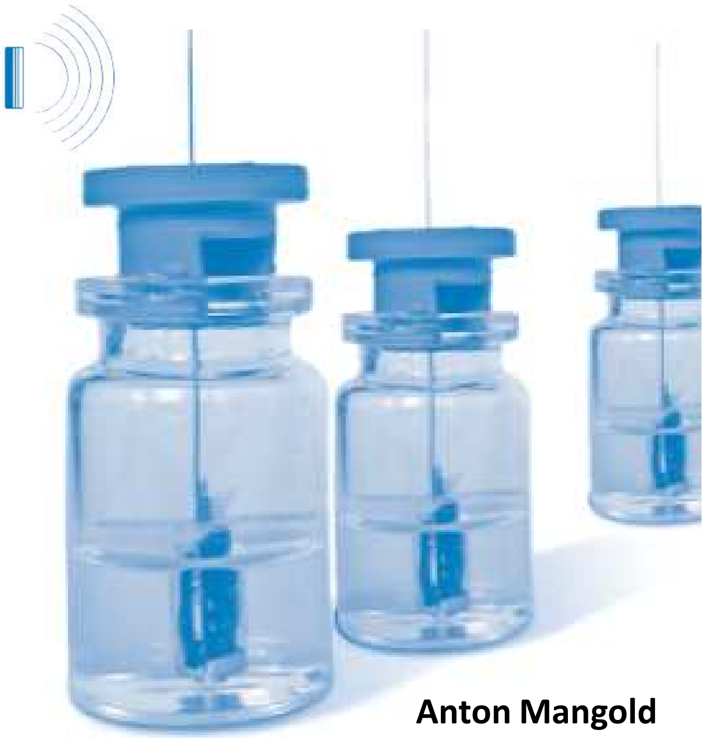
TEMPRIS® PAT TOOL



Precise Measurement of Product Temperature in Lyophilization

Lyo-Cycle Development – Scale-up – Process Optimization and Control

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Content of Presentation

1. Introduction
2. TEMPRIS Operation Principal
3. Customer Evaluations
4. Use of TEMPRIS Data to Transfer a Lyo-cycle from Lab to Production Scale
5. Lyo-cycle Optimization with TEMPRIS®
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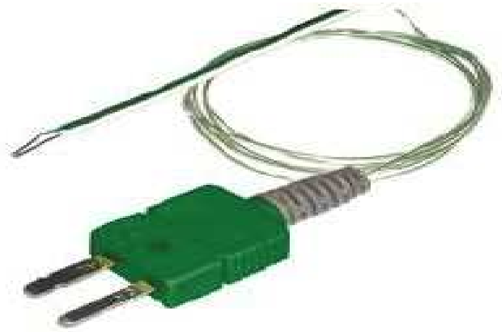
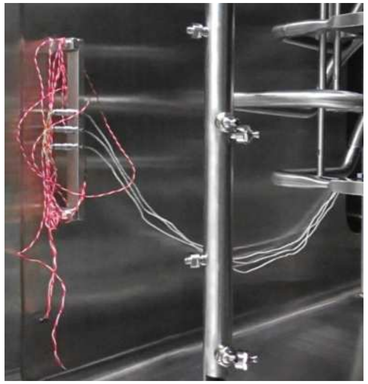
7. Conclusion

Introduction
Product Temperature T_P in Freeze Drying

- T_P **is a critical product parameter** which determines important quality attributes such as physical appearance, residual moisture, storage stability, reconstitution time, etc.
- T_P **cannot be controlled directly,** but is influenced by shelf temperature, chamber pressure, product resistance and various other factors such as supercooling, environment, etc.
- T_P **must not exceed the critical formulation** collapse temperature T_C or eutectic temperature T_E during primary drying to avoid collapse and meltback
- T_P is the **most relevant parameter for design space, robustness testing and qualification** of freeze drying cycles
- T_P is a key parameter for cycle scale-up and transfer

Introduction
Typical Temperature Sensors in Lyo Processes

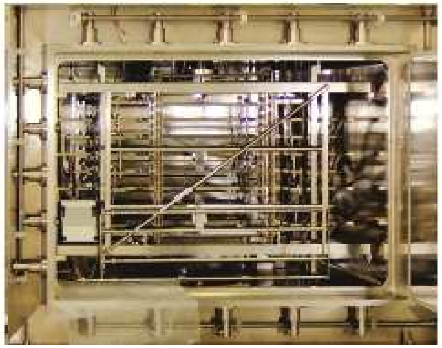




TC
(thin-wire thermocouples)

RDT - PT100
(positive temperature coefficient)





