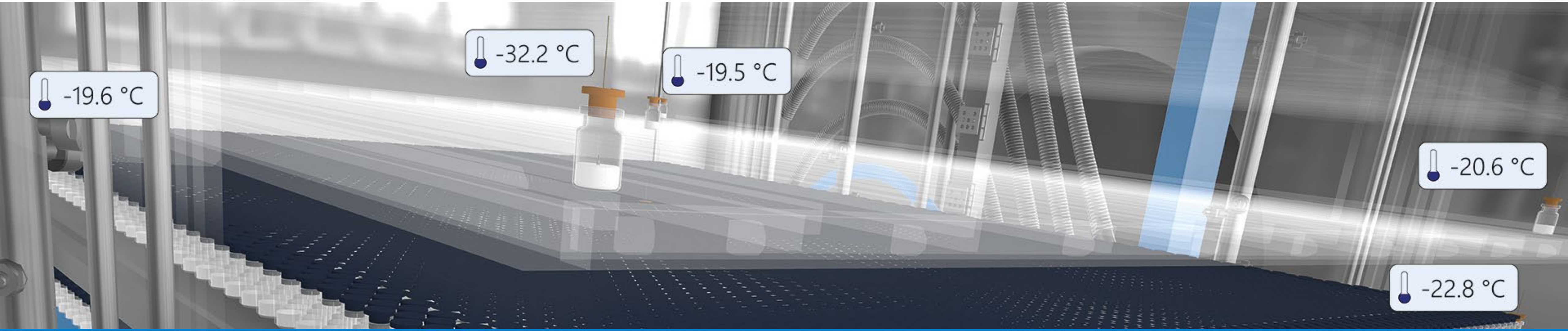
Closed-Loop Control in Lyophilization:

Ensuring batch quality and process optimization by live statistics

Lyo Summit 2024 June 12th
Mangold Anton

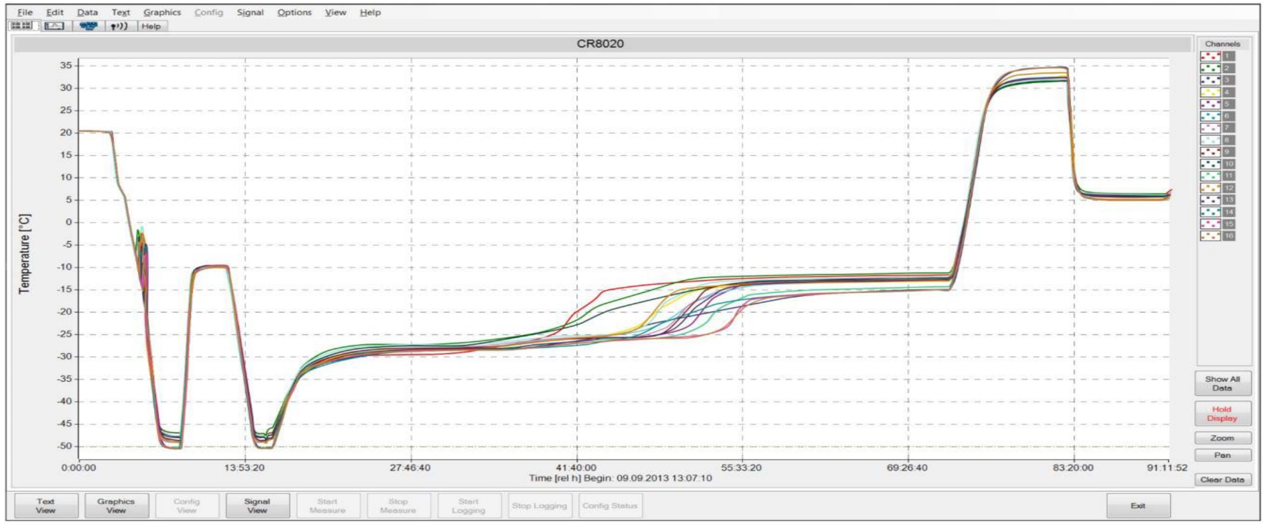


Where do we come from?

IFPAC 2023 + 2024

- Tp the most important parameter in lyophilization
- Tp data allow faster regulatory filing
- Tempris was identified as a low-hanging fruit to move LYO ahead

Tp = product temperature



Voice of Regulatory Approval (IFPAC 2022)

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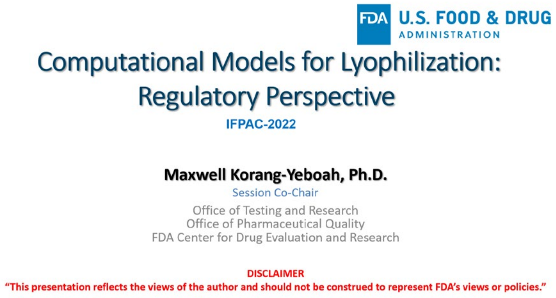
Current State of Lyophilization *

- Despite being an ancient Practice dating back to the 13th Century
- Process Design was (and still is in some Cases) more of an Art than Science - " Quality by Accident"??[1]
- Batch Process, Process Failure can lead to Batch reject
- Average Process Time of 3 -7 Days
- Cost intensive
- Limited or no Product Monitoring at Manufacturing Scale
- Limited Adoption of mathematical Models, Feed Back Control at Scale or advanced Manufacturing Practices


FDA U.S. FOOD & DRUG ADMINISTRATION

Computational Models for Lyophilization: Regulatory Perspective

IFPAC-2022

Maxwell Korang-Yeboah, Ph.D.
Session Co-Chair
Office of Testing and Research
Office of Pharmaceutical Quality
FDA Center for Drug Evaluation and Research

DISCLAIMER
"This presentation reflects the views of the author and should not be construed to represent FDA's views or policies."

Conclusion *

- There is an urgent need for the Adoption of advanced Manufacturing Practices such as Real Time Product Monitoring and Computational Models for Lyophilization of Pharmaceuticals
- Verification and Validation Activities for Lyophilization Computational Models should be appropriate for the Context of Use and Model Risk
- Not "one Size fit all"
- Current regulatory Standards/Guidelines offer a useful Framework for Lyophilization Model Verification and Validation
- ICH points to consider, ASME V$V 40 and FDA/CDRH Guidance for Assessing the credibility of Computational Modeling and Simulation

*** FDA U.S. FOOD & DRUG ADMINISTRATION / Maxwell Korang-Yeboah, Ph.D**

The Situation in a Nutshell

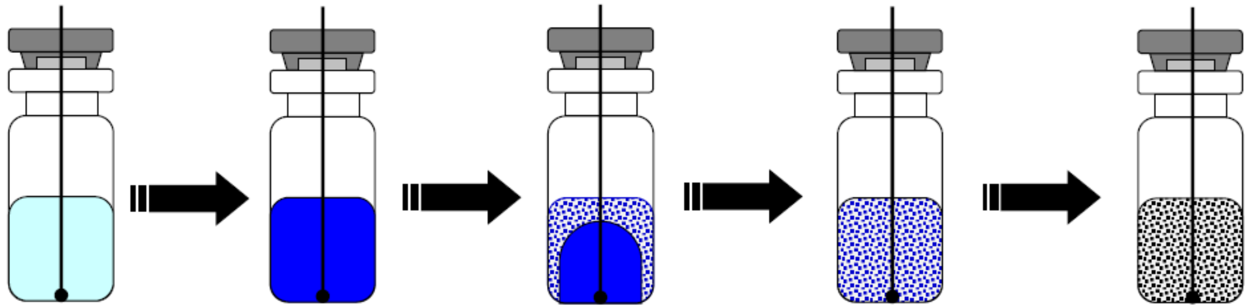
Freeze Drying or Lyophilization

- is a protocol-driven standard process (freezing, primary and secondary drying)

- is carried out sequentially at fixed time stamps

- are kept constant within each phase to maintain Critical Process Parameters

-The most critical process parameter is the **Tp**, which **cannot be controlled directly** but is influenced by the Ts, Pc, Rp, and various other factors



