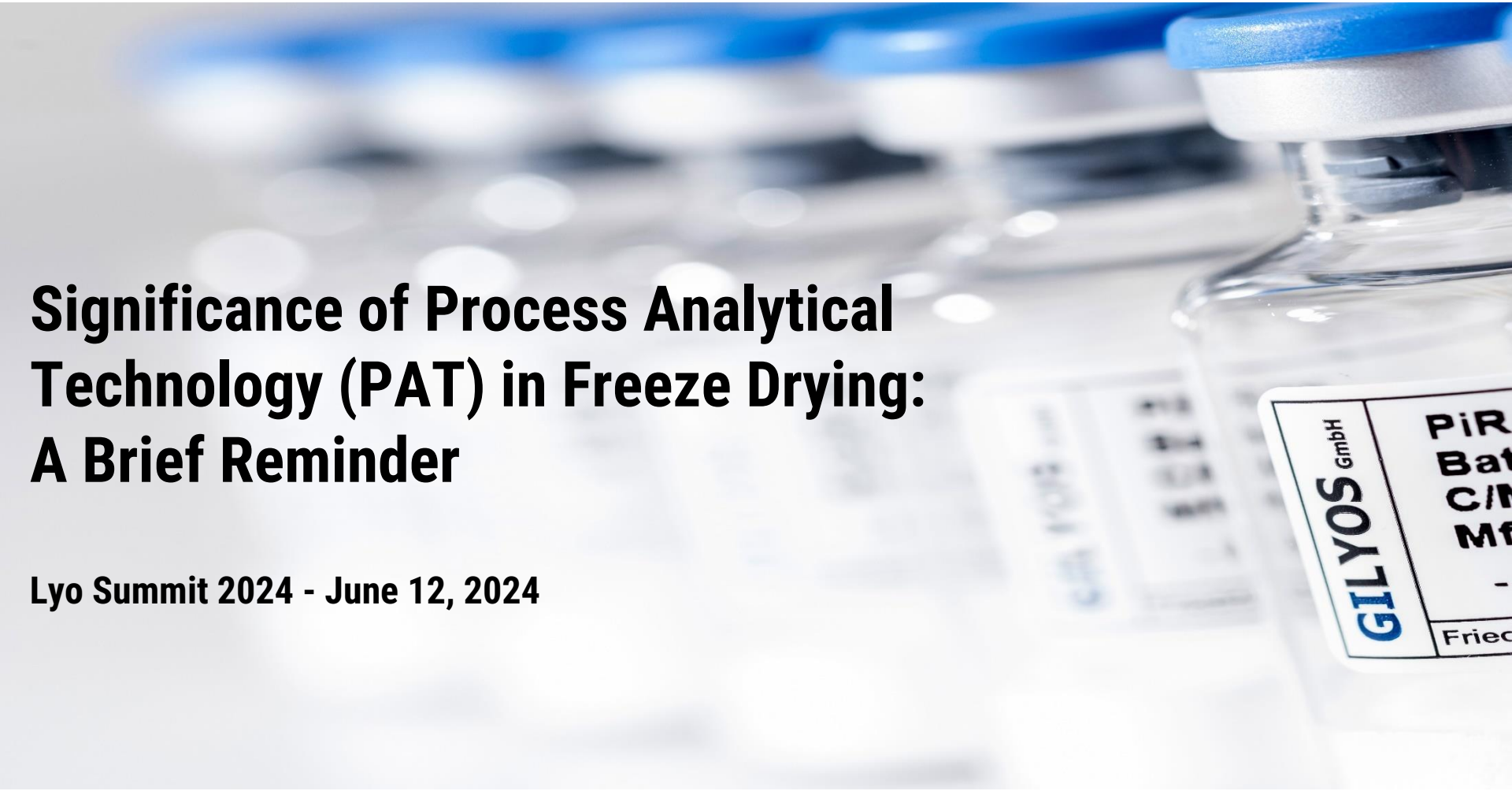

Significance of Process Analytical Technology (PAT) in Freeze Drying: A Brief Reminder

