(c)GMP Annex 1 for Lyophilization Technology- Lyocycle Process Control - Regulatory

Annex 1, Lyocycle Process Control by applying the Concept of Product Temperature of Critical Positions and how to implement into Regulatory Files.

Dr. Andrea Weiland

explicat® pharma GmbH
Development and Consulting

Modern Lyo - Annex 1 (Process Control, Regulatory)

Annex 1:

- see Lyophilization 8.121-8.126
- Lyo is a critical step – minimize operator intervention – Utensils used should be sterile
- See Aseptic Process Simulation (APS-media fill), 9.32-9.49
- See 9.33: vi-vii- process simulation procedure for lyophilized products
- See 9.34: interventions know to occur need to be part of the APS

Modern Lyo - (Annex 1) Process Control - Regulatory

- Process Control: FDA/EMA/ICHQ8(R2)- see Pharm Dev 2.3 (CTD32P23), manufacturing process development: …. process control 2.5., Control Strategy (3.3), see Manufacturing Control Strategy (process controls) (CTD (32P33), see appendix 1 -page 19

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Overall Pharmaceutical Development	Mainly empirical Developmental research often conducted one variable at a time	Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs Multivariate experiments to understand product and process Establishment of design space PAT tools utilised
Manufacturing Process	Fixed Validation primarily based on initial full-scale batches Focus on optimisation and reproducibility	Adjustable within design space Lifecycle approach to validation and, ideally, continuous process verification Focus on control strategy and robustness Use of statistical process control methods
Process Controls	In-process tests primarily for go/no go decisions Off-line analysis	PAT tools utilised with appropriate feed forward and feedback controls Process operations tracked and trended to support continual improvement efforts post-approval

Modern Lyo - (Annex 1),Process Control - Regulatory

- EMA Guideline on process validation: see specialised processes of established processes known to be complex, Processes with critical steps: e.g. lyophilisation, Aseptic processing
- FDA: Guide to Inspections of Lyophilization of Parenterals (07/93): “lyophilizer should have the necessary instrumentation to control and record the key process parameters….. importance of product temperature”
- FDA: Process Validation (2011): importance of process control to meet product quality attributes, process control; use of process analytical technology (PAT)- use of control loops to adjust the processing conditions to that the output remains constant
- FDA: PAT- A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, 2004
- Regulatory parts – CTD 32P2 (pharmaceutical dev), CTD 32P33 manufacturing process, 32P34 control of critical steps, 32P35 Process validation

USE of a PAT Tool – Process Control - Closed Loop during Lyophilization under Annex 1 requirements

tempris® Easify Your Lyo Process

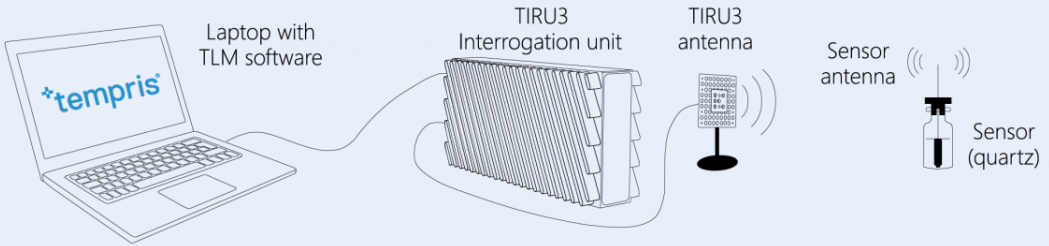
- TEMPRIS to monitor, respectively as closed loop to control Product Temperature
- with Consideration of Critical Intervention

USE of a PAT Tool – Process Control - Closed Loop during Lyophilization under Annex 1 requirements

Components and Operation Principle, Passive, wireless, battery free

Tempris Technology for Product Temperature Measurement
Tempris – Temperature remote interrogation system

The Tempris Lyophilization Monitoring Software TLM is used to control the interrogation unit (TIRU3), record data, set all parameters, visualize and export data. TLM gets the data of the Tempris Interrogation Unit TIRU3 which in turn gets temperature data from the antennas in the freeze-dryer. The antennas collect all the temperatures which are measured by the quartz based sensor (operating on the principle of temperature dependent resonance).



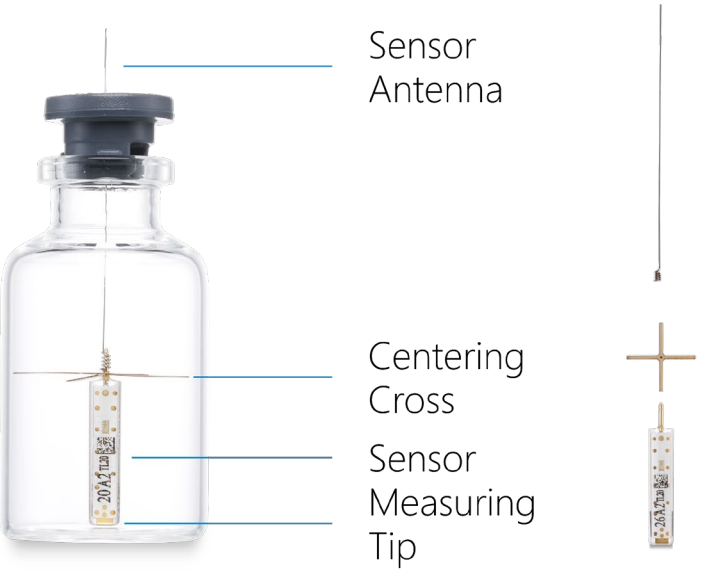
Quartz based sensor, operating on the principle of temperature dependent resonance: after excitation by a modulated microwave signal (2.4 GHz), the sensor keeps on oscillating in a temperature dependent frequency. Overlaying the sensor response with the carrier signal leads to a frequency
shift from which the product temperature T_{Pb} can be derived.
https://www.tempris.com/freeze-drying-lyophilization/products/#c61342c6ec168e219

