Precise measurement of product temperature in freeze drying allows development of a scientifically justified lyo-cycle adaptable to scale and specific freeze dryer equipment features and the control of the lyo-cycle in commercial production

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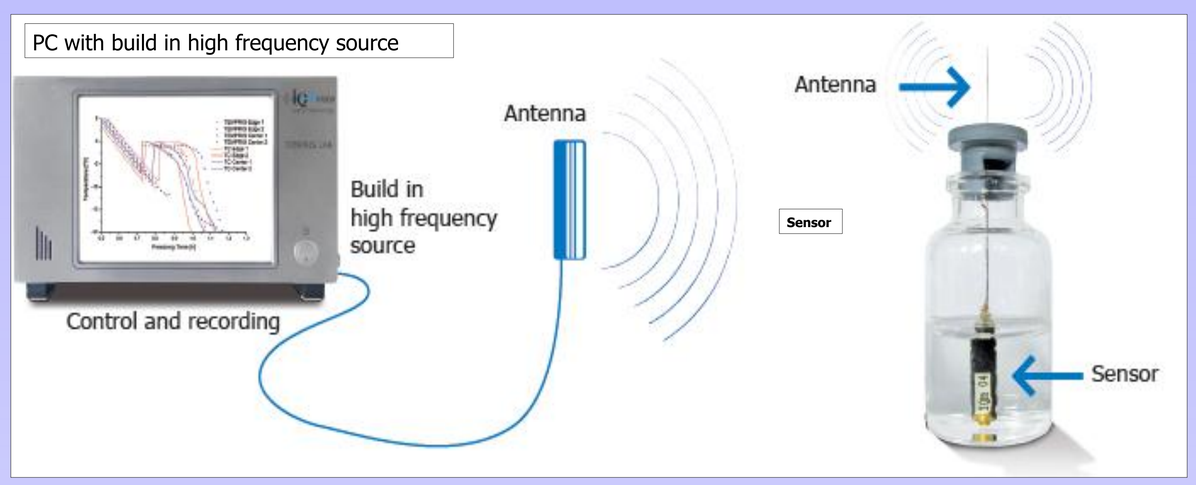
INTRODUCTION:

The precise measurement of product temperature (T_p) is the most important parameter in rational development of lyo-cycles. The use of T_p as parameter in laboratory/pilot scale up to transfer into commercial production of different lyo-formulations will be presented. Also T_p can be applied to control the lyo-cycle of commercial production by integration of the T_p signal provided by TEMPRIS® into the PLC (SCADA - supervisory control and data acquisition) of the lyophilizer.
The application of precise measurement of T_p using a PAT tool in freeze dryers allows to scientifically justify and rationalize lyo-cycle development during all stages of lyo-cycle development from lab to commercial production leading to significantly increased process knowledge and more reliable and robust processes. T_p may be used to control the lyo-cycle by integration of the data provided by TEMPRIS into the PLC and by defining acceptance criteria for the control.

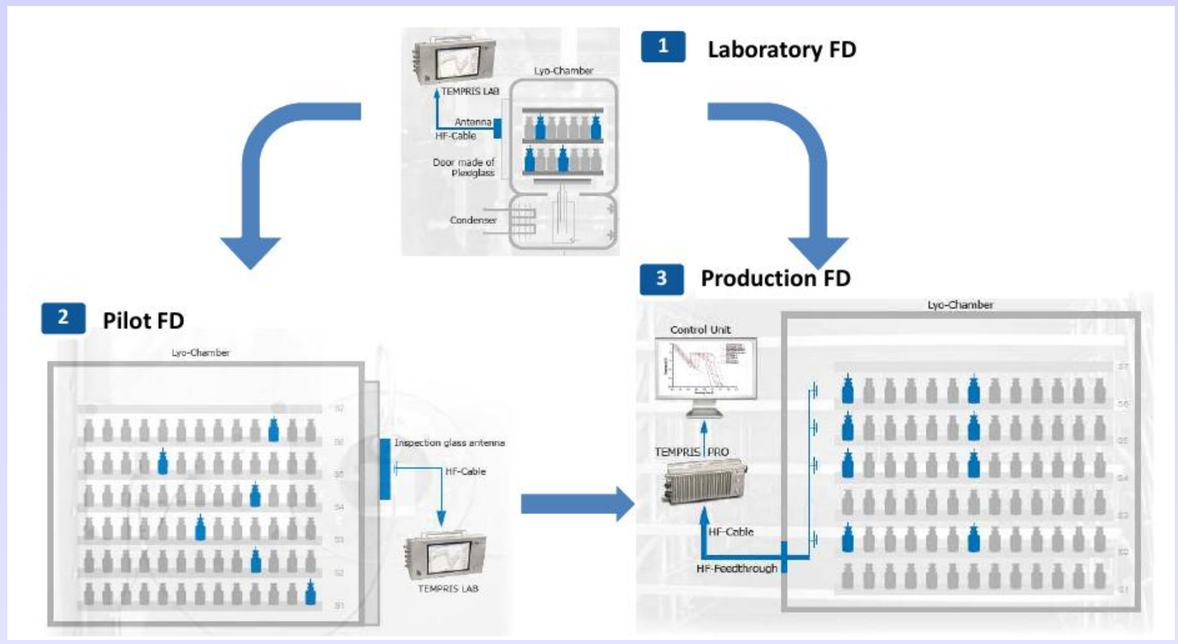
MATERIALS & METHODS:

Functional principle



Quartz based sensor, operating on the principle of temperature dependent resonance: after excitation by a modulated microwave signal (2.4 GHz, worldwide available ISM-band) the sensor keeps on oscillating in a temperature dependent frequency.
Overlaying the sensor response with the carrier signal leads to a frequency shift from which the product temperature T_p can be derived.

TEMPRIS® modular system for cycle development, scale up, transfer



RESULTS & DISCUSSION (I):

Precise measurement of T_p

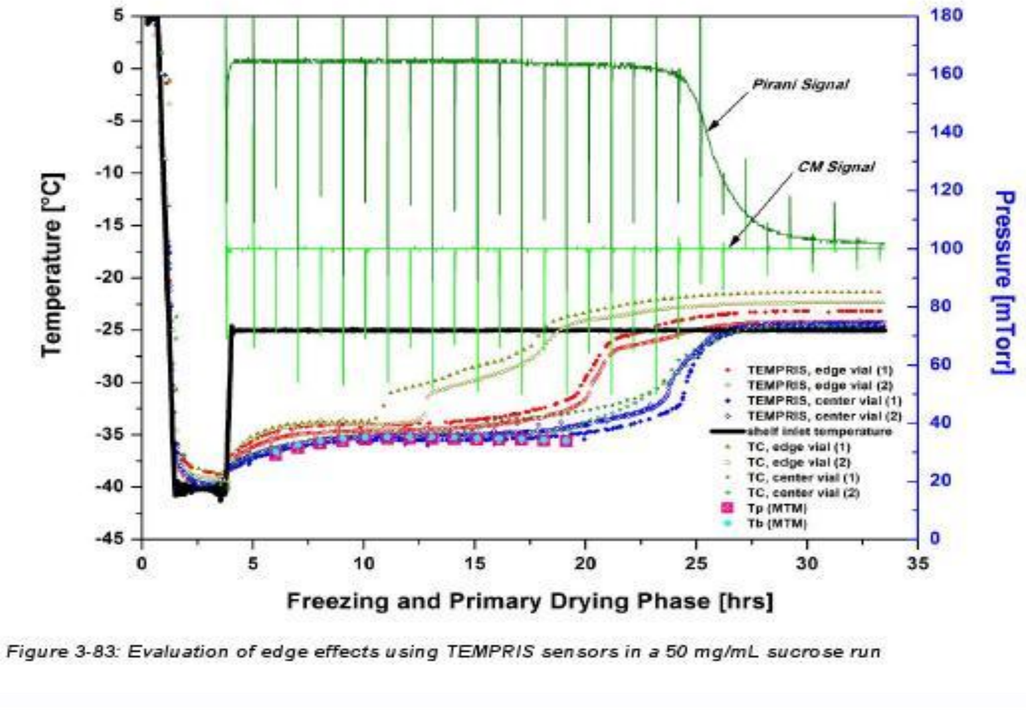
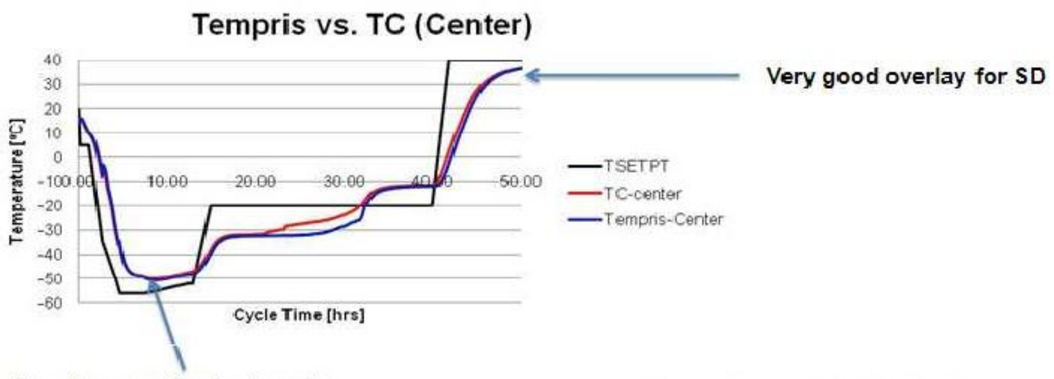