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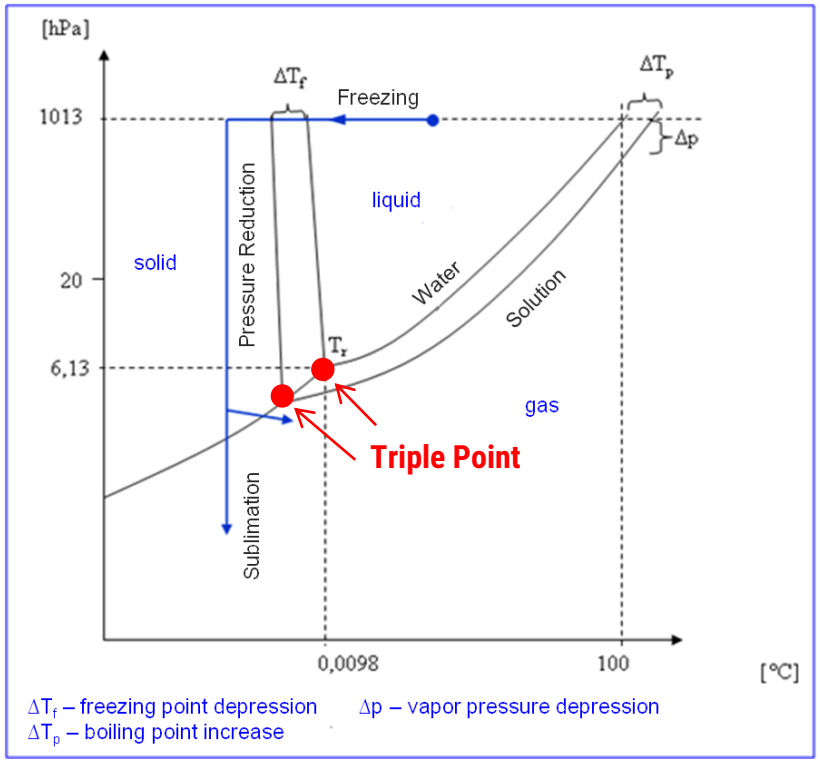
Margit Gieseler

GILYOS GmbH I Friedrich-Bergius-Ring 15 I 97076 Würzburg I E-Mail: info@gilyos.com I Web: www.gilyos.com