1 **Laboratory FD** → **2** **Pilot FD** → **3** **Production FD**

Introduction
Objectives for T_P Measurement

- Reliable, continuous and accurate T_P monitoring in real time to allow feedback by the user
- Representative product temperature for majority of vials
- Use of the identical technology in laboratory, pilot and manufacturing freeze dryers for representative data comparison
- Passive operation to avoid heat input into the product through the thermal probe
- As little manual handling as possible in production to mitigate sterility risks for the product
- Minimize invasive monitoring effects which may influence freezing behavior

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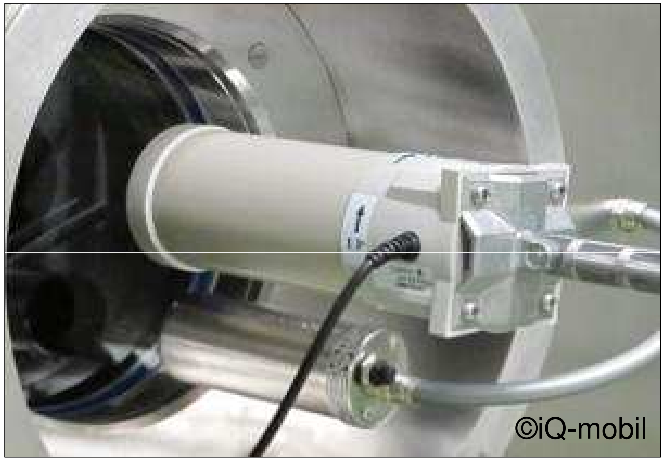
TEMPRIS®
Components

TEMPRIS – the wireless, battery-free and real-time temperature measurement system

Sensor in Vials

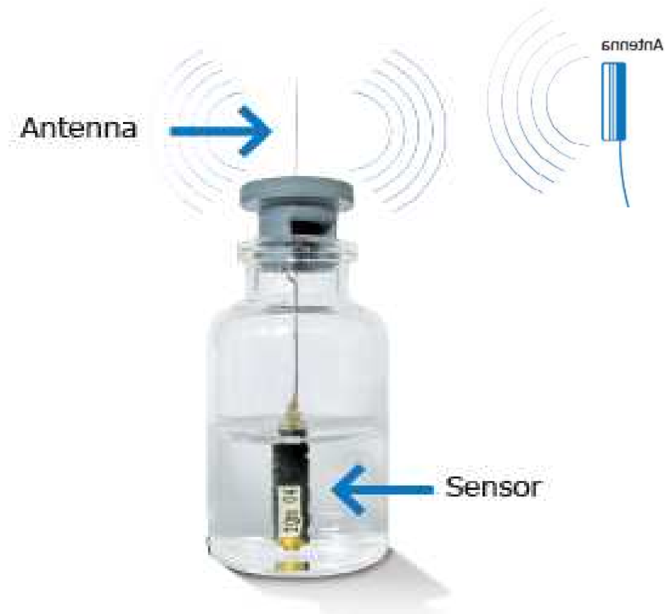


Antenna

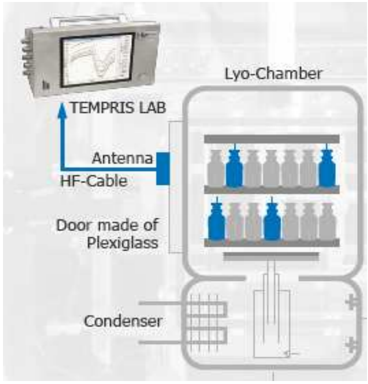
Interrogation Unit (IRU) with Computer

TEMPRIS®
Operation Principle

1. Up to 16 battery-free temperature sensors are excited by an amplitude-modulated microwave signal (2.4 GHz ISM=„Industrial Science Medical“)
2. Quartz-based resonance circuit in the sensor is stimulated, stores energy and continues to oscillate at a characteristic temperature-dependent frequency
3. Carrier signal modulation is activated and deactivated at defined time intervals
4. The oscillation of the sensors is mixed with the carrier signal and re-transmitted to the interrogation unit which registers the frequency shift
5. The TEMPRIS system continuously calculates and records the temperature of each sensor

