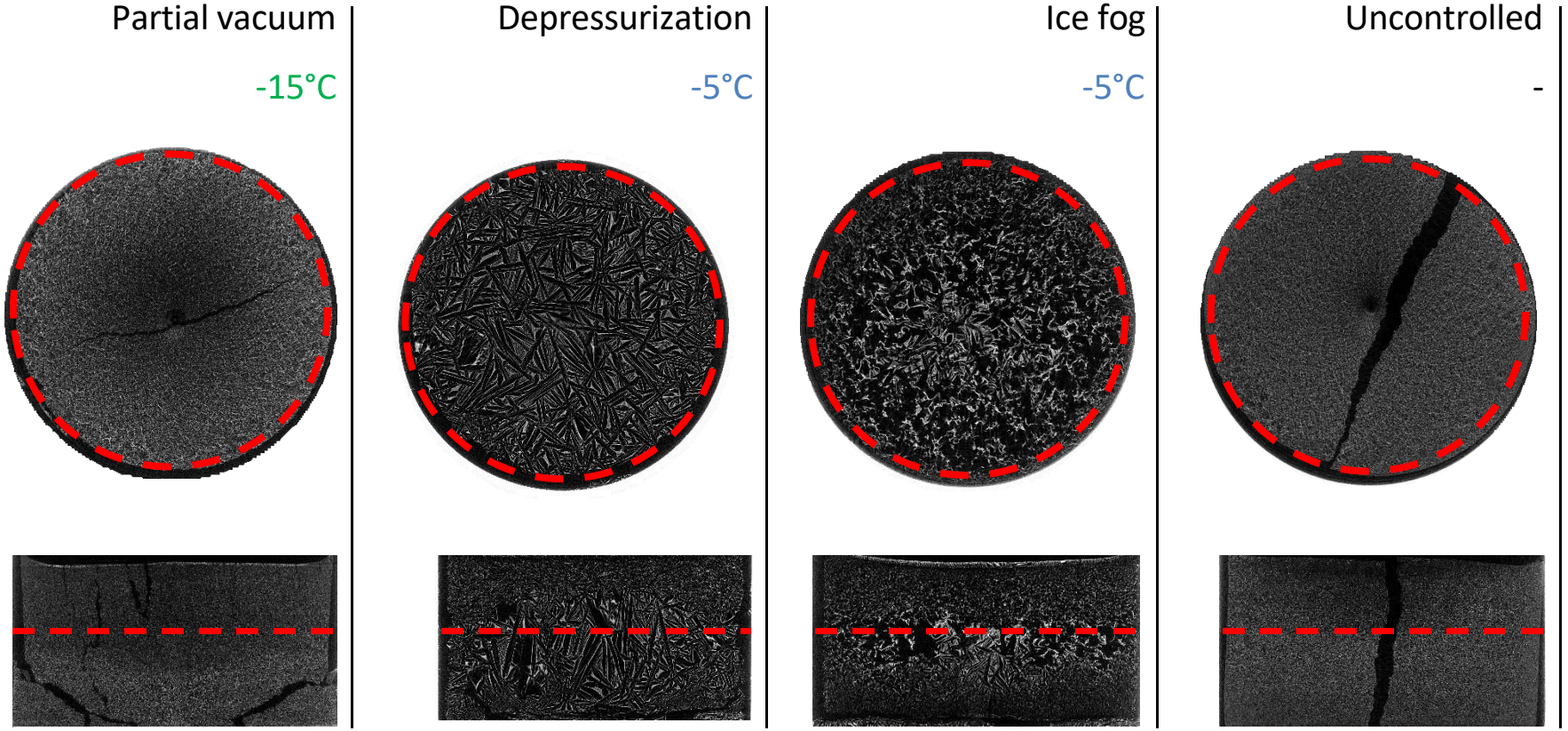
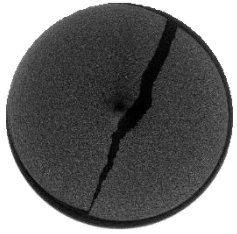


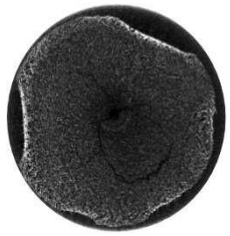
- Nucleation ten degrees apart resulted in large changes in cake structure and macroscopic cake structure
- Depressurization and Ice fog samples revealed crystal-like patterns but differed to each other

Summary

- Robustness testing for formulation and vial configuration revealed
  - Depressurization method struggled with 2cc vials
  - Partial vacuum method struggled with formulation with very high total solid content



- Nucleation at the same temperature resulted in comparable solid state properties like residual moisture and specific surface area, which directly relates to stability behavior dependent on the molecule studied



- Specific example showed that macroscopic structure (top layer) may be different between nucleation techniques, which may impact drying behavior, and is currently further studied

Take-home message

- Each technology has limitations
  - Depending on vial format and formulation you may need to nucleate at lower temperatures to ensure robust nucleation, which triggers formulation and configuration dependent process development
  - If operating conditions result in microcollapse, comparability between material produced with the different CIN technologies is not guaranteed
- Each technology has different installation and operation requirements like availability, location and size of ports or availability of liquid nitrogen