Fundamentals of Freeze Drying

- **Freeze Drying (Lyophilisation)**

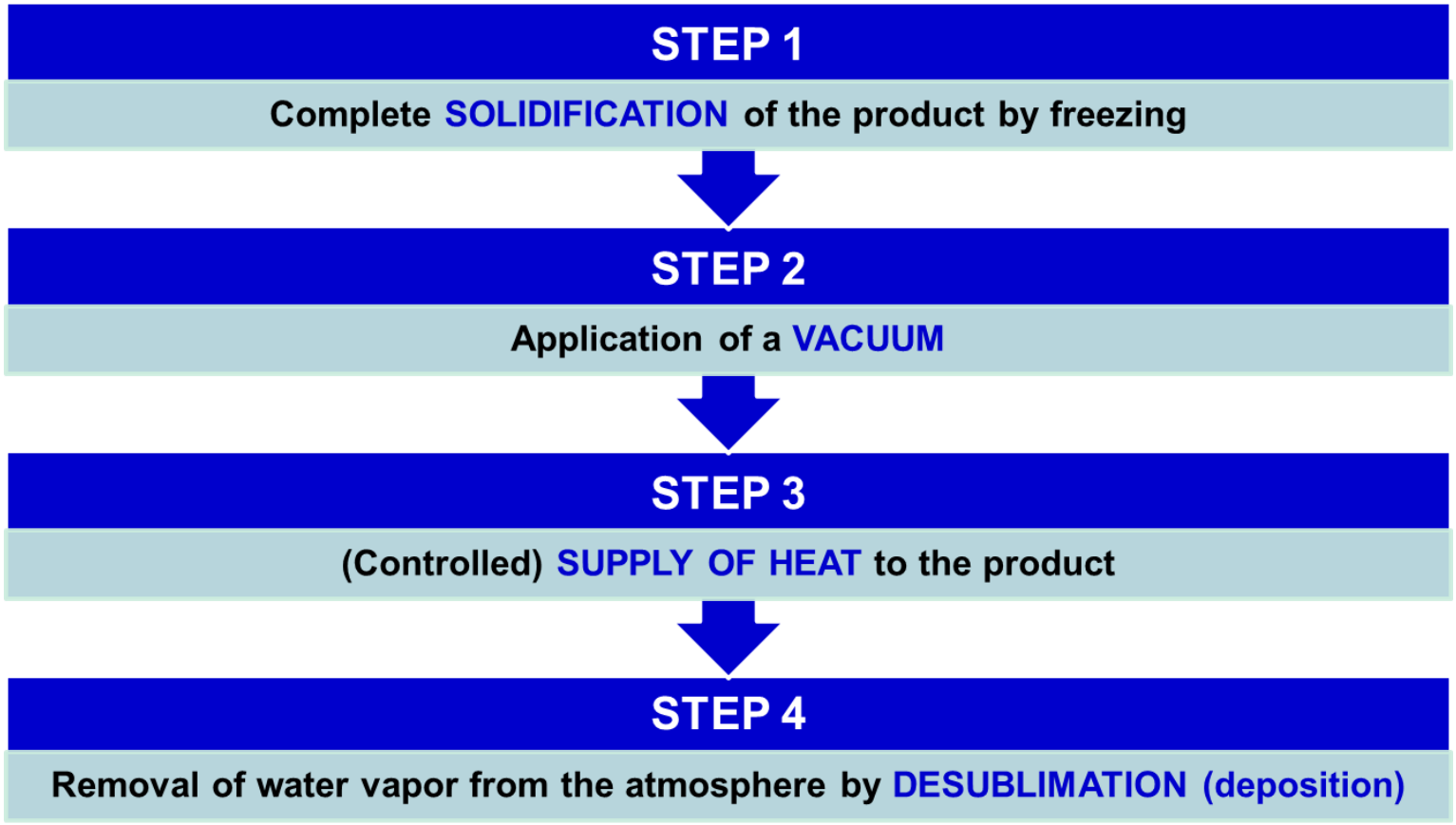
⇒ **Gentle drying by sublimation:**



⇒ **Mainly used for temperature-sensitive or parenteral products.**

- **Freeze Drying (Lyophilisation)**

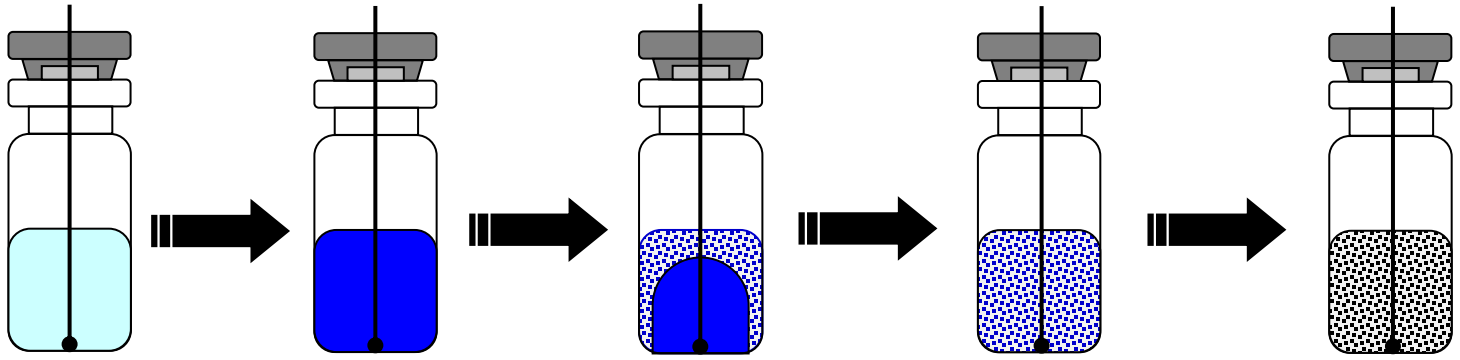
  ⇒ **Sublimation requirements:**



Fundamentals of Freeze Drying

Process Phases, 1

Freezing	Primary (1°) Drying	Secondary (2°) Drying
Solidification Nucleation and physicochemical properties of the formulation as important factors SHORT (few hrs)	**Ice Sublimation** Removal of ice dictated by various parameters (e.g. shelf temperature, chamber pressure, product resistance, etc.) Control of product temperature mandatory MOST TIME CONSUMING PHASE (1-7 days)	**Diffusion & Desorption** Complete removal of ice during 1° drying important before ramping into 2° drying Relevant for final residual moisture content of the product SHORT (few hrs)



- **Primary (1°) Drying**
  - ⇒ **Driving force for sublimation: difference between the vapor pressure of ice at the sublimation interface (P_{ice}) and the chamber pressure (P_c):**

$$\frac{dm}{dt} = \frac{P_{ice} - P_c}{R_p + R_s}$$

dm/dt: mass flow rate
P_{ice}: vapor pressure of ice
P_c: chamber pressure
R_p: product resistance
R_s: stopper resistance

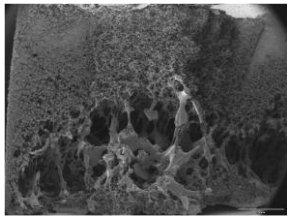
  - ⇒ **P_{ice} is a function of product temperature, T_p (at ice sublimation interface).**
  - ⇒ **Short primary drying, if:**
    - ***T_p is high.***
    - ***R_p is low.***
  - ⇒ **Critical parameters for successful primary drying:**
    - ***T_p.***
    - ***Endpoint detection.***