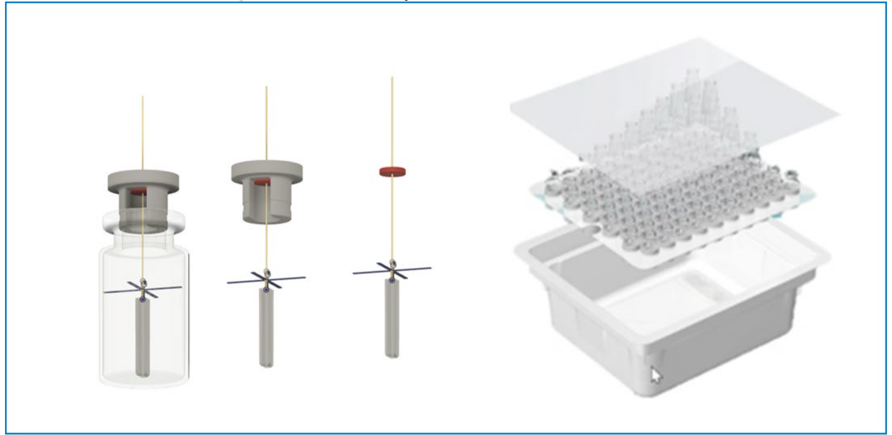
* CPPs = critical process parameters; Tp = product temperature; Ts = shelf temperature; Pc = chamber pressure; Rp = product resistance

Impulses for Comprehensive Process Control

Wireless, battery-free, real-time

Ready-to-use-Sensors

calibrated, sterilized



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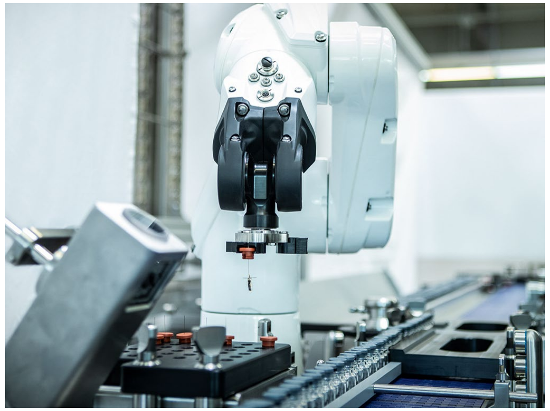
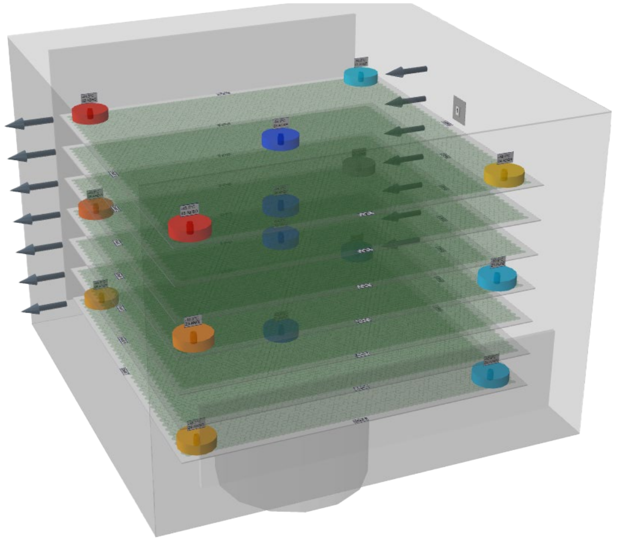
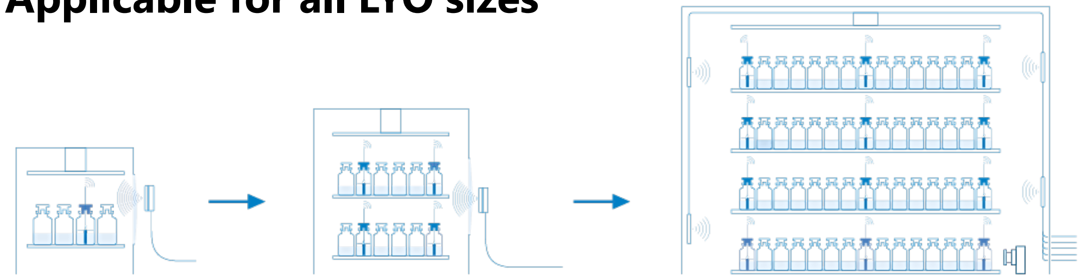


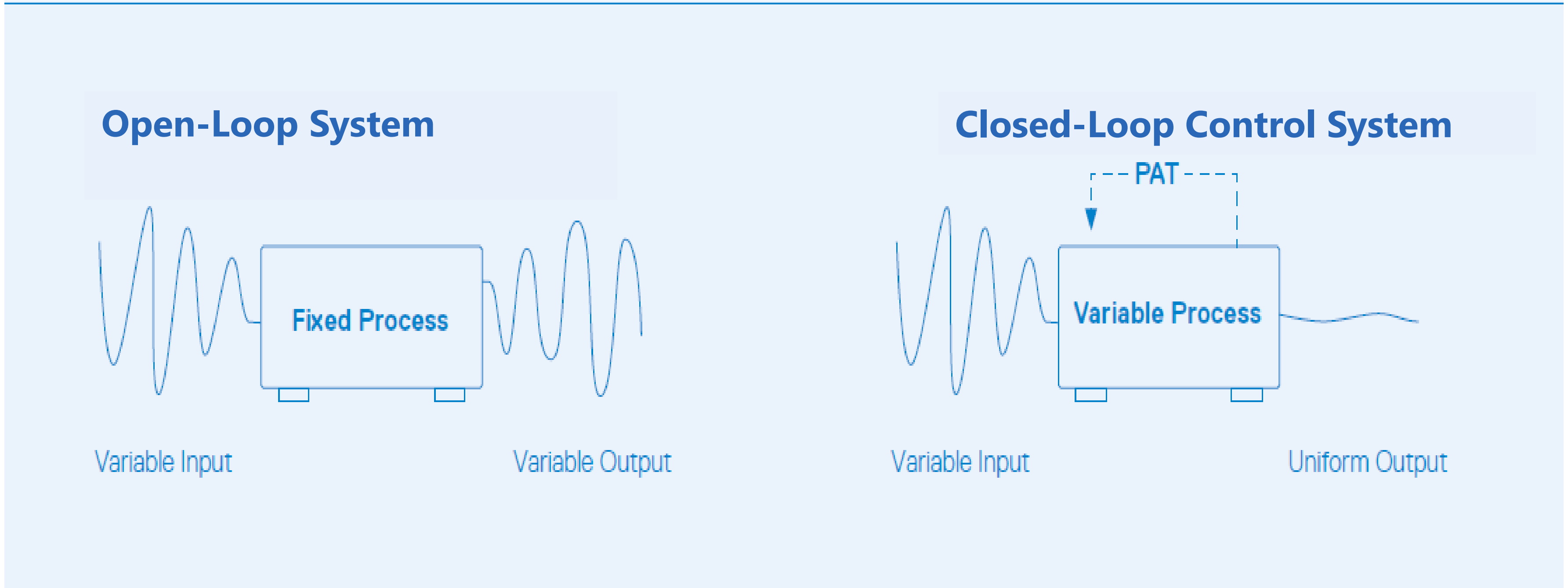
Digitalization:
Digital-3d-Twin visualizes potential areas of optimization