USE of a PAT Tool – Process Control - Closed Loop during Lyophilization under Annex 1 requirements

Use of TEMPRIS® for Dev./Scale Up/Production

Components and Operation Principle

- wireless & battery free
- Passive sensor operation – no heat impact
- real-time temperature measurement system
- Characteristics
- Sensors can be sterilized
- Sensors can be placed and positioned aseptically with RABS/ ALUS/ Isolators at „hot and cold“ (critical) positions of the freeze-dryer
- sensors for 2R-100H available



Accuracy of the complete system
+/-0.7 °C to +/-0.3°C (-60 °C to 40°C)
(extended -70°C to +70°C)
see for details www.tempris.com

Modern Lyo - (Annex 1) and Process Control
Critical Quality Attributes of a Lyo Product

Analysis of **critical quality attributes (CQA's)** of a lyo product

- Appearance (of Lyo cake)
- Reconstitution Time
- Clarity/Colour of solution
- Identity/Assay/Purity
- Water content
- Sterility
- Endotoxins
- Subvisible and visible particles
- Container closure integrity (no leaks)

In blue – CQA driven by Formulation and Lyo process

Modern Lyo - (Annex 1) and Process Control
Critical Formulation Temperature

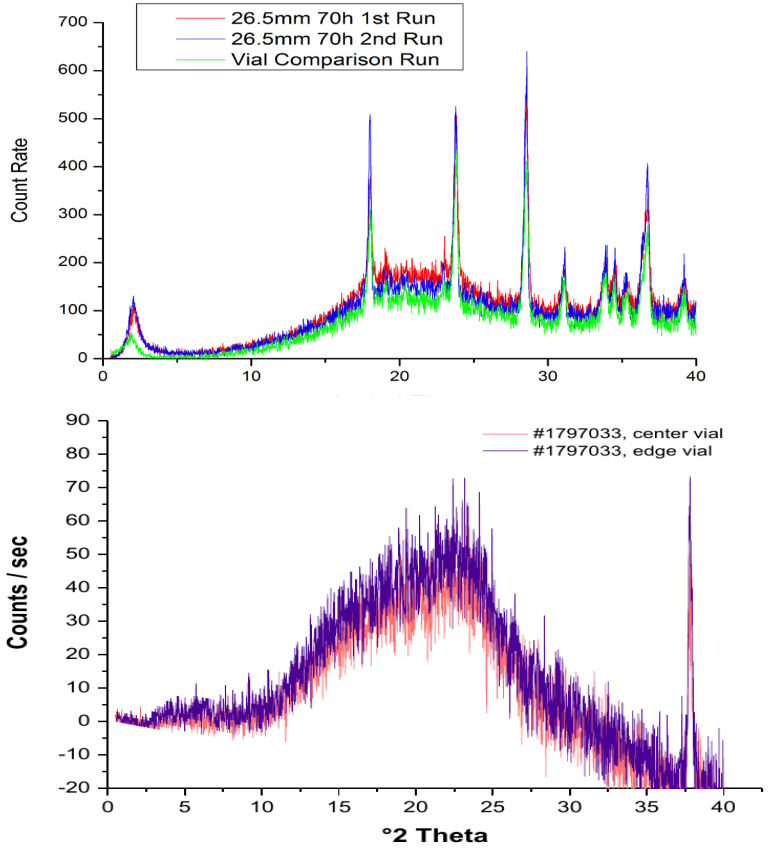
critical formulation temperatures (CFT) in freeze drying

Crystalline matrix* - T_{eut}

Amorphous matrix* - T_g'/T_c

*(predominantly)

CFT depending on the physical state drives the design of the lyo cycle



Modern Lyo - (Annex 1) and Process Control Product Temperature

Importance of Product Temperature T_P in Freeze Drying

T_P is a critical product parameter which determines important product 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 super cooling, 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 melt back

Modern Lyo - (Annex 1) and Process Control

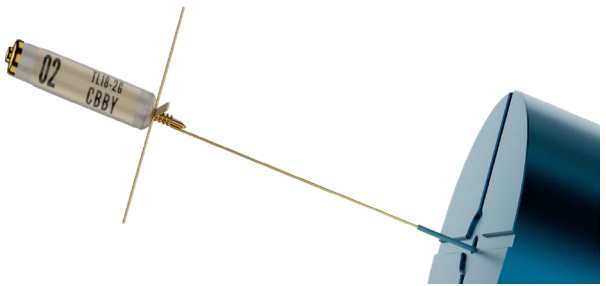
Critical Product Parameter -
Tp determines whether
product will
comply to **critical quality attributes (CQA`s)**

Critical **P**roduct **P**arameters (**CPtP**):