Relevance of T_p

Relevance of T_p

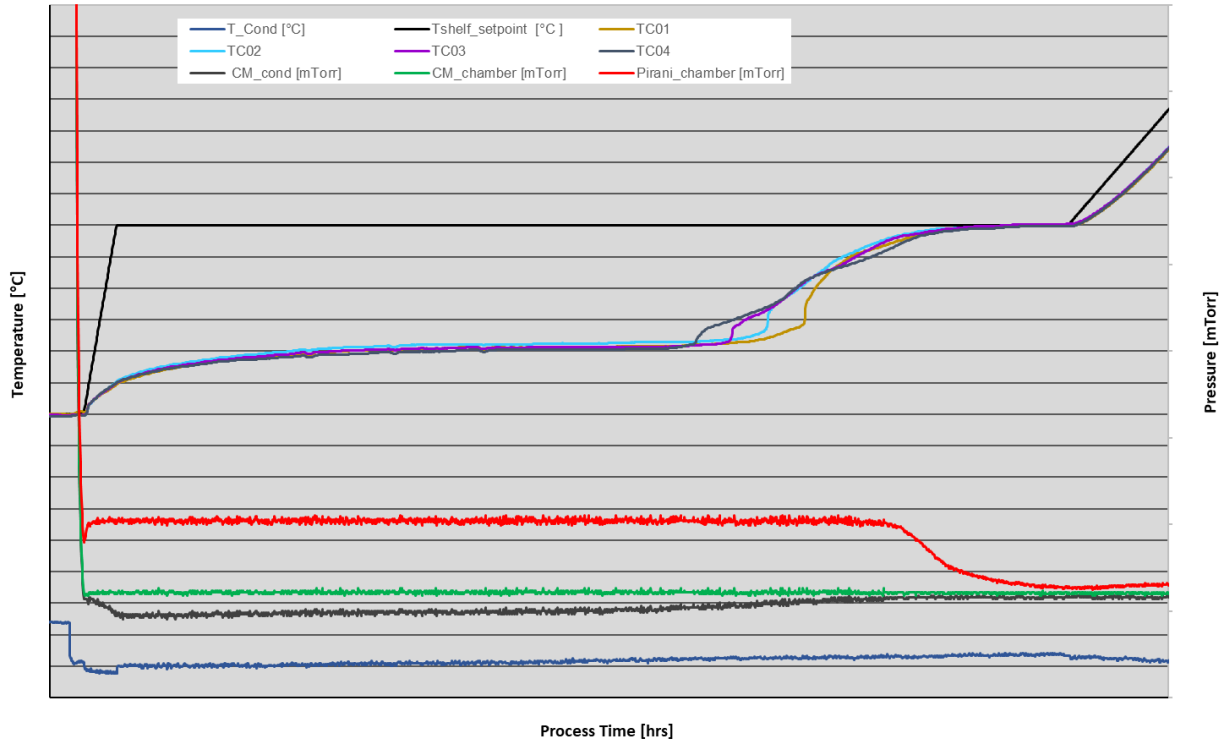
Critical Formulation Temperature

- **Critical Formulation Temperature (CFT)**
  - ⇒ **Product temperature (T_p) which must not be exceeded during primary drying in order to avoid product defects.**
  - ⇒ **Depends on the qualitative and quantitative composition of the formulation.**
  - ⇒ **Types:**
    - ***Glass transition temperature of the maximally freeze-concentrated solute (T_g').***
    - ***Collapse temperature (T_c).***
    - ***Eutectic temperature (T_{eut}).***
  - ⇒ **Risks during primary drying related to the CFT:**
    - ***Shrinkage / collapse → $T_p > T_g' / T_c$.***
    - ***Meltback → $T_p > T_{eut}$.***
  - ⇒ **Potential impact on product quality (examples):**
    - ***Stability issues.***
    - ***Prolonged / incomplete reconstitution.***
    - ***Compliance issues due to product appearance.***



- **Rational Process Design**

⇒ **T_p is the resultant of (among others) the total solid content of the formulation, freezing conditions, shelf temperature (T_s), and chamber pressure (P_c).**

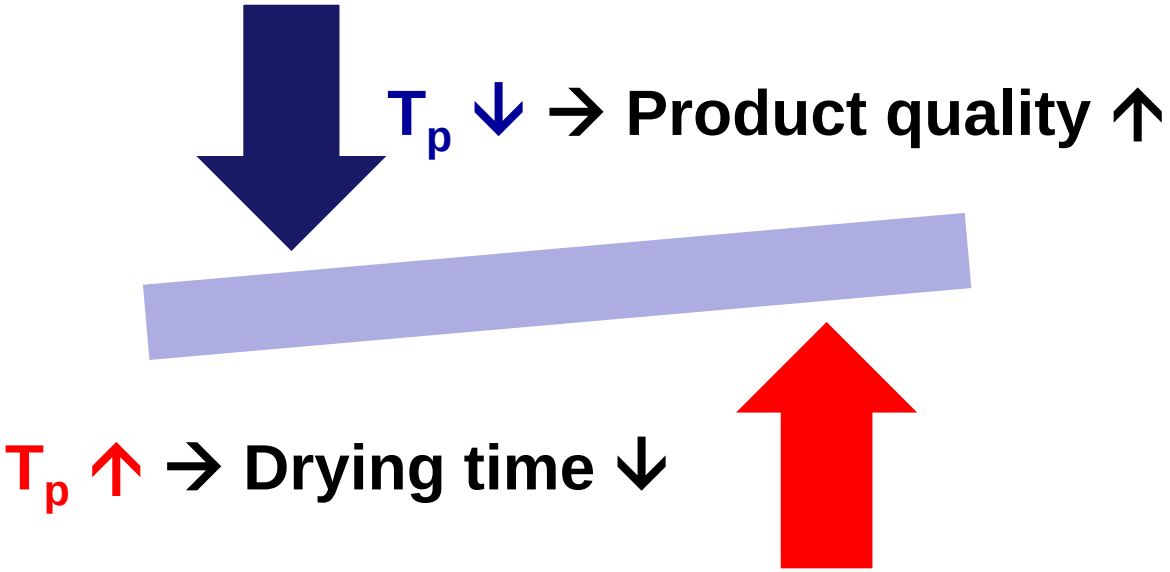


Note: T_p cannot be directly measured, only T_b (product temperature at vial bottom).