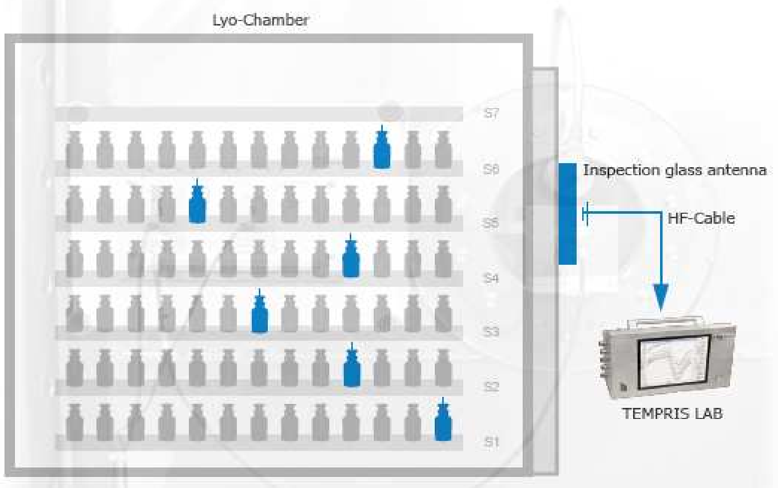


TEMPRIS®
Designed as a Modular System

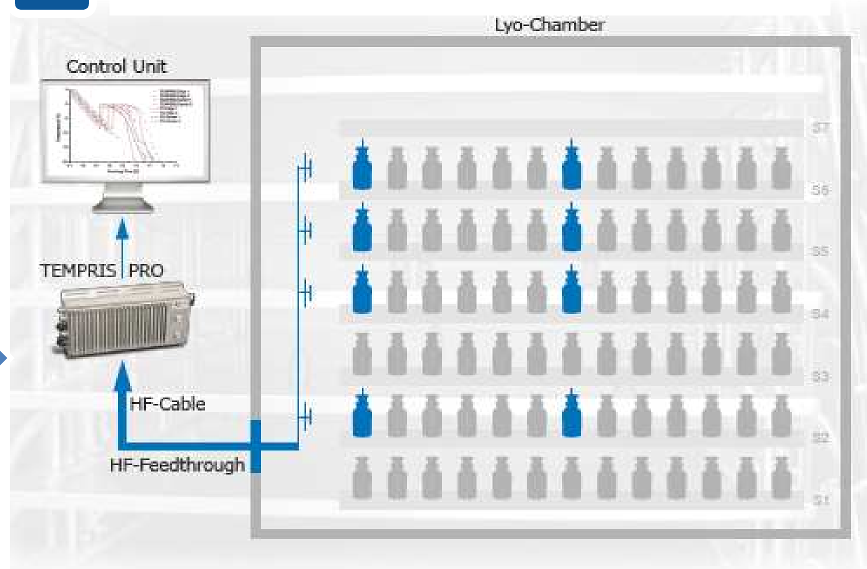


1 Laboratory FD

2 Pilot FD



3 Production FD



TEMPRIS®
System Advantages

1. **Battery-free and wireless sensors**
   - no heat input by the sensors,
   - no time limitation for use,
   - no disturbance of measurements caused by wires,
   - robust over a wide temperature range
2. **Real-time** T_P with an **accuracy of +/- 0.5 K**
3. Up to **16 sensors** for monitoring hot and cold spots also in large freeze dryers
4. Sensors
   - are sterilizable,
   - can be used for laboratory, pilot and production FDs,
   - are GMP compliant (TEMPRIS System according to GAMP-5),
   - shows optimal comparability of temperature profiles
5. **Free sensor positioning** on shelves
6. Designed for **automatic loading systems**