Applicable for all LYO sizes



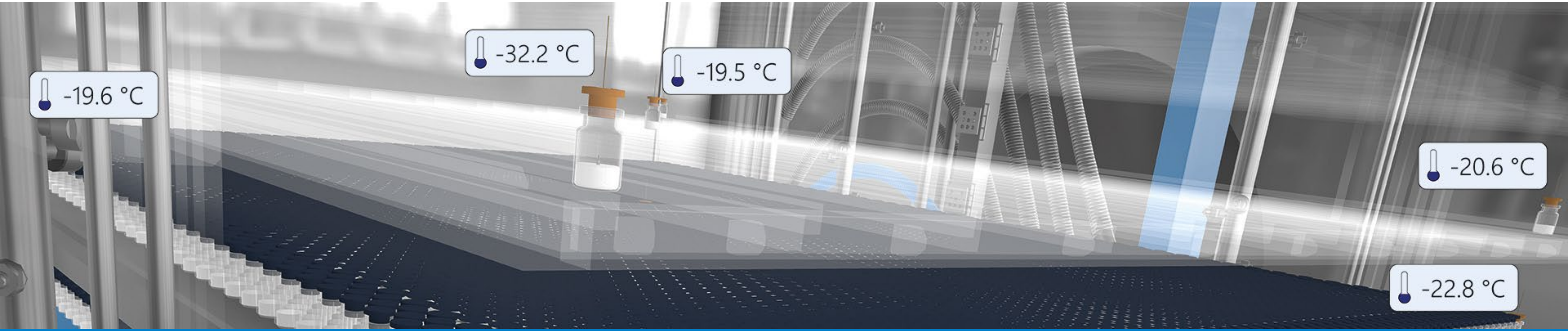
Impact of Active Control



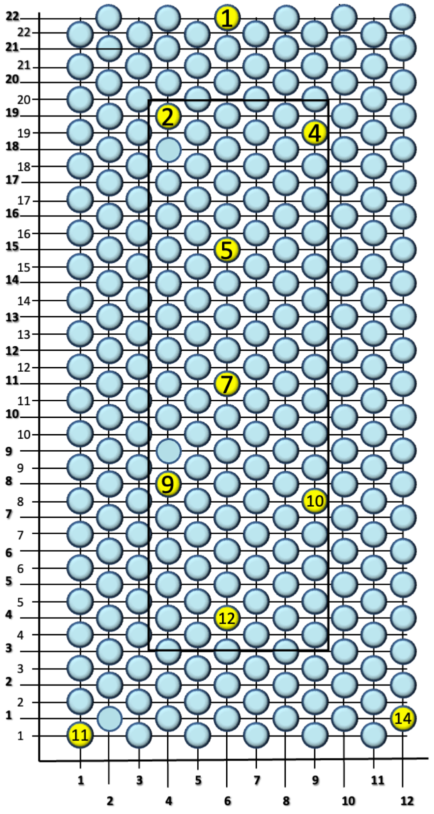
Source: FDA

Introducing Closed-Loop Control on a Laboratory Scale in Lyophilization:

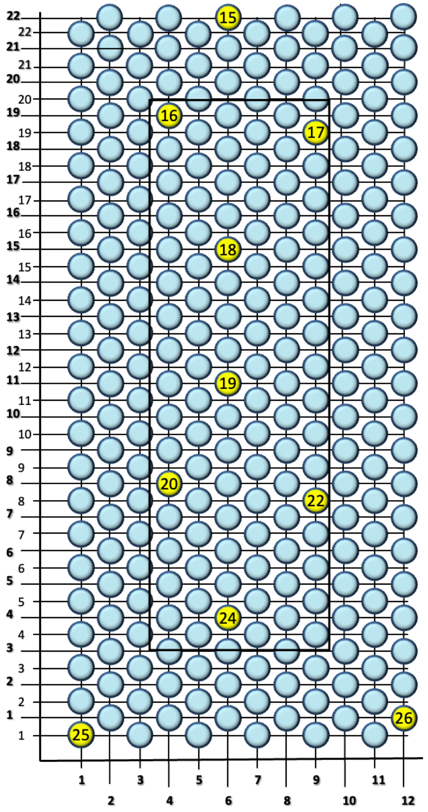
Ensuring batch quality and process optimization by live statistics



6R, 2.5 ml



Top/Door



Mid/Door

Two plates were each filled with 10 sensors in a 6R vial. The formulation consists of a 5% trehalose solution, filling volume is 2.5 ml. The vials are loaded using a frame (approx. 30 mm high), the base is removed so that all vials have direct contact with the positioning plate.

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Freeze drying (continued):
Recipe:

- A total of two cycles were performed with the following standard parameters for trehalose:

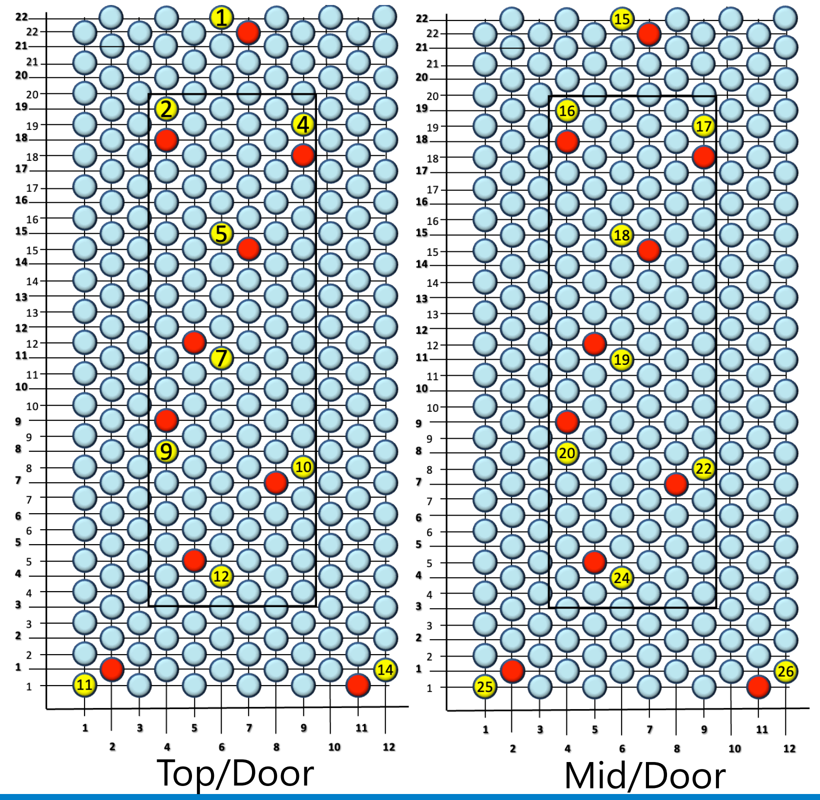
Phase	Step	T_s [°C]	RR [°C/min]	t_{hold} [min]	P_c (CM) [mTorr]
Freeze	1	5	1	30	-
	2	-5	1	30	-
	3	-40	1	120	-
Primary Drying	1	-20	1	tbd[1]	60

[1]) Following ending criteria were applied:

1) Ending the cycle when the Pirani pressure falls to 1.3 times the Capacitance pressure (50% of the Capacitance - Pirani difference)
2) Ending the cycle after the end of primary drying; indicated by the absence of a rise in temperature of the product

Karl Fischer Titration (continued):
Sampling:

- Sensor vials (yellow) and direct neighboring vials (red) were chosen according to the following scheme:



2. Methods: Estimation of shelf temperature

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New algorithm for calculating the individual shelf temperature

$$Heat\ transfer\ (Q, A, K_v, C_p)\ simplified:\ T - T_\mathrm{b} = k_1 \frac{dm}{dt}$$