- **Rational Process Design**

  ⇒ **The process conditions must be selected**

  - ***as economically as possible, but***
  - ***as conservatively as required (based on the formulation`s needs (CFT)).***



PAT and Scale-Up Challenges

GILYOS GmbH I Friedrich-Bergius-Ring 15 I 97076 Würzburg I E-Mail: info@gilyos.com I Web: www.gilyos.com

PAT and Scale-Up Challenges

PAT, 1

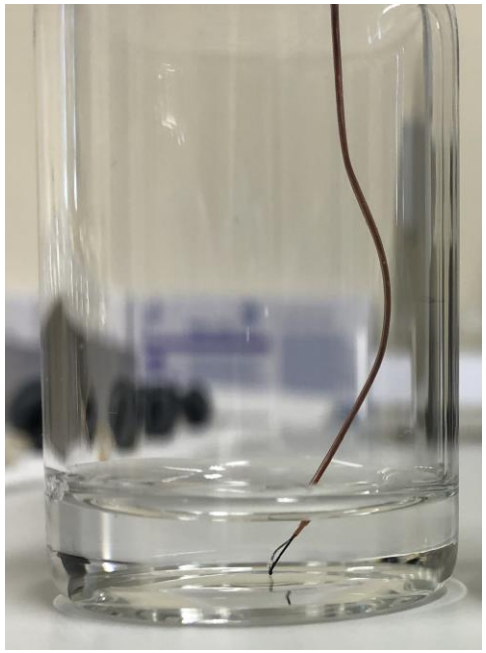
- **FDA Perspective: PAT**
  - ⇒ **= "… a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality." [1]**

[1] *Guidance for Industry, PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. 2004. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington DC.*

- **PAT Technologies in Freeze Drying [2]**
  - ⇒ **Batch methods.**
  - ⇒ **Single vial methods.**
  - ⇒ **Biggest challenge: applicability of the same technology in all scales (laboratory, pilot, production), cf. "Rule of Four".**

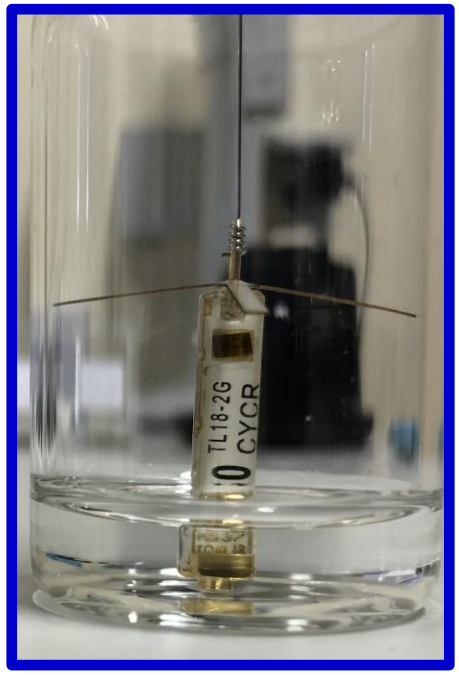
[2] *Gieseler H. Quality by Design (QbD) in Freeze Drying. Encyclopedia of Pharmaceutical Science and Technology, Fourth Edition, 2013.*

- **Product Temperature Measurement**
  - ⇒ T_p: only indirect evaluation (by calculation).
  - ⇒ T_b: direct measurement possible:



TC

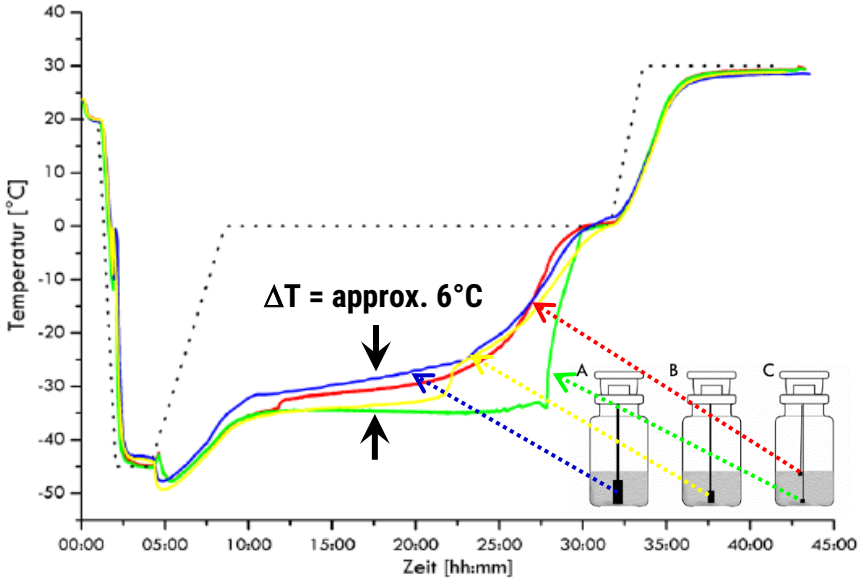
RTD



Tempris®

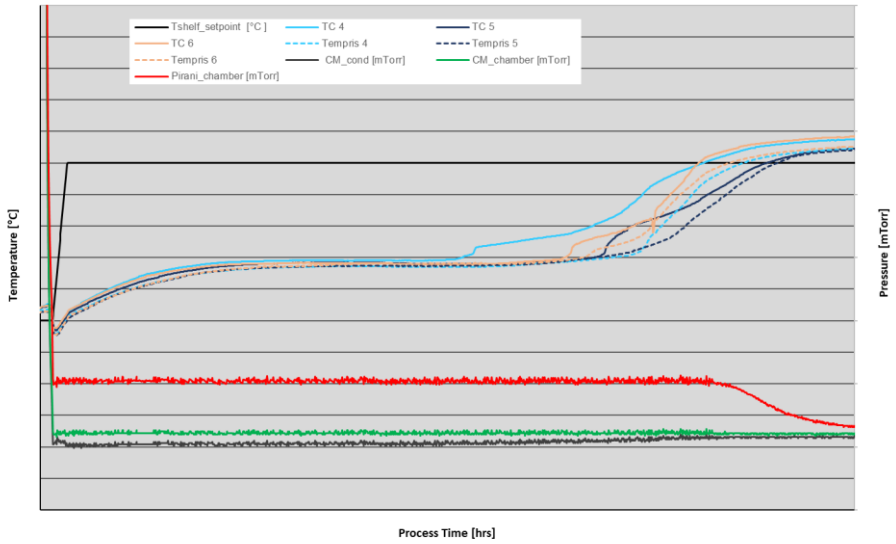
- **Product Temperature Measurement**

  ⇒ **Comparability of probes**



Presser, I. Innovative Online Messverfahren zur Optimierung von Gefriertrocknungsprozessen. PhD Thesis, University of Munich, 2003.