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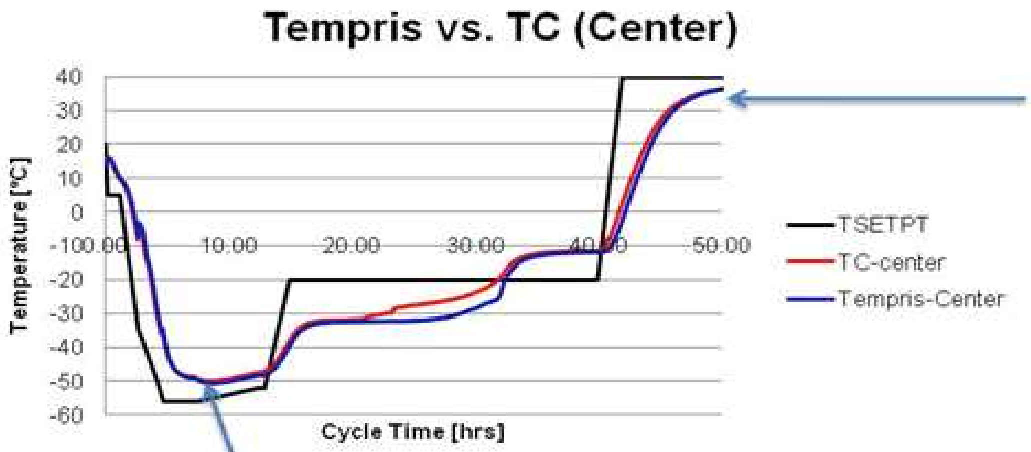
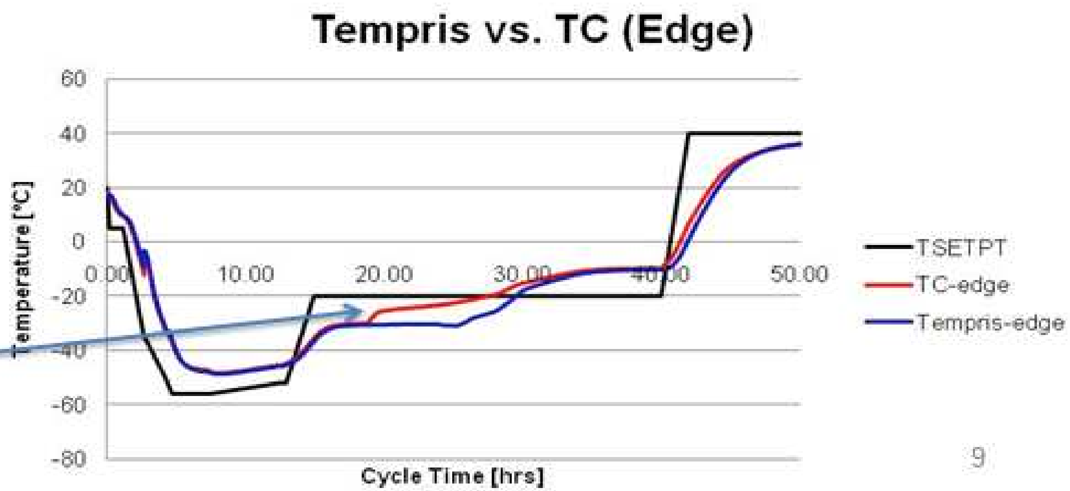
TEMPRIS® vs. TC
Pfizer Confirms TEMPRIS Accuracy



Very good overlay for SD

Excellent overlay for freezing



Excellent overlay for PD until TC loses contact with ice

Slide courtesy of Brian Wilbur's presentation, Process Development of a Dual-Chambered Syringe, presented at CHI PepTalk 2012.

TEMPRIS® vs. TC
Precise Measurement of T_P

Observations/Conclusion (Tempris)

1. **Excellent correlation of Tempris with TC for freezing and early primary drying**
   - Difference ≤ 0.5ºC
   - Possibly due to the radial direction of heat flow in the dual-chamber syringe?
2. **Tempris profiles maintained better contact with ice than TCs during primary drying**
3. **Steel guide tubing did not interfere with signal reliability**
   - Steel tubing may have acted as antenna extension
4. **Testing supports the Tempris compatibility with dual-chambered syringe configuration**

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Slide courtesy of Brian Wilbur's presentation, Process Development of a Dual-Chambered Syringe, presented at CHI PepTalk 2012.

TEMPRIS® vs. TC
Precise Measurement of T_P

Recommendations for Temperature Sensors

1. **Determine which sensor most accurately and reliably measures your product temperature**
2. **Determine as early as possible which sensors are available at the production site**
   - Do they accurately measure product temperature?
   - Can they be used for in-human production?
3. **Consider implementing Tempris for commercial production**
   - Comparable with TCs for product temperature measurement
   - Wireless sensor allows for aseptic placement in most locations including the center of shelves
   - CIP/SIP compatible
   - Customizable sensors

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Slide courtesy of Brian Wilbur's presentation, Process Development of a Dual-Chambered Syringe, presented at CHI PepTalk 2012.