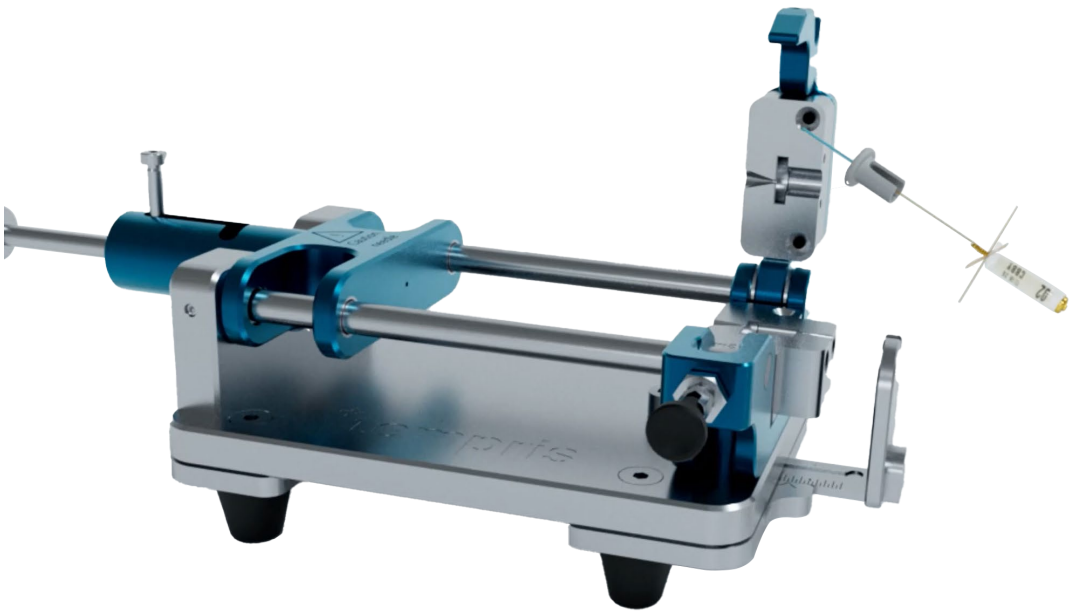
- $T_{P(b)}$ (Product Temperature) (°C) is **crucial for process control**
- Product Resistance (Rp) (cm² x Torr x h/g: area normalized product resistance) (stopper resistance normally negligible)
- Desorption Rate (DR) (%/h)
- Residual moisture (RM) (%)

Tp must comply to the critical formulation temperature

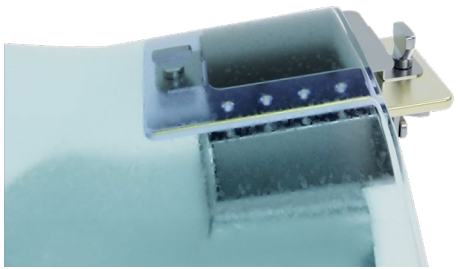
Sensor Preparation Piercing Tool PIT2

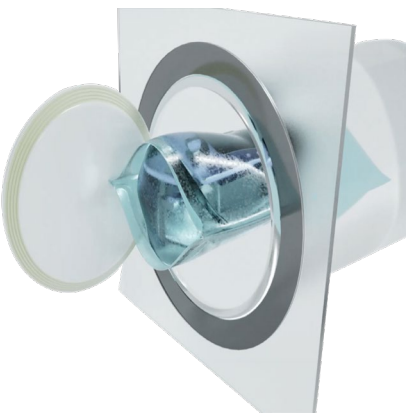


tempris® Easify Your Lyo Process



Autoclave to sterilize Sensors





Sensor Sterilisation and Insertion

- Autoclave → through gloves in RABS
- **Autoclave →into isolator:** desinfection with H_2O_2 (VHP)
- **or through RTP (Rapid Transfer Port) e.g. DTPE® Port into Isolator**
- https://www.getinge.com/int/products/dpte-alpha/, **See videos**

https://www.getinge.com/int/products/dpte-alpha/

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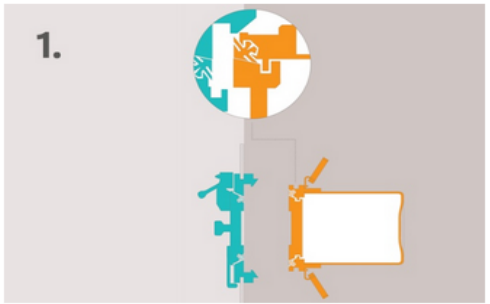
DPTE®-XS Alpha Port

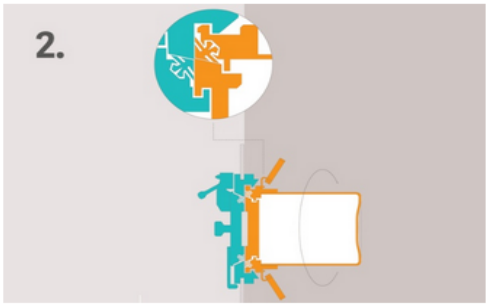
How does the DPTE®-XS system work?



1. Line up the DPTE®-XS Alpha and Beta parts

The Alpha part is mounted on a support – commonly an isolator, RABS, BSC, or cleanroom.

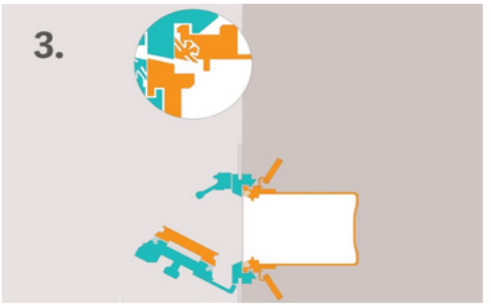
The Beta part consists of a container, bag, or other Beta device used for the transfer of components, solids, or liquids.



2. Rotate the Beta part 60˚ to ensure leak tight seal

The Alpha parts and Beta parts are connected by a manual 60˚ rotation which detached the doors from their supports and joins them together.

Tightness is secured by the lip seals of the new assembly.