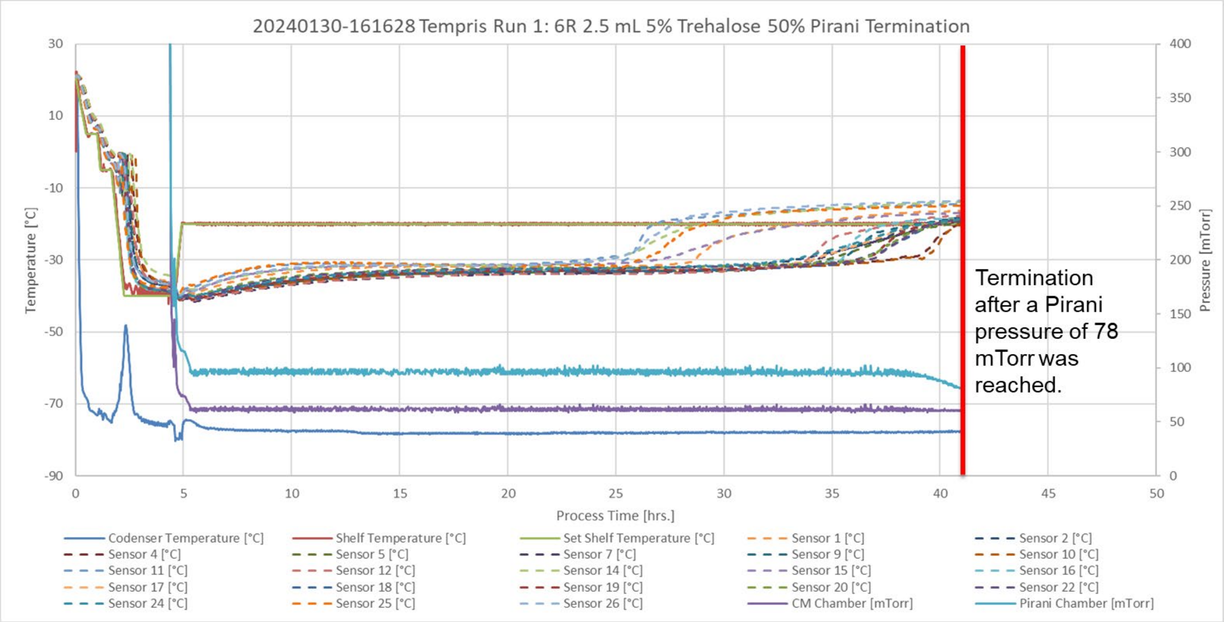
1. Find border to exponential section after temperature rise
2. Linearize using T_lin = ln (- T + T_base)
3. Try to fit linear output using linear regression
4. Calculate quality of fit using linear regression r value
5. Try iteratively different T_base, use best fit T_base value

$$End\ of\ sublimation\ negative\ exponential\ section:\ \frac{dm}{dt} = -k_2\, m$$

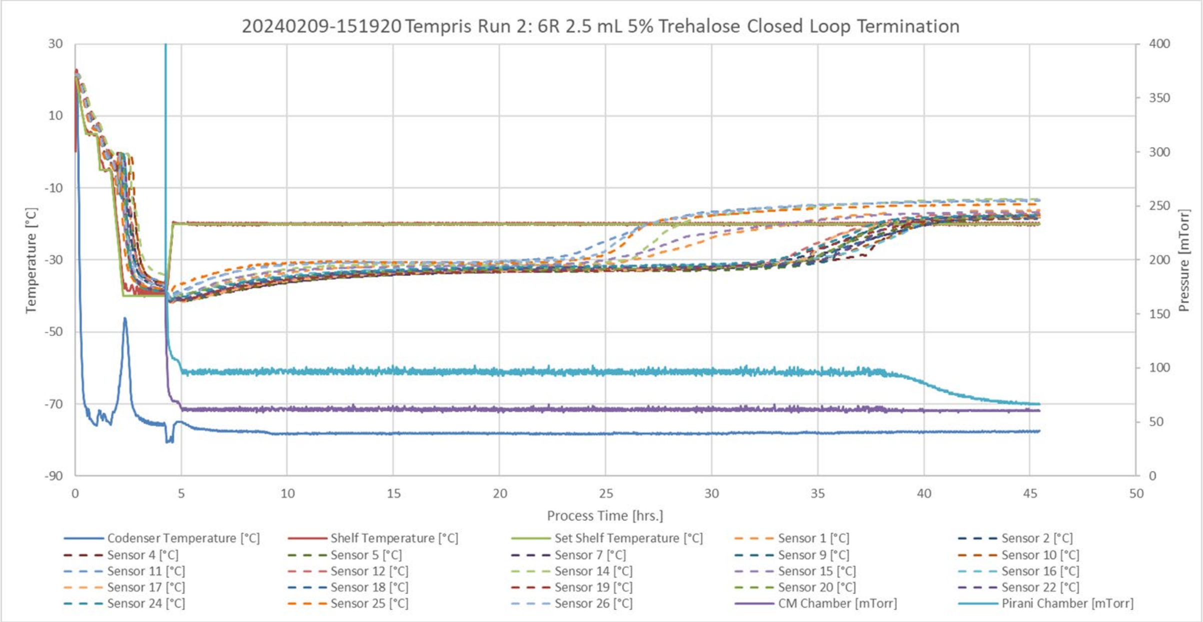
This new algorithm is completely independent of the formulation, the size and fill level of the vial etc.

3. Results: Ground Truth

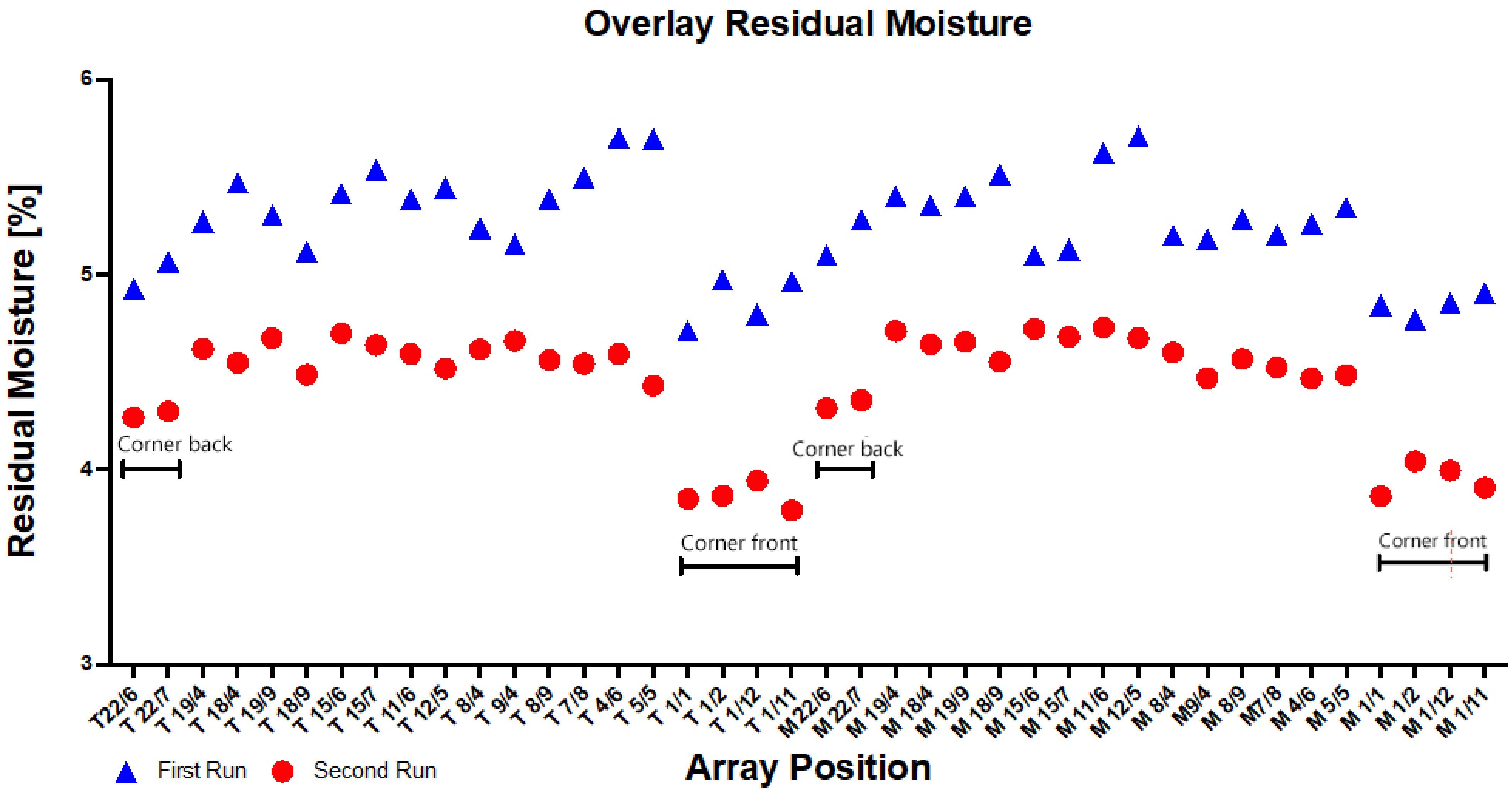
Process plot 1st run:



Process plot 2nd run:

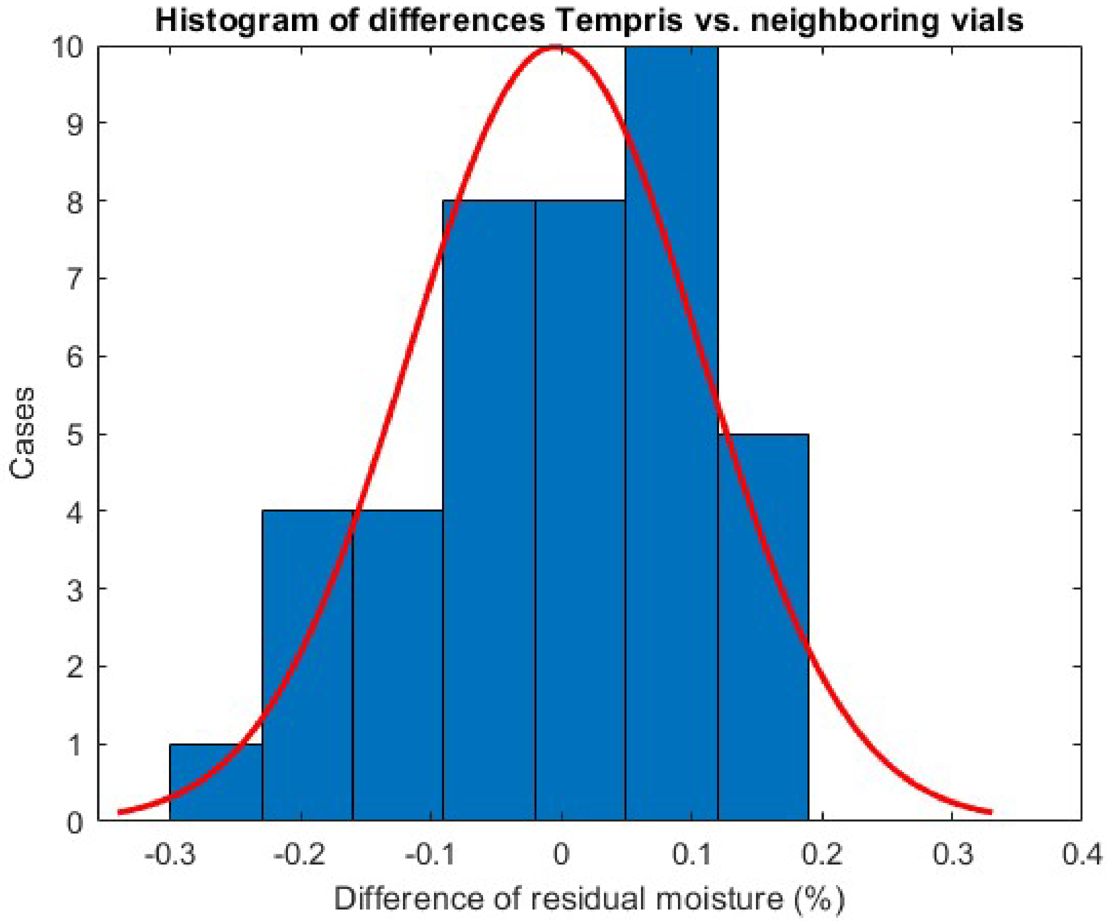


Karl Fischer Titration: Residual moisture comparison



3. Results: Ground Truth

Hypothesis: There may be a difference (%) of moisture (bias) between Tempris and neighbor vials



Applicable test:
- parametric preferred, as most precise
- but requires normal distribution
- Test of differences only is acceptable

(see Hederich Sachs (2020), Angewandte Statistik, p. 564)

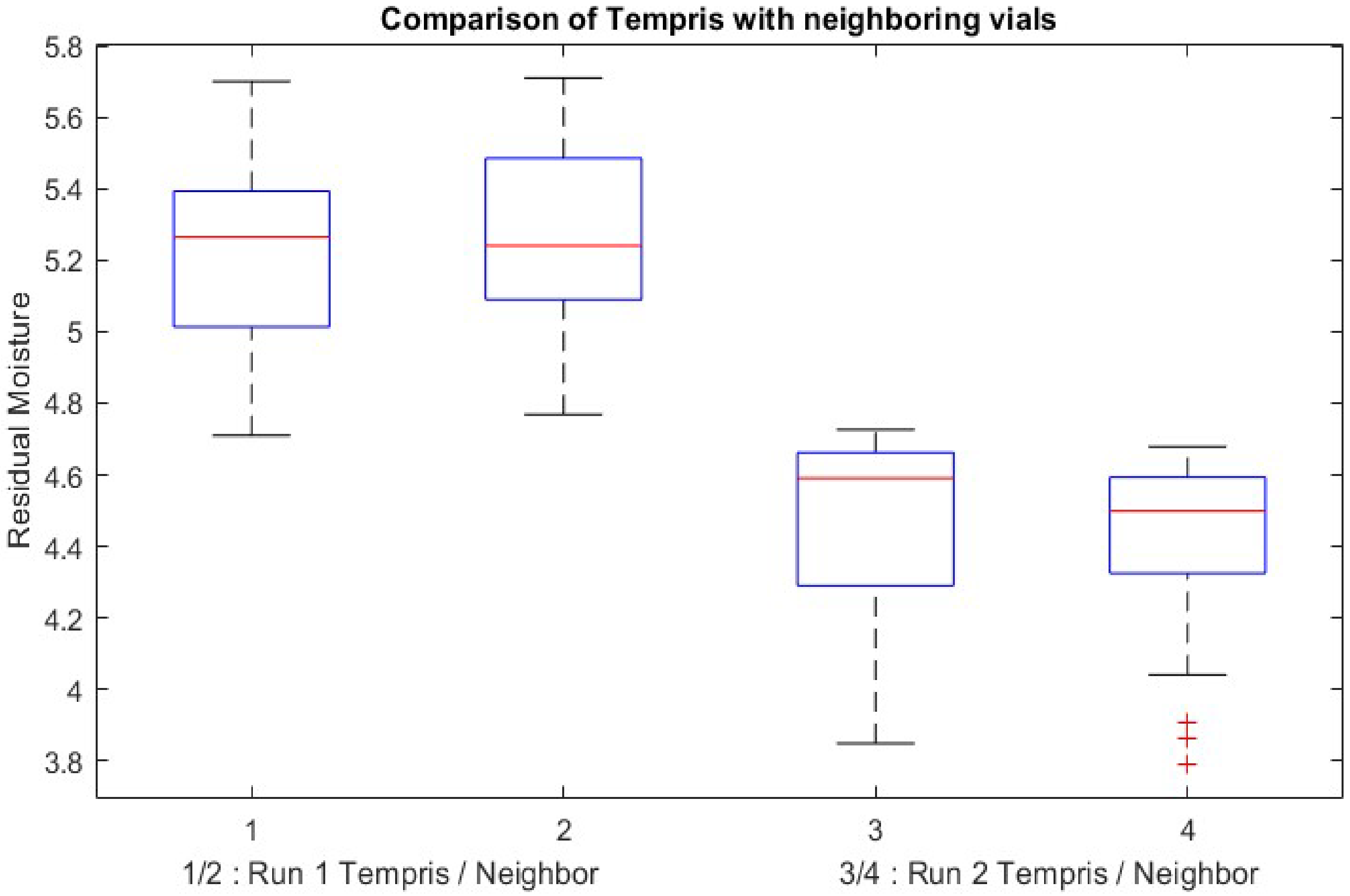
Kolmogorov-Smirnov test signals alternate hypothesis ($p<.01$), not a normal distribution.

But with larger n we can assume that the t test is robust against violations of the normal distribution
(see Eid Gollwitzer Schmitt (2017), Statistik und Forschungsmethoden, p. 371).

Thus we may and should combine the difference pairs from both runs!