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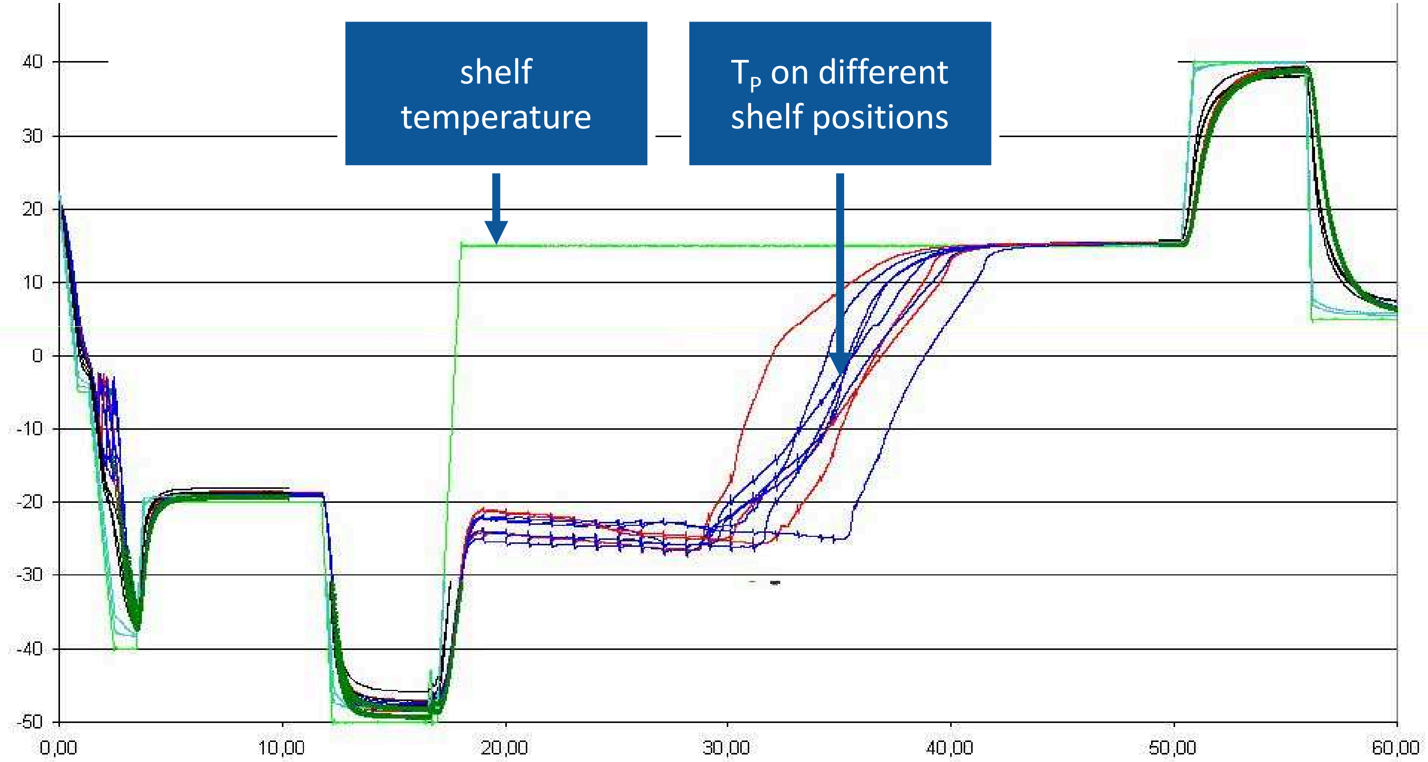
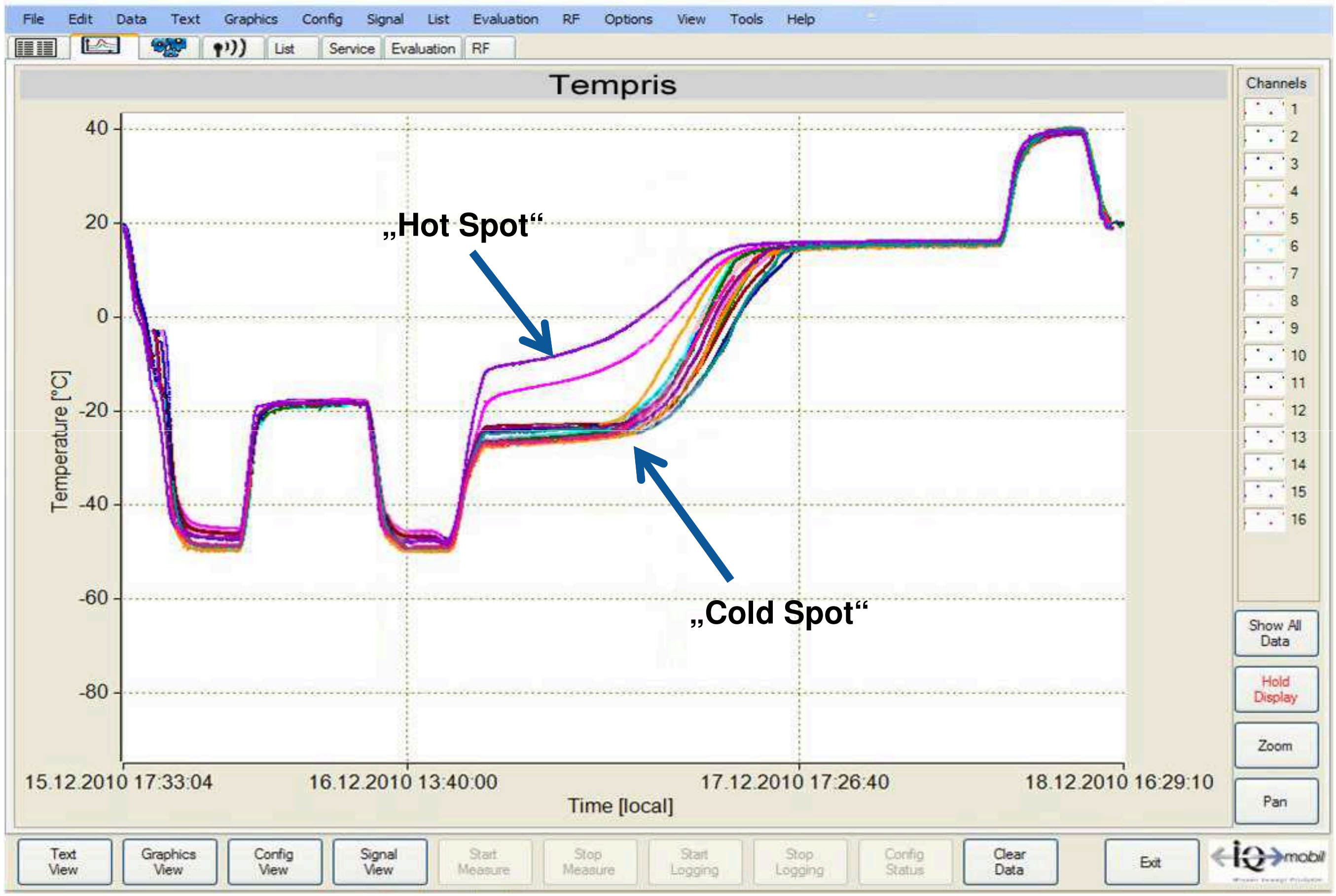
Transfer Example with TEMPRIS® on Lyostar 2