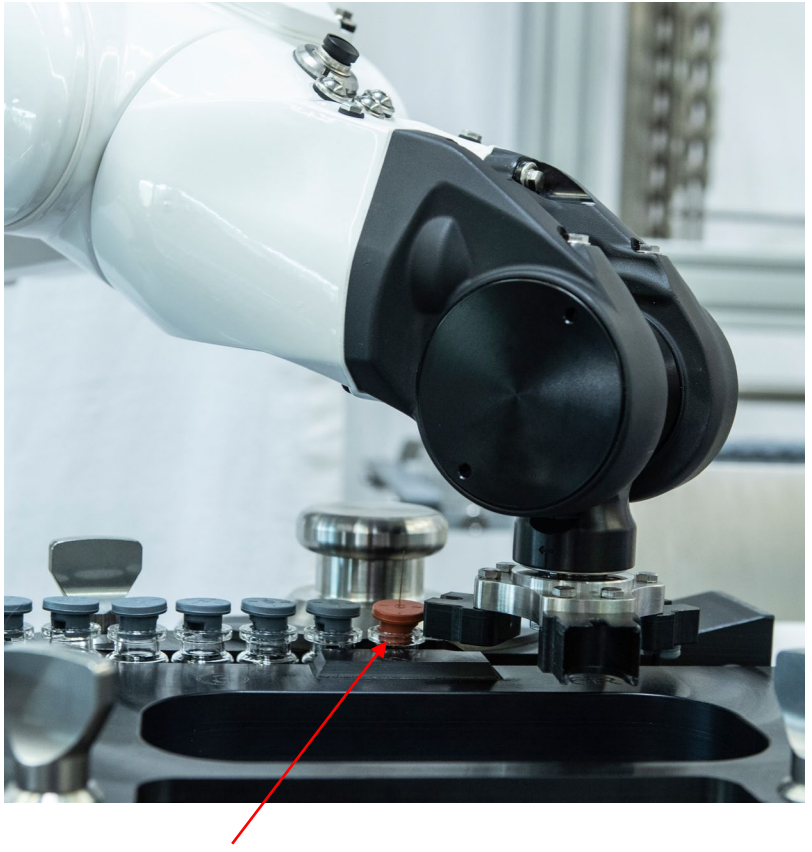
3. Open the doors without breaking sterility or containment

The doors can now be opened without breaking sterility or containment.

The combination of DPTE® Alpha and DPTE® Beta parts is a validated solution. Used together, they provide highly secure transfer and protect your production.

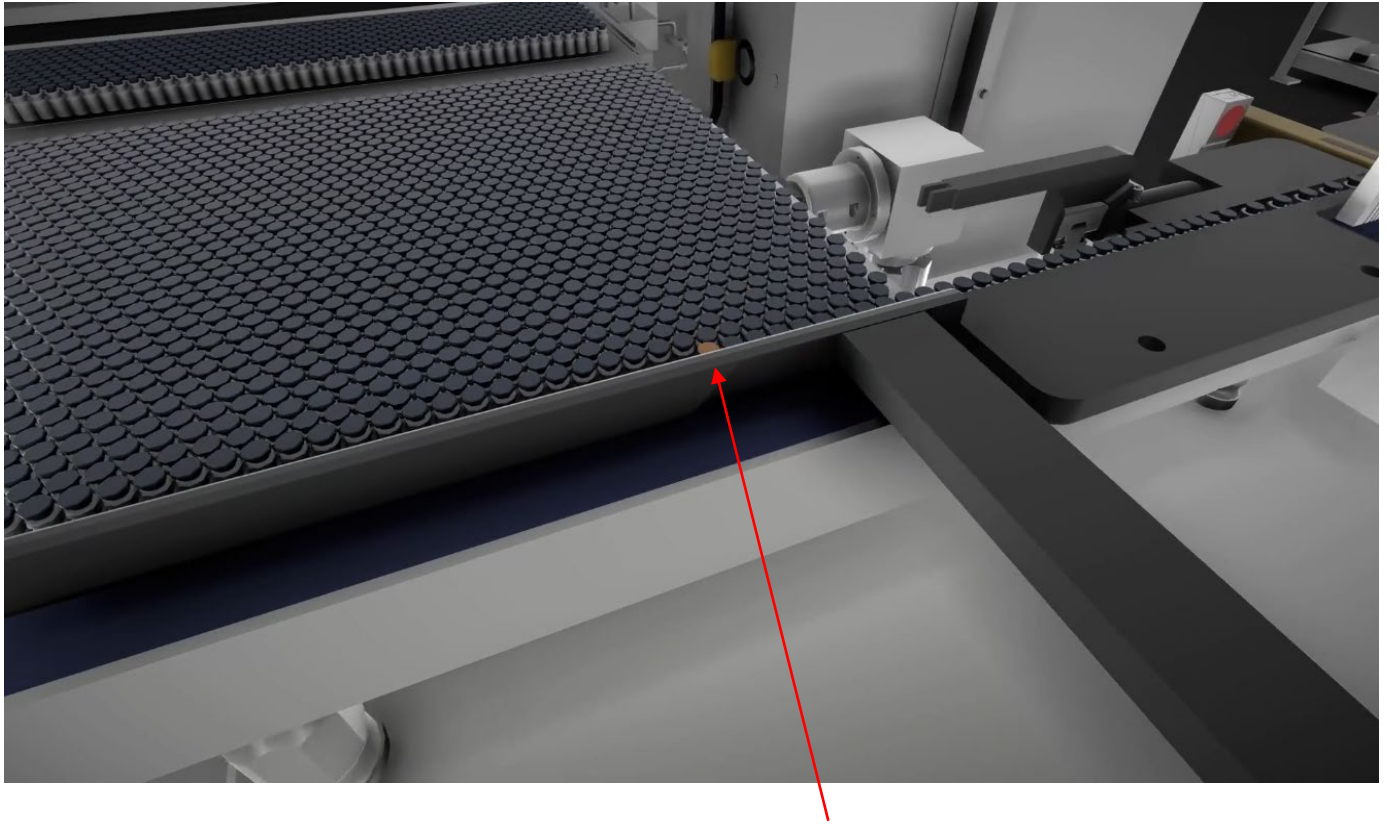
RABS or Isolator, Sensor positioning with Gloves and use of sterile forceps or Tempris Tweezer