3. Results: Ground Truth

Moisture difference between Tempris equipped and neighbor vials, Barlett's (Levene) test for equivalent variance



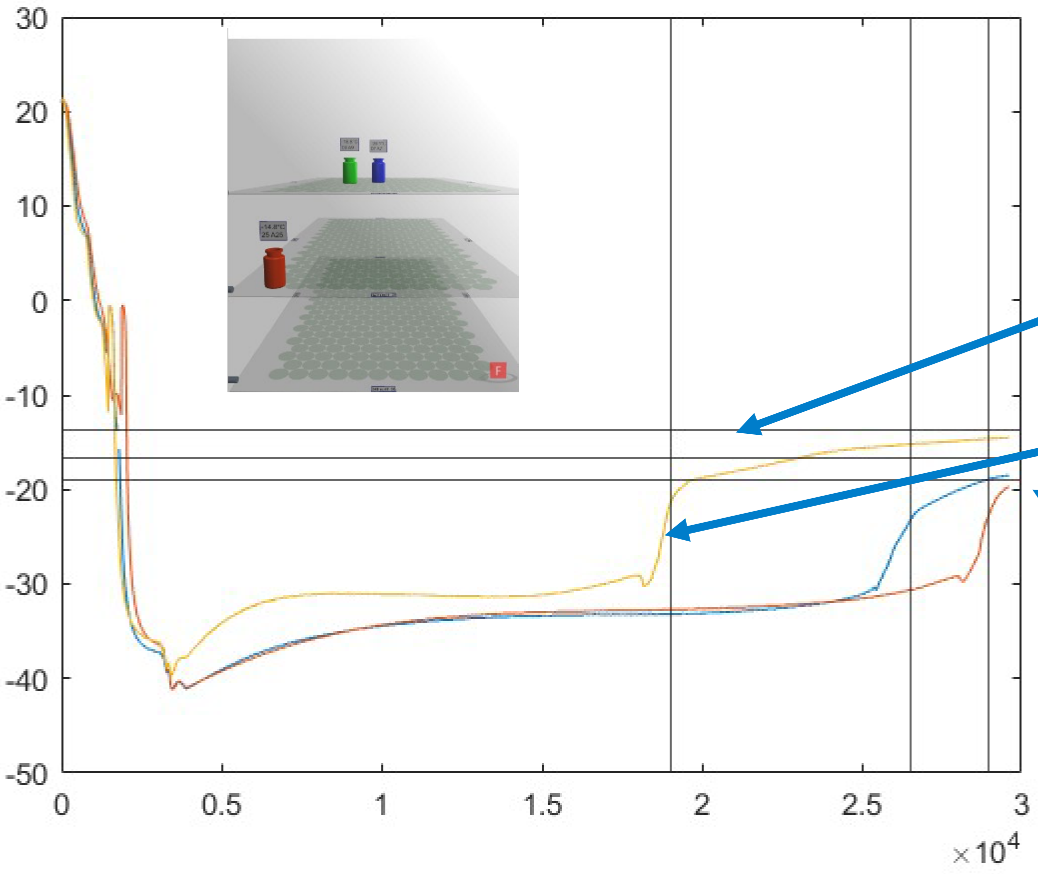
Group	Count	Mean	Std Dev
1	20	5.2093	0.27125
2	20	5.2647	0.26362
3	20	4.4502	0.30192
4	20	4.40385	0.27964
Pooled	80	4.83201	0.27948

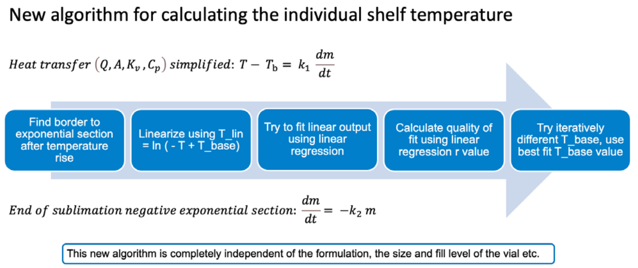
Bartlett's statistic	0.38828
Degrees of freedom	3
p-value	0.94265

As all groups have similar variances, we can combine them in a single t test.

3. Results: Estimation of shelf temperature

Typical temperature diagram of three different vials
Visualised in our freeze-dryer





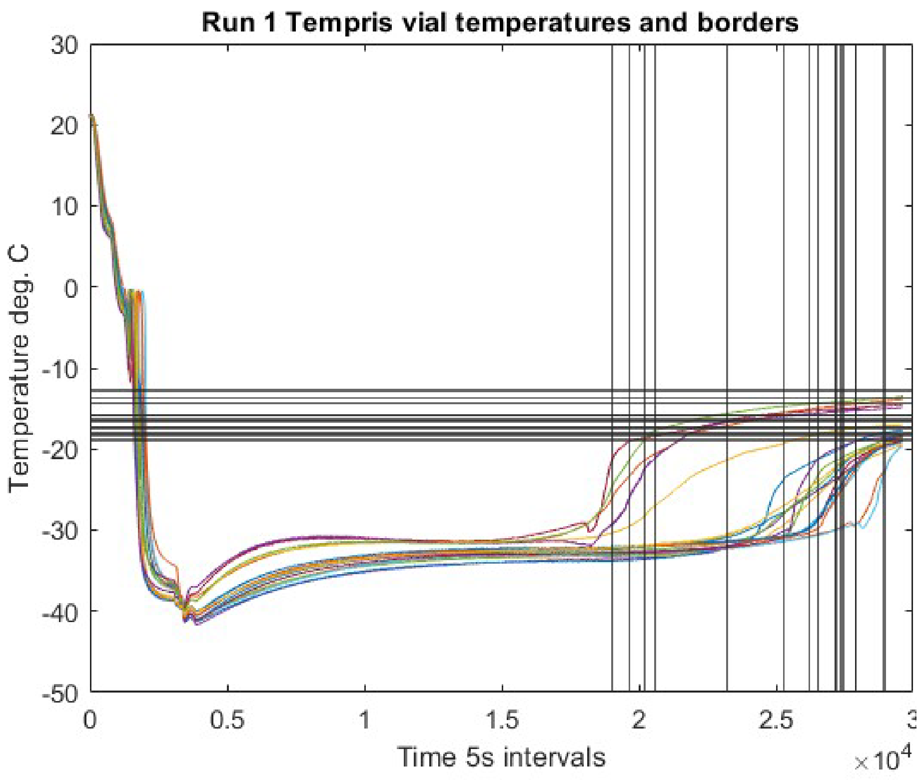
Base line = shelf temperature

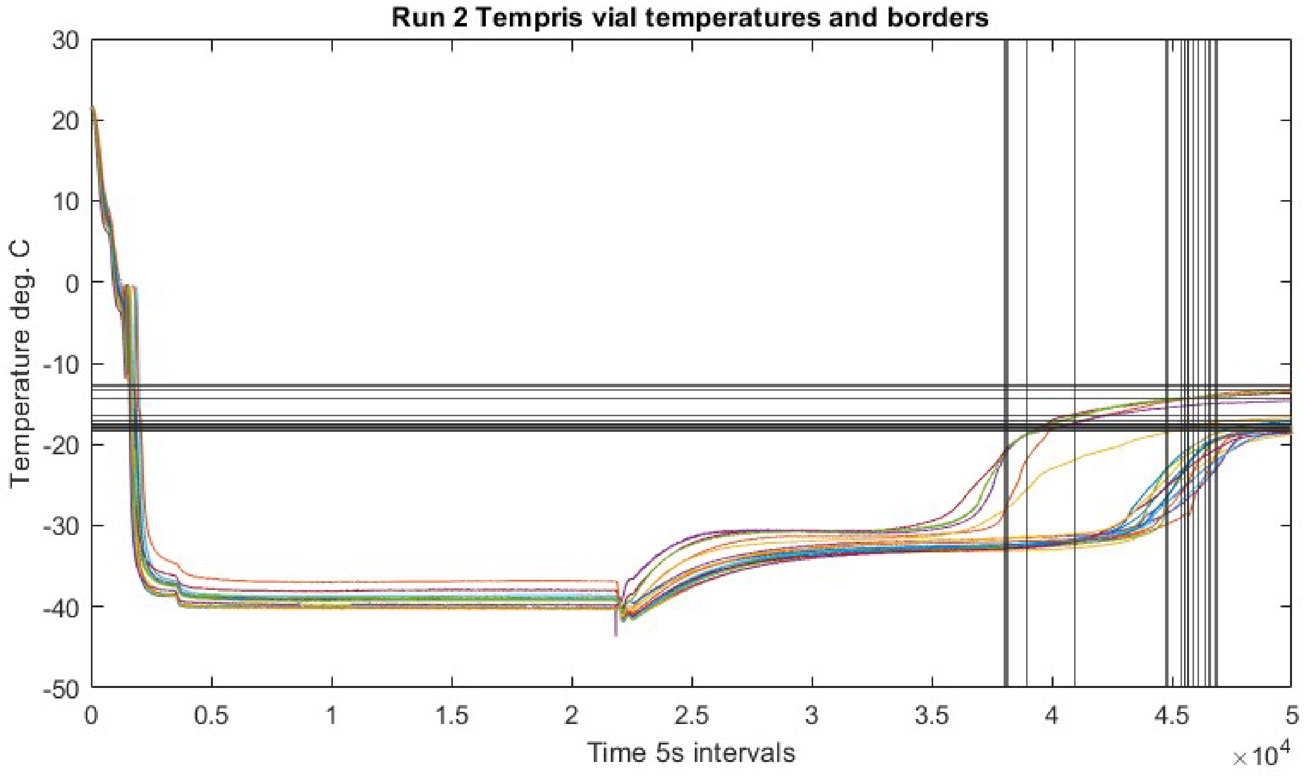
Negative exponential trend (starts here)