Cycle development on Lyostar 2



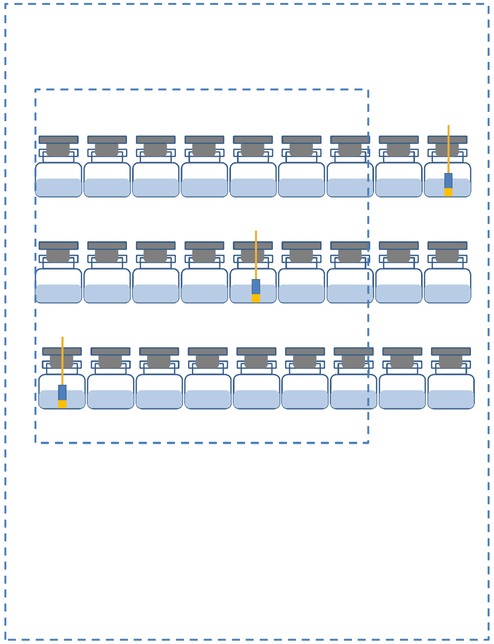
Picture: Property of Freeze-drying Research Group Erlangen; explicat and iQ-mobil

Transfer: „Hot and Cold Spot“ Detection



Lyo-cycle production scale 30 sqm Lyo, 18 shelves,

- T_P variability (see arrows)
- Sensors located at different positions throughout the lyo („Hot and Cold- Spots“)