Use of Robotic for Sensor positioning

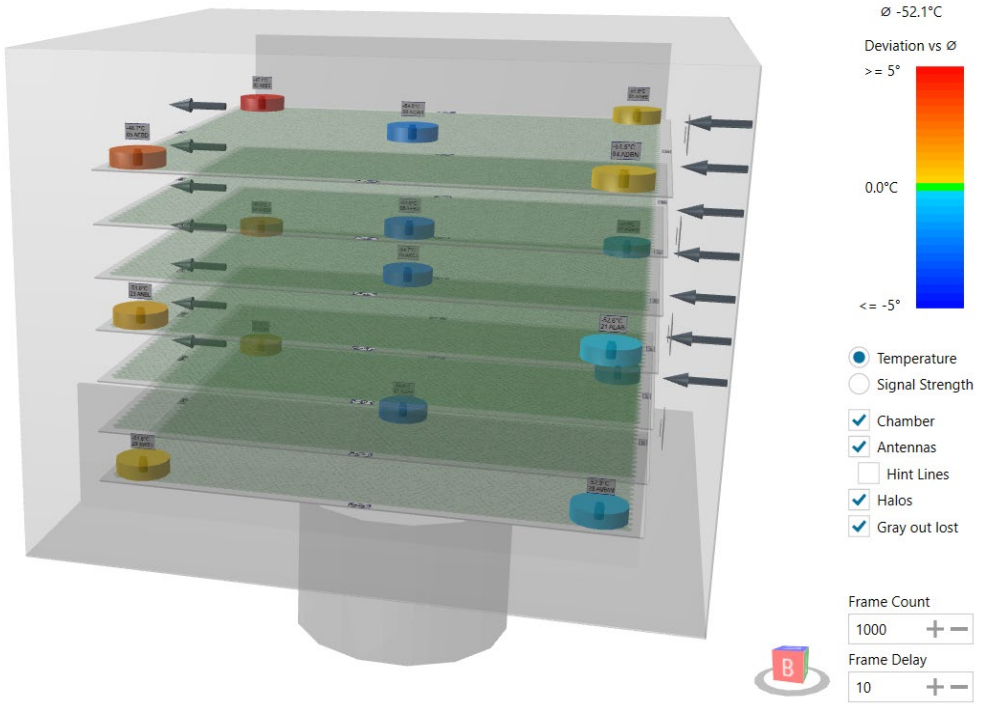


Adding sensors to the shelve

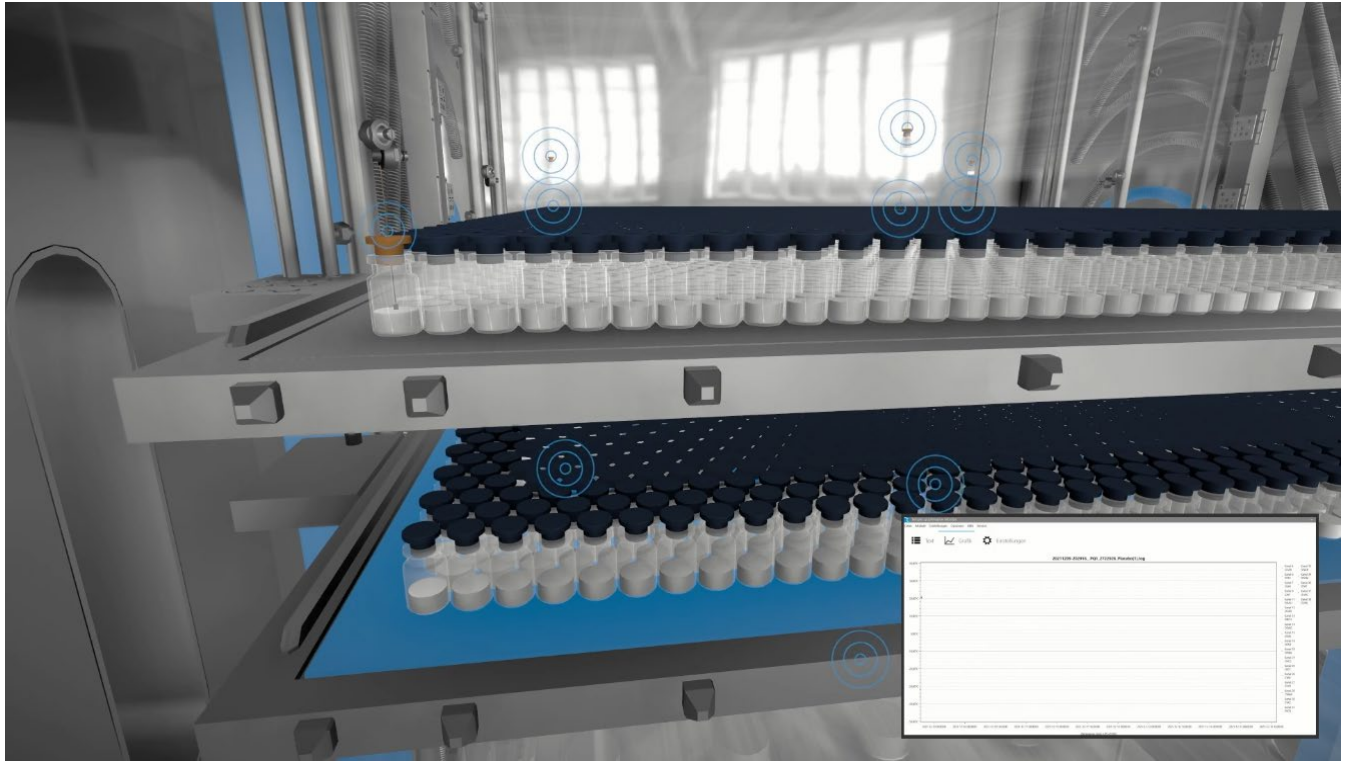
Automatic Loading



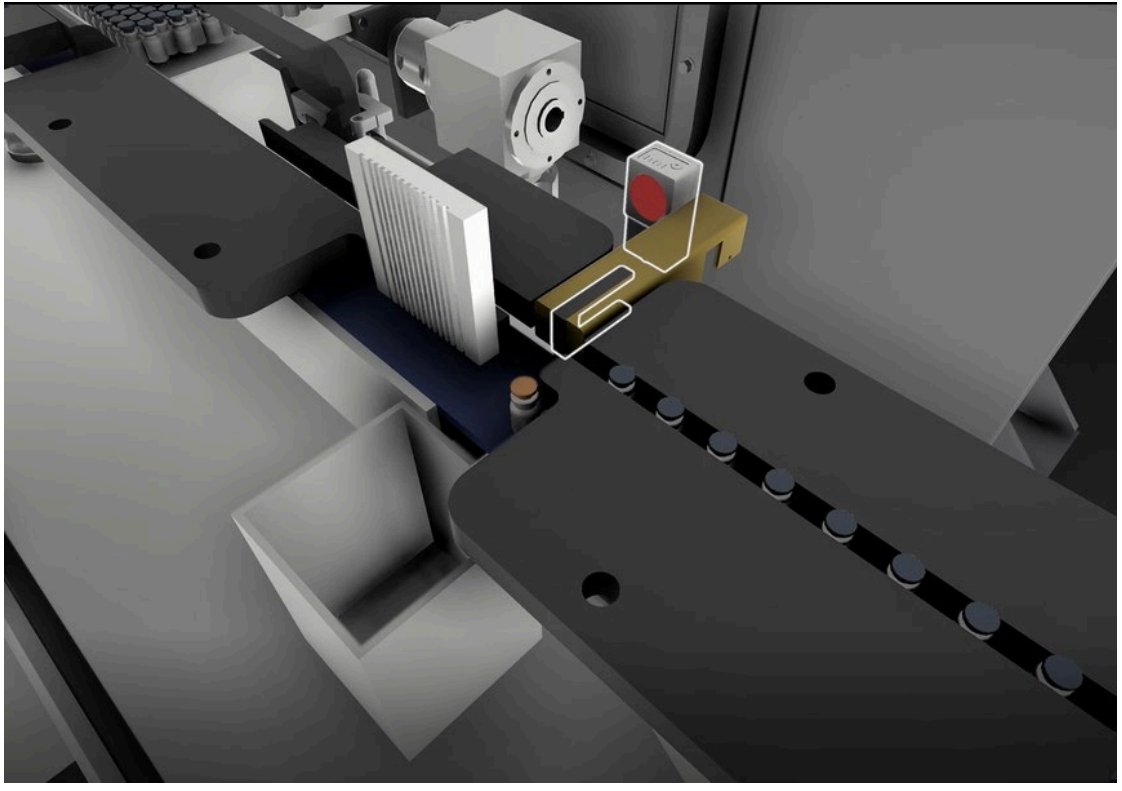
Sensor positioning Hot and Cold spots



Sensor positioning Hot and Cold spots



Automatic unloading



Lyoprocess dev. and the regulatory implementation - Design Space

Example for Production Scale Batches –
T_P of 16 sensors located at different critical positions in the lyo –
(„Hot –Cold - spots“);
sensors: shelves 1, 3, 5, 6, 9, 12, 15, 18 center and front door position or duct position (45.000 vials scale)

„PV1“ (PPQ2) more homogeneous Tp compared to #2eng (Transfer Batch)

Due to adaptations to the freezing step

All CQA`s within acceptance criteria,
0% cake defect, residual moisture map:
very uniform low residual moisture results

Lyoprocess dev. and the regulatory implementation

Predominantly Crystalline Matrix:

- Freezing Tp < Tg‘
- Annealing to crystallize bulking agent/ Ostwald ripening
- Tp max. -45°C at the beginning of primary
  drying (due to Tg‘ of the amorphous phase)
  then can be run „agressive“ until Tp=Ts, steady state primary drying Tp around -25°C to -30°C (Ts set to +15°C)
- secondary drying Ts 40°C same pressure
  as during primary drying

Regulatory Implementation using Tp by PAT Tool TEMPRIS®

Module 3 Lyocycle development
In 32P2 Pharmaceutical development – 32P22 Drug Product:
Development of the Lyocycle based on the matrix and the Critical Formulation Temperature; Tg', T_{eut} Discussion and Laboratory Scale Lyocycle Robustness Development to establish the boundaries

In 32P23 Manufacturing Development:
Translation into commercial scale freeze-drying process using PAT Tool TEMPRIS® to monitor Tp in critical positions – further adaptations done to address full scale/freeze dryer performance boundaries
Physico chemical analysis to demonstrate Critical Quality Attributes are constantly met