Difference between actual vial and estimated shelf temperature proportional to heat flow

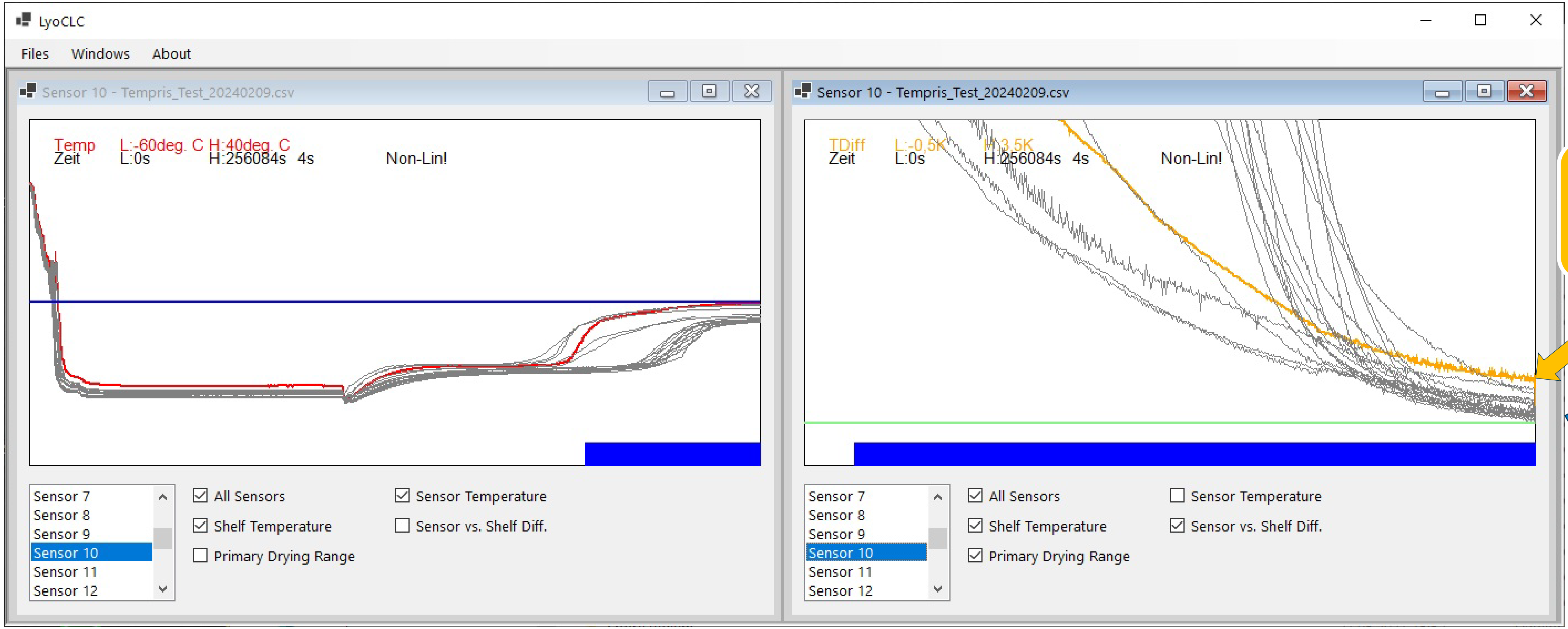
3. Results: Estimation of shelf temperature

Temperature diagrams from both runs with base lines





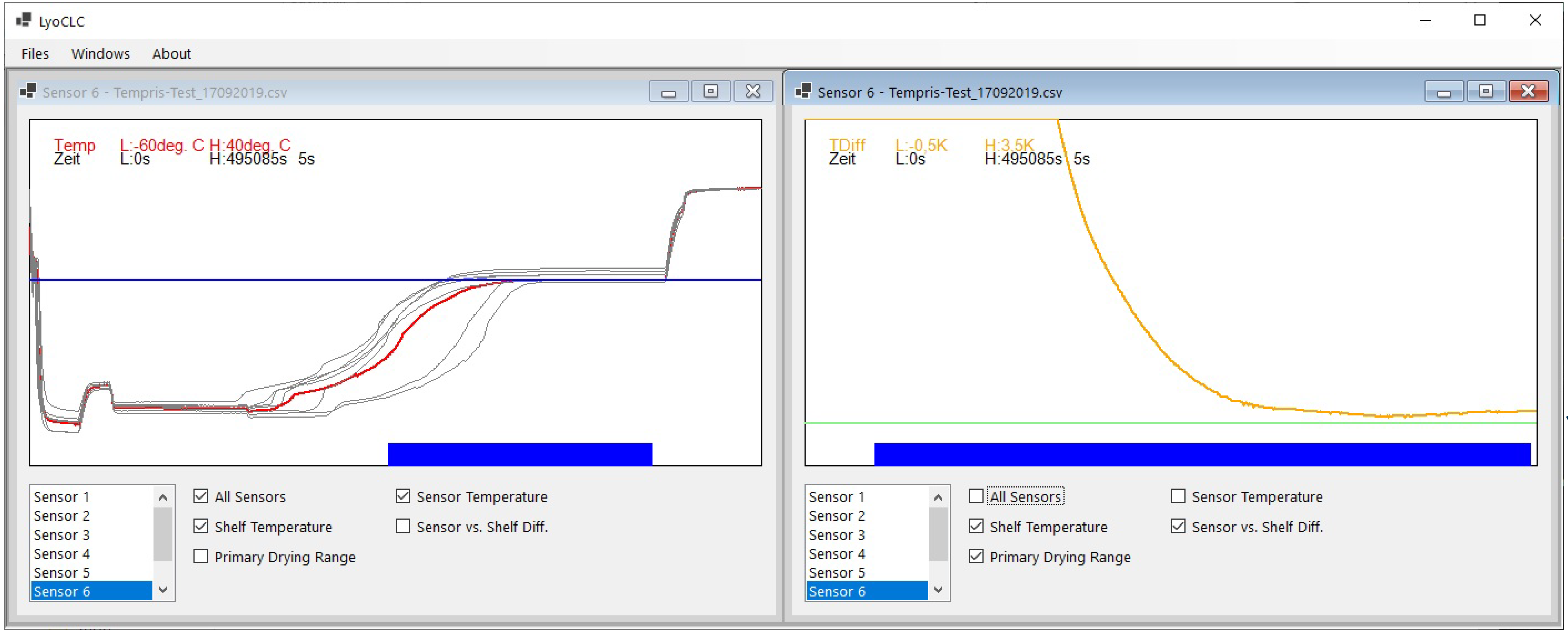
Run 2 stayed longer in the initial freeze state due to commercial process access restrictions tempris®



Few sensors signal: Humidity still too high!

Most sensors signal: Humidity is now within acceptable range.

LyoCLC : The new Tempris closed loop software provides for auto-update during the process. Temperature difference to estimated shelf temperature is calculated in real time.