RTD vs. TC



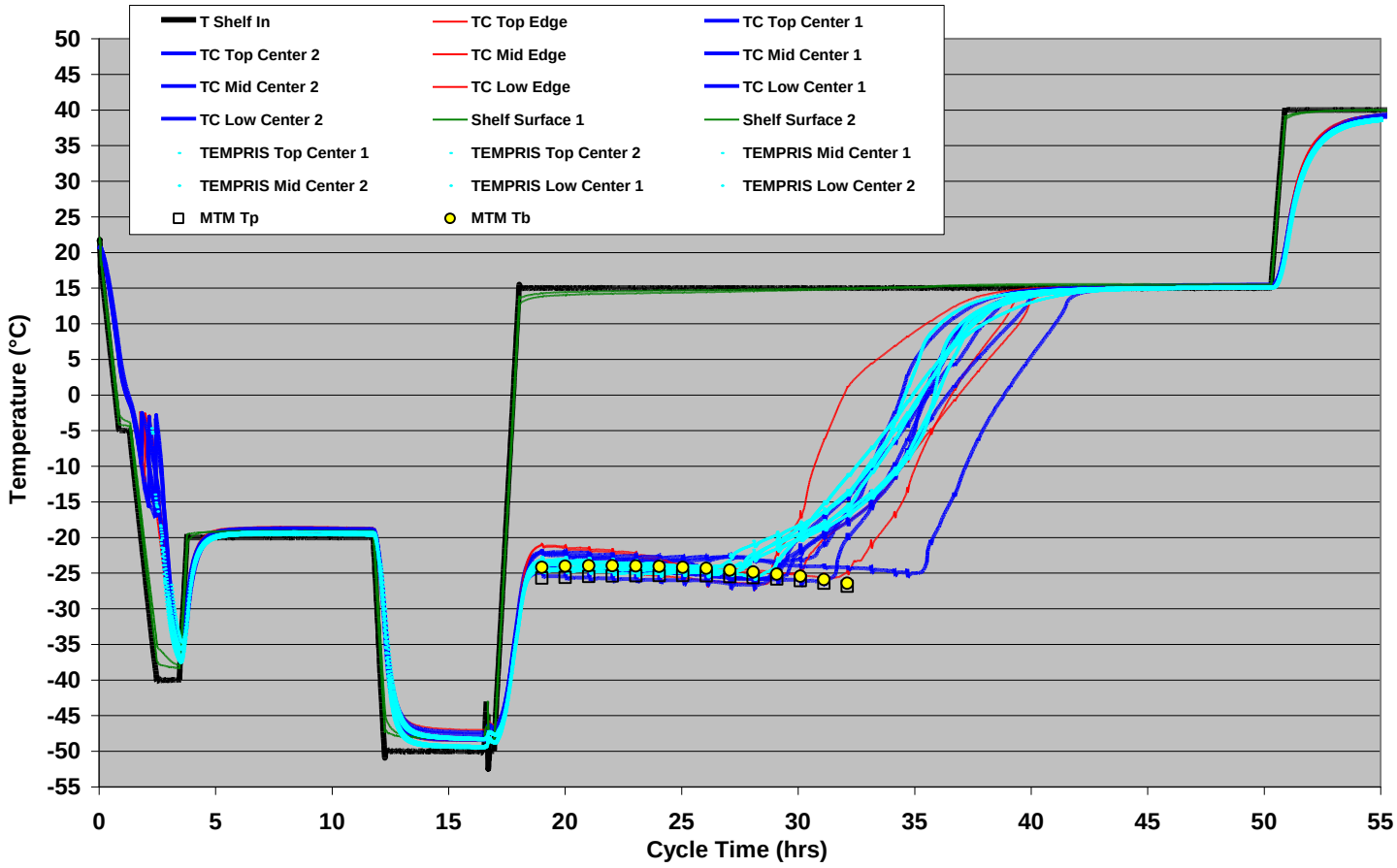
TC vs. Tempris®

PAT and Scale-Up Challenges

Scale-Up, 1

- **Scale-Up Goal**
  - ⇒ **Transfer of the product temperature over time profile between scales and freeze drying equipment.**
  - ⇒ **Reliable primary drying endpoint detection (ideally batch method-based).**
- **Scale-Up Challenges**
  - ⇒ **Environmental conditions.**
  - ⇒ **Equipment:**
    - ***Design and performance of freeze dryers of different manufacturers.***
    - ***Design and performance of freeze dryers of different scales.***
    - ***Availability of PAT.***
      - ❖ **Tempris®: usable in all kind of freeze dryers and in all scales, providing representative and reproducible product temperature data.**

- **Example: Laboratory Scale**



- **Example, continued: Production Scale**