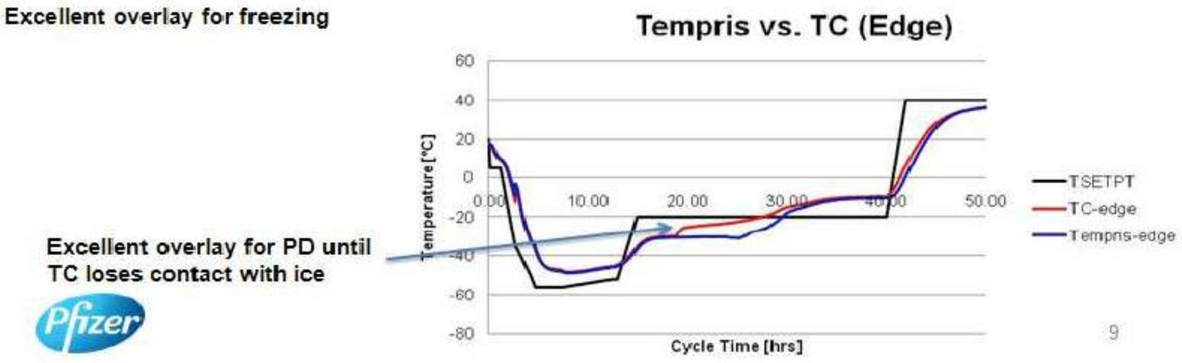
Figure 3-83: Evaluation of edge effects using TEMPRIS sensors in a 50 mg/mL sucrose run

Tempris edge sensors are more accurate than thermocouple T_p is lower. [1)]

RESULTS & DISCUSSION (II):

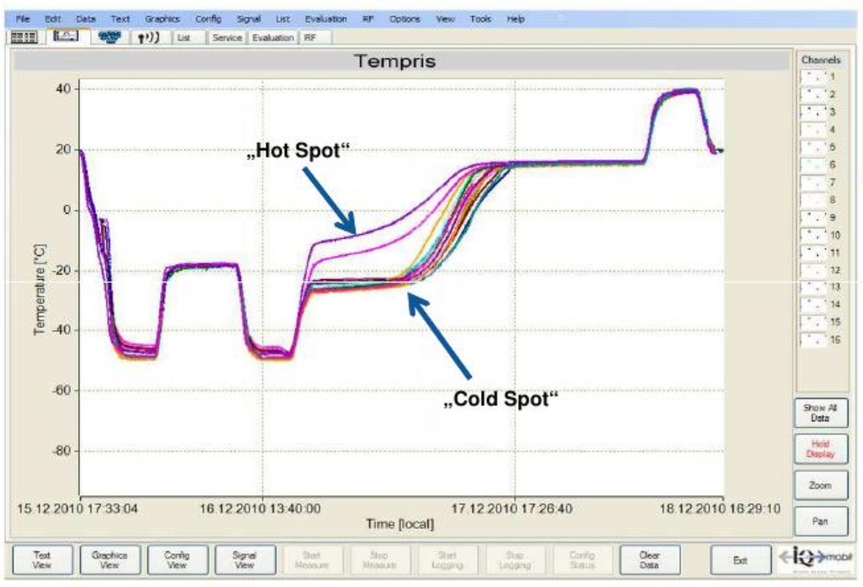
Testing in dual-chambered syringe by Pfizer [2)]



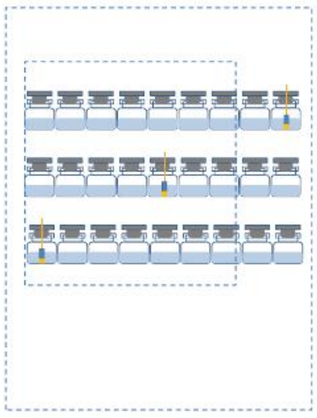


Slide courtesy of Brian Wilbur's presentation, Process Development of a Dual-Chambered Syringe, presented at CHI PepTalk 2012.

Transfer: „hot and cold spot" detection [3)]



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



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

CONCLUSION:

- As TEMPRIS® is a modular – mobile system it may be applied in all stages of lyo-cycle development from lab to commercial production.
- TEMPRIS® allows for the most precise measurement of T_p of all currently available PAT tools usable also in commercial scale aseptical lyophilization.
- Take the possibility and use data about T_p gained by TEMPRIS® as parameter to actually control the freeze drying process by placing TEMPRIS® into vials, located at the worst case positions of the lyo and by using their T_p signal as the criterion to start the next process step in the lyo-cycle.

REFERENCES:

1) cf. Schneid, S. PhD Thesis 2009; p. 163
2) Brian Wilbur, Pfizer; CHI PepTalk ;2012
3) Dr. Andrea Weiland-Waibel, Explicat Pharma GmbH; 2010