All sensors signal: Humidity within range for several hours

LyoCLC shows in real time that this lyo cycle may be shortened, saving time and energy.
Increase the throughput of your lyo engines by closed loop control.

4. Applications: Closed loop control

AI versus GMP : What can AI do for process development and control with the digital twin?

GMP

- Strict process control.
- A hypothesis requires scientific evaluation.
- Use well-known statistical models.

AI

- May provide helpful assumptions.
- But no scientific explanation.
- Thus requires separate evaluation.
- Requires lots of data input, e.g. Tempris.
- Supports formulation development for human researchers.

4. Applications: Estimation of shelf temperature

Determination of heat transfer proportional to temperature difference

Build a model of the Lyo process *with additional input* in real time

Calibrate existing models, making them *robust* against parameter variations

Provide *robust* model results in real-time

Temperature of a large set of individual vials

Estimate individual shelf temperature and calculate heat flow

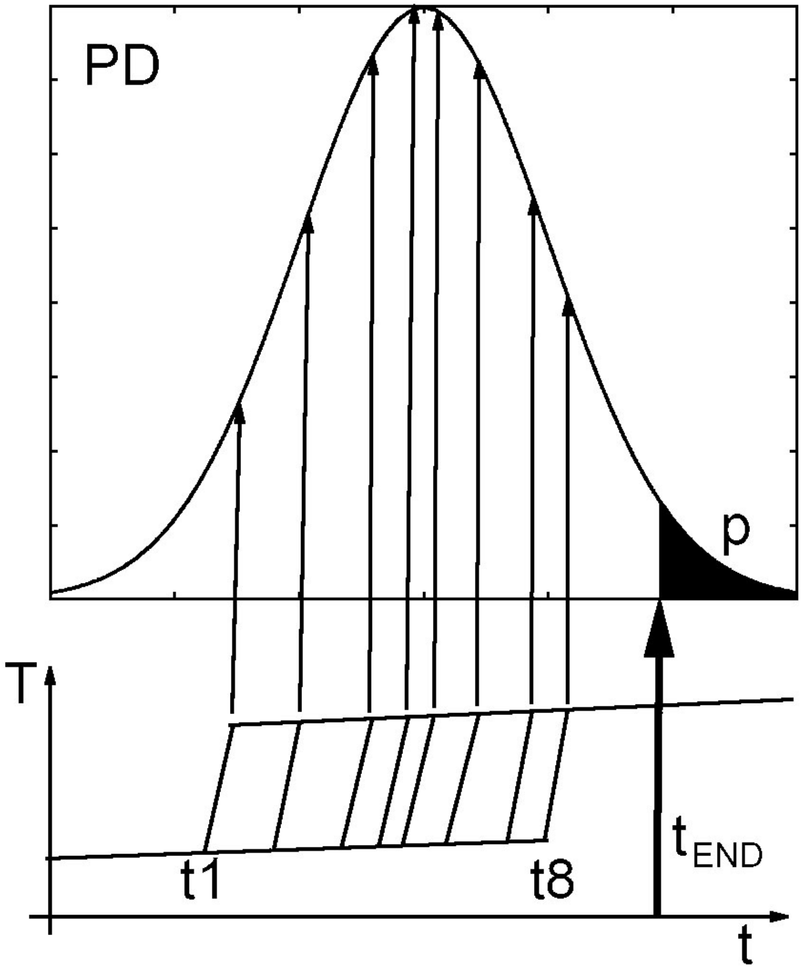
Position of those vials

Adjust k_v constants!

Shelf temperature estimation works independently of vial type and size, formulation, FD type, etc.

Permits robust simulation and thus closed-loop control.

4. Applications: Closed-Loop Control



The statistical live analysis enables the **detection of moisture levels below a specified threshold** during the lyo run.

Live statistics then permits to determinate the probability that all (Tempris and non-Tempris) vials are below this limit

Lyo cycle control may then be shortened or enhanced in case of problems

Tp measurement – faster Lyo cycle – better quality

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Wireless, battery-free, real-time

Ready-to-use-Sensors

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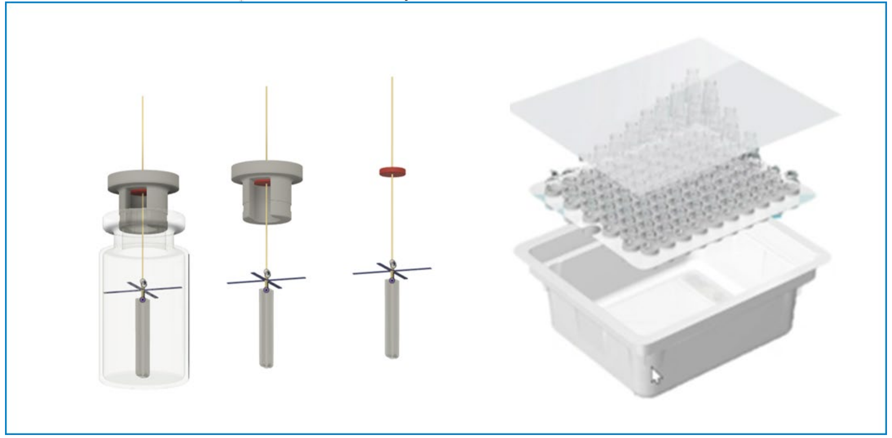

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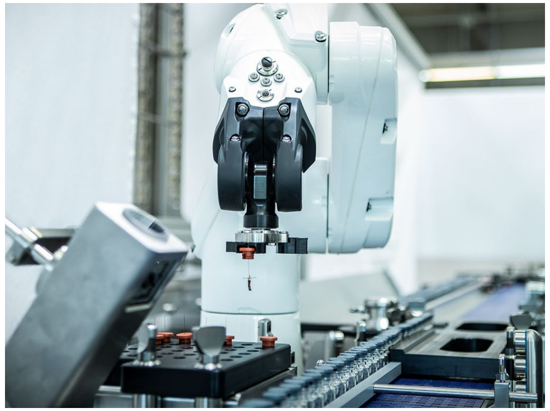

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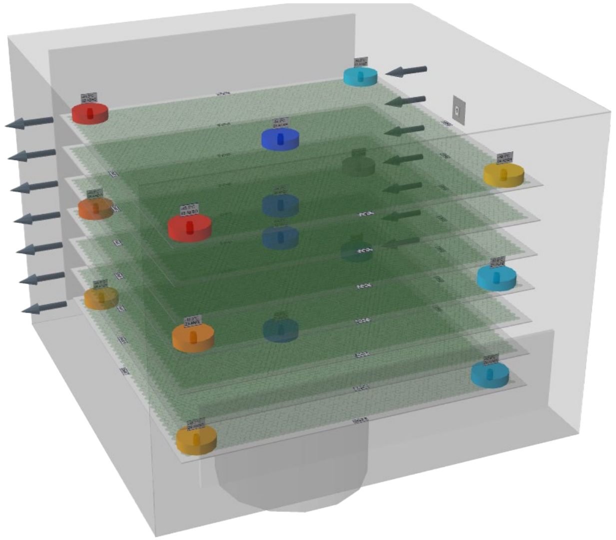

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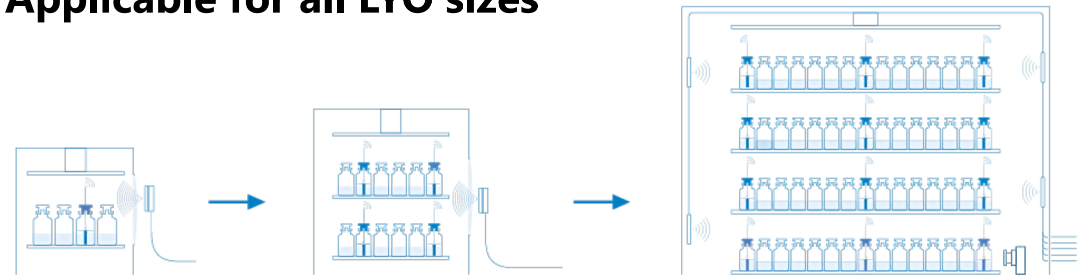

Thank you!

For further information, please get in touch with us at

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