Regulatory Implementation using Tp by PAT Tool TEMPRIS®

Module 3: Process Validation Lyocycle: in Module 32P35

General Lyocycle Approach controlled by real time feed back system TEMPRIS®:

Tp („hot/ cold“ spot)- Control Temperatures to be used as online feedback system to be programmed into SCADA

SCADA: Supervisory control and data acquisition for supervisory management and also uses PLC: Programmable Logic Controllers

Regulatory Implementation using Tp by PAT Tool TEMPRIS®

Module 3: Process Validation Lyocycle: in Module 32P35

General Lyocycle Approach controlled by real time feed back system TEMPRIS®:

"**For approval** in the following a **general lyocycle** is presented that can be used in industrial scale lyophilizers with different construction/performances in relation to design,
lyochamber - condenser design, condenser type, water capacity (how much water can be frozen on the condenser), connection (duct) between chamber and condenser where the water vapour gas stream will be directed, use of aluminum tray or automatic loading (vials directly loaded on the shelf with direct heat transfer), use of controlled nucleation technology if available at approx. -5°C to – 10°C etc."

Regulatory Implementation using Tp by PAT Tool TEMPRIS®

Module 3 Process Validation Lyocycle: in Module 32P35

General Lyocycle Approach

A general lyocycle is presented driven by Tp and chamber pressure control criteria

Some example text

“Key in Freezing step is to reach **Temperatures < Tg'** and achieve complete freezing, nucleation
and crystallization of the bulking excipient and Ostwald ripening to obtain uniformly frozen vials amongst positions **by annealing** to achieve homogeneity within batch over shelves and within batches; if no controlled nucleation available - supercooling to be addressed, if controlled nucleation moderate adaptation of the lyocycle possible”

The detailed lyocycle that was subject of process validation/PPQ including the details of the industrial lyophilizer used is an exemplary cycle meeting the criteria defined in the general lyocycle.

Regulatory Implementation using Tp by PAT Tool TEMPRIS®

Module 3 Process Validation Lyocycle: in Module 32P35

General Lyocycle Approach

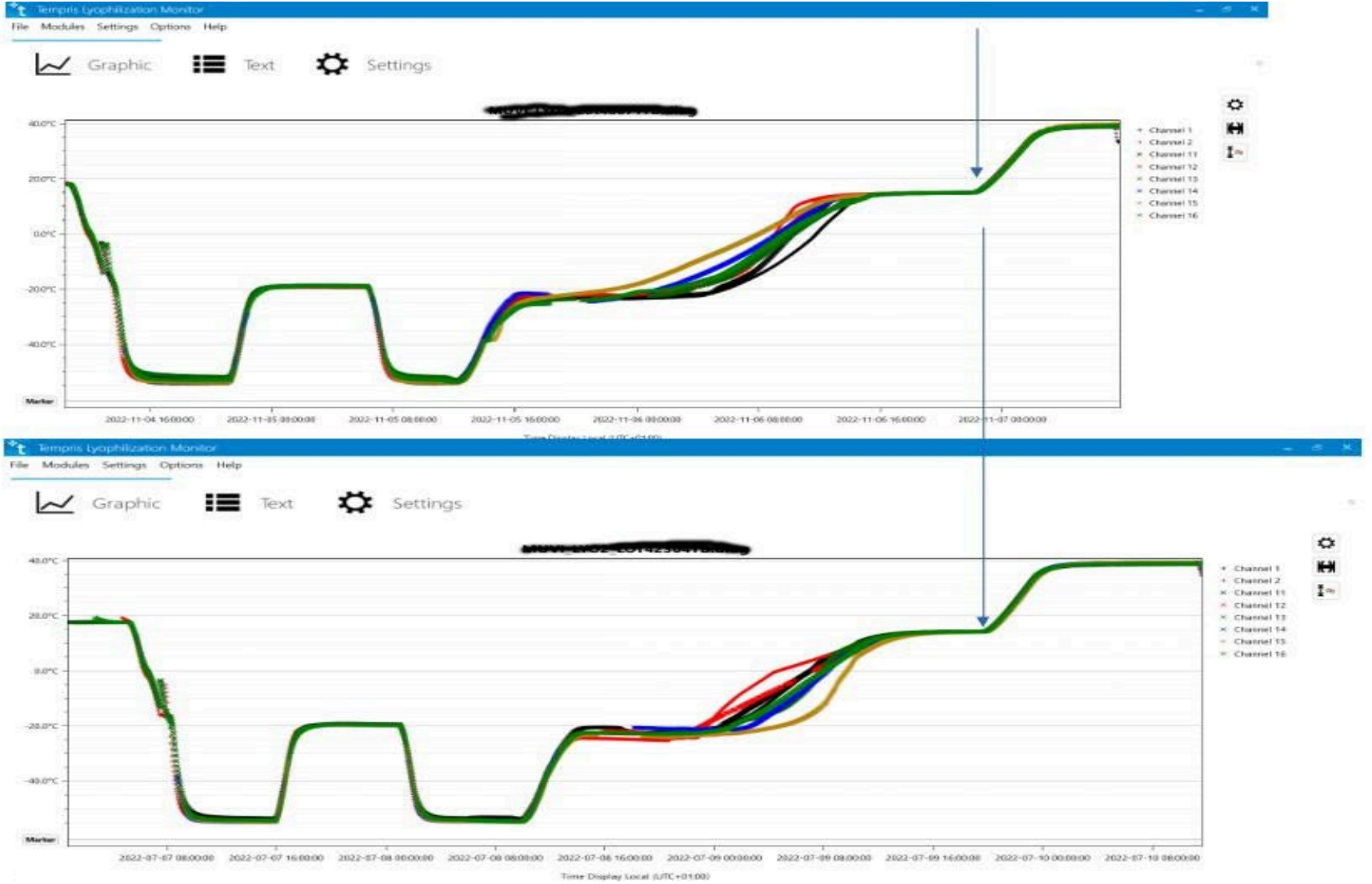
A general lyocycle is presented driven by Tp and chamber pressure control criteria

- Also by applying the Tp control concept (a real PAT tool) alternative loadings are possible as the general lyocycle is adaptable. This might be needed for cases of technical defects occurring.
- As long as the boundary conditions are kept, i.e. the Tp characteristics, the product quality attributes will be similar.