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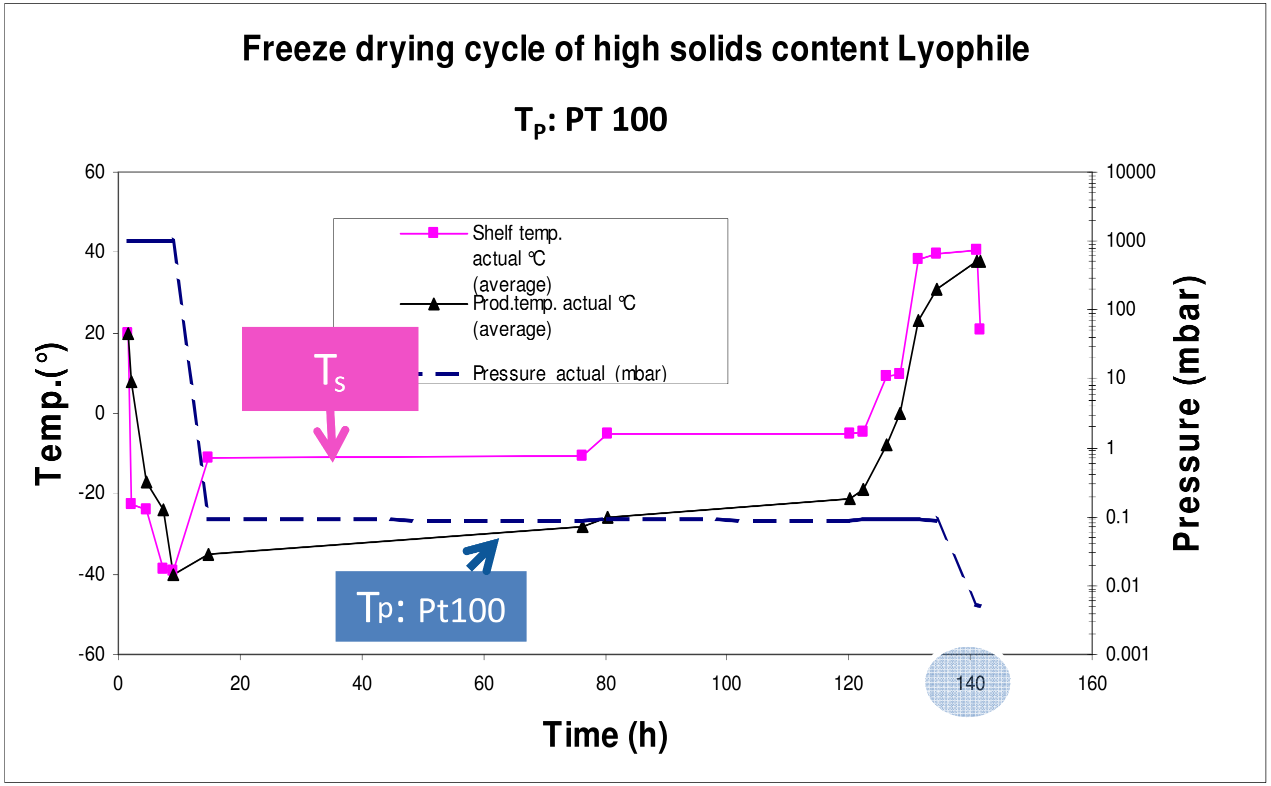
Lyo-cycle Optimization with TEMPRIS® (1/2)



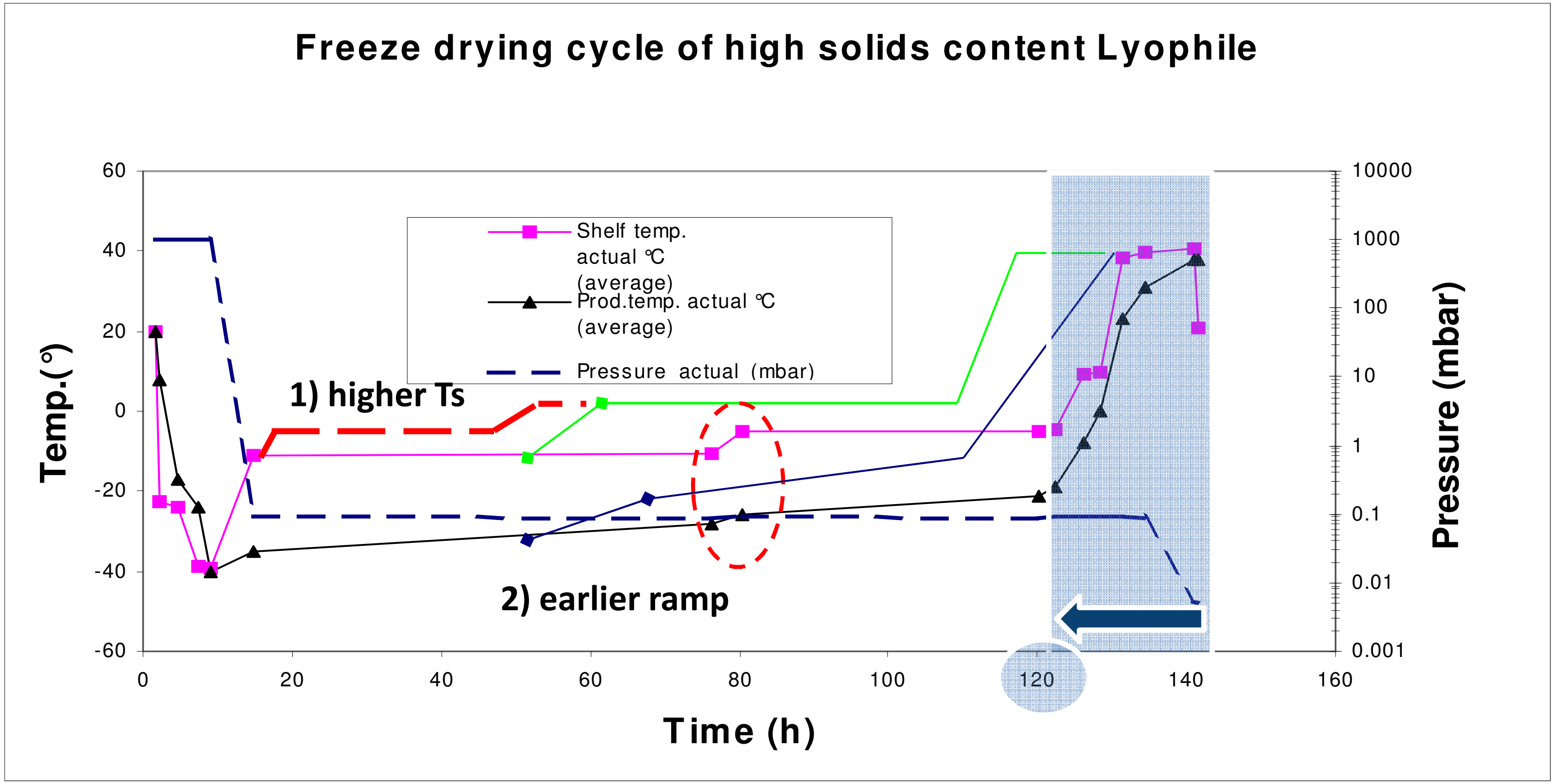
Product: Sulfobutylether-beta-cyclodextrin (16% weight per formulation) - Amorphous formulation