Continous Process Verification – Ongoing Life cycle verification using Tp by PAT Tool TEMPRIS®

Product was approved 05/2018

- Tp as process control – interface to SCADA
- Hot and cold positions defined over the shelves positioned into the previously identified critical positions
- Lyocycle is evaluated after each run
- Data collected and meta analysis is done
- Also allows for scientific interpretation of data in case of deviations (e.g. delays with loading, loss of power) on basis of the development data (lyorobustness – lyo design space)


Tempris Lyophilization Monitor
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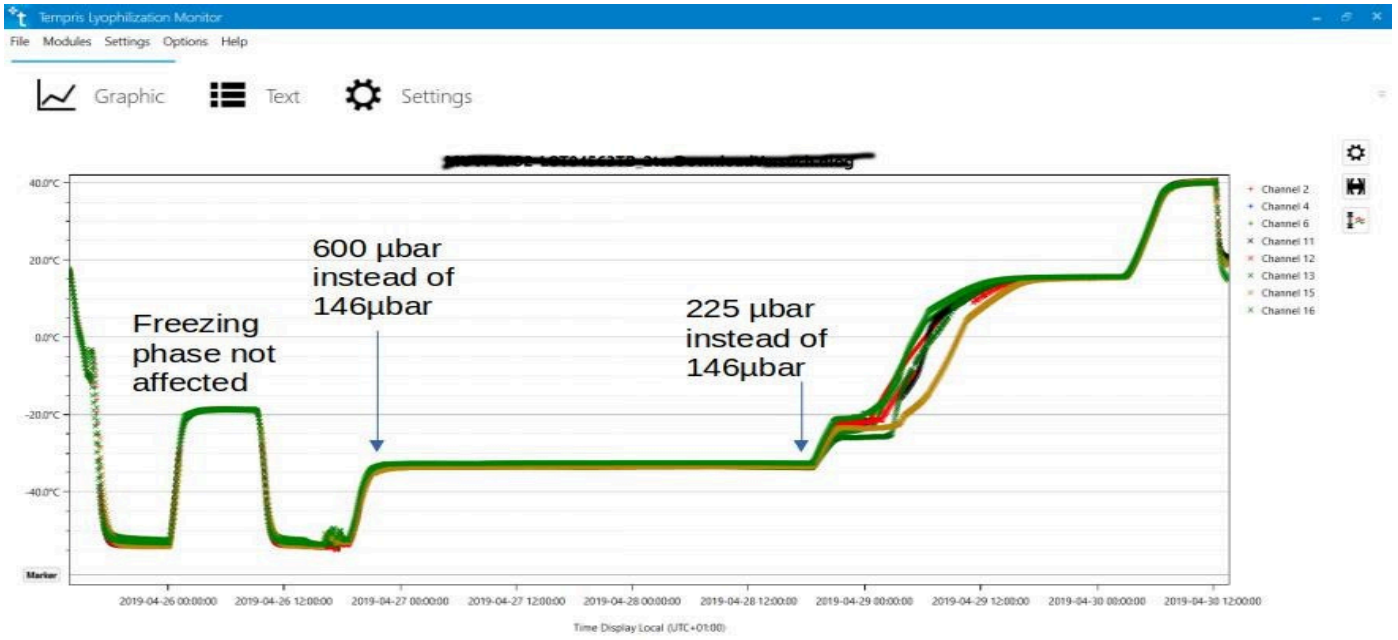
Continous Process Verification – Ongoing Life cycle verification using Tp by PAT Tool TEMPRIS®

Product was approved 05/2018- actual status 06/2024

- 174 lyo`s routine production: not one reject batch due to lyophilization process
  - Residual moisture as CQA very uniform- overall average 0.4%;
  - (samples B-M-E of filling (taken from shelf1 – shelf 18) is robust
- Handling of deviations (e.g. vaccum control, leaks) supported by Dev Package and hot/cold spot Tp data (5 deviations linked to lyo: all positively closed
- All stability studies are homogeneous, they all fit to the known stability pattern as developed
  - No complaints from market to do with lyocake appearance and or reconstitution up to today

Lyocycle process verification Deviation Pc (weekend cycle)



Batch was on ongoing stability – is stable and complies to the known stability pattern; spec and all CQA are met
e.g. appearance
Batch completely sold to market and used

Primary drying: Due to leak - chamber pressure higher- elongated cycle-Tp conforms

Ultimate Ratio PAT-Closed LOOP

Closed Loop in Lyophilization,
Process control of lyo by applying hot and cold spots: TEMPRIS
Product temperature data (Tpb), a real time process control to determine e.g. endpoint of primary drying
Currently under development by TEMPRIS as a statistical tool
Refer to ICHQ8, FDA-PAT

https://www.tempris.com/applications/hot-and-cold-spot-recognition-in-lyophilization/

Videos

Tempris Video - Piercing Tool

Tempris Video - Easify Your Lyo Process

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GET LYO SOLUTIONS, A ONE-STOP-SHOP FOR FREEZE DRYING

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Thank You for Your Attention.

Questions?

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