$T_{g'}$: -26°C per DSC measurement - S**avety rule:** stay 10K below Tg‘ (or Tc) due to inhomogenities

Important: T_P must be kept below $T_{g'}$ respectively T_C during primary drying

The Objective: Develop more „aggressive“ cycles

Lyo-cycle Optimization with TEMPRIS® (2/2)



Improvements:

1. Primary drying at higher T_S
2. Ramp earlier in process

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ROI Calculation
Cost Savings as a Consequence of a Optimized Lyo-cycle

I. Return on Investment	Calculation (I)	Calculation (II)
Costs per 24 hrs.	25.000 €	25.000 €
Lyocycle in hrs. (days)	140 (5.8)	120 (5)
Reduction in hours		20
Reduction in %		14,3 %
Batches per year	25	25
Costs per batch	**145.000 €**	**125.000 €**
Costs per year	**3.625.000 €**	**3.125.000 €**
Savings per year (I-II)		**500.000 €**
Saving in 10 years		**5.000.000 €**
Investment: TEMPRIS incl. Customer Qualification		**-200.000 €**
Total Savings (w/o maintenance)		**4.800.000 €**

ROI achieved within 1 year, despite regulatory and additional development costs

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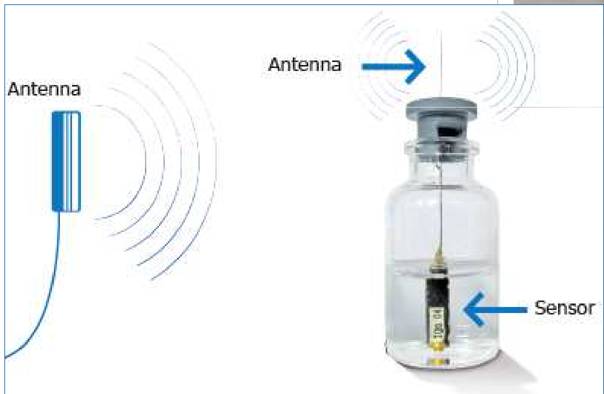
Conclusion

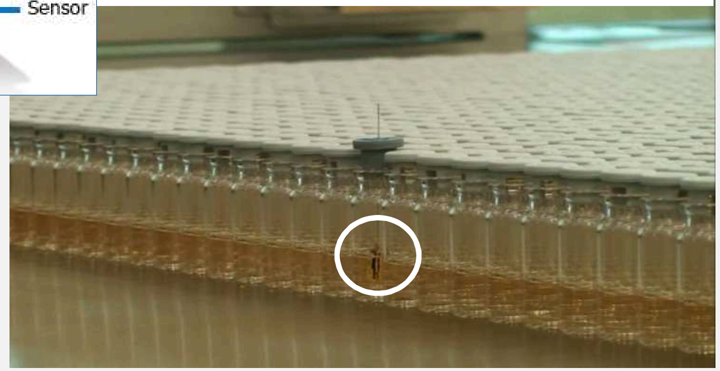
TEMPRIS Features:

- Wireless, battery-free sensors
- Highly accurate
- Sterilizable and cleanable
- Positioning anywhere in the FD
- Designed for ALUS
- PLC / SCADA interfaces
- GMP, GAMP-5 compliant

Isolator: sensor positioning on conveyor belt



TEMPRIS sensors on desired positions



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*Slide (page 12 to 14) courtesy of Brian Wilbur’s presentation, Process Development of a Dual-Chambered Syringe, presented at CHI PepTalk 2012.

Thank You & Questions

For further details and TEMPRIS® demonstrations please visit us at our exhibition booth