tempris® sensor technology

TEMPRIS - A Powerful PAT Tool

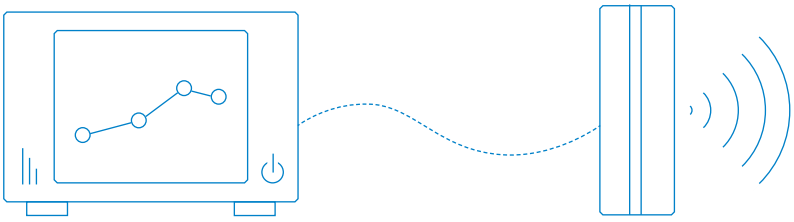
wireless, battery-free and real-time
temperature measurement system for
biotech and pharmaceutical applications

Real-time temperature measurement system for lyophilization

Tempris is a powerful PAT tool

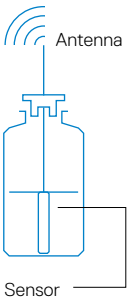
Biotech and pharma companies worldwide are using Tempris to:

- Prepare data for Regulatory Submissions
- Capture product temperature Tp for lyo-cycle scale-up & transfer
- Measure Tp exactly at the center bottom position (Tb) of the vial
- Optimize lyophilization processes
- Perform real-time monitoring of hot & cold spots (HCS) in production



Tempris Interrogation unit with
Windows PC for data monitoring

Antenna



Functional Principle

Introduction

- Tempris is a temperature measurement system
- Tempris works wirelessly and without batteries
- Tempris is used for real-time product temperature Tp measurement in pharmaceutical applications such as lyophilization, sterilization, granulation, etc.

Tempris is cGMP, GAMP5 and 21 CFR Part 11 compliant as required by the United States Food and Drug Administration (FDA), the European Commission (CE) and other regulatory bodies in Asia and elsewhere.

Tempris is the only real-time product temperature measurement system used in laboratory as well as pilot and production freeze-dryers at commercial scale.

Breaking new grounds

The start of FDA's PAT initiative in 2004 lead to a paradigm shift in the development of lyophilized products towards a thorough understanding of critical process and product parameters rather than a trial and error approach.

One of the most critical parameters in a freeze drying process is the product temperature at the sublimation interface (Tp) and at the bottom of the vial (Tb), respectively.
The product temperature must not exceed the critical formulation temperature given by the physicochemical properties of the formulation in order to prevent shrinkage, collapse or meltback.

Several methods for Tb measurement are currently available, albeit with certain limitations. With Tempris, many of these limitations can be overcome, thus making your process development faster and easier.

Functional principle

Quartz based sensor, operating on the principle of temperature dependent resonance: after excitation by a modulated microwave signal (2.4 GHz) the sensor continues oscillating at a temperature dependent frequency. Overlaying the sensor response with the carrier signal leads to a frequency shift from which the product temperature Tb can be derived.

Key Features and Benefits

- **System features:**
  - Wireless and battery-free sensors without additional heat contribution to the product
  - Real-time monitoring of up to 16 sensors in any scale of freeze dryer
  - Sterilizable, compliant to FDA 21 CFR Part 11 and GAMP 5 / cGMP
  - Centering cross pieces for exact vial center bottom temperature measurement (Tp/Tb)

- **Sensors are highly accurate**
  Tempris sensor accuracy is ± 0.7 K at a temperature range from -60°C to +60°C. Further accuracy ranges available from ± 0.5 K to ± 0.15 K Case studies show that Tempris sensors measure more accurately than manometric temperature measurement (MTM) systems and thermocouples (TC)

- **Sensors are suitable for different vials and filling volumes**
  Standard Tempris sensor sizes can be used in standard and non-standard vials with filling volumes from 0.1 ml to 30 ml; customized sensor sizes are available on request.

- **Sensors have no adverse effect on the freeze-drying profile of your product**
  Sensor is wireless and battery-free, hence no energy input to the product compared to wired RTDs or TCs and has negligible effect on freeze-drying profile of the product.

- **Suitable for aseptic manufacturing conditions**
  Tempris sensors are wireless and sterilizable and compatible with automatic loading and robotic handling systems and supports aseptic manufacturing. Sensors can be inserted into the vials aseptically inside the isolator or RABS.

- **Sensors are robust and reusable**
  Tempris sensors are highly accurate, specified for many freeze-drying and sterilization cycles. For Lyophilization an annual calibration of the Tempris system is recommended.

- **Tempris is available for new and existing freeze-dryers**
  Tempris systems can easily be retrofitted to all types of existing FD equipment. Tempris is the only real-time product temperature mesuring system, which can be used in laboratory as well as pilot and production freeze-dryers at commercial scale.

- **Tempris data can be used for regulatory submission**
  Tempris systems come with the Tempris DataServer software for capturing measurement data in compliance with cGMP / GAMP 5 and FDA 21 CFR Part 11. Automation interfaces to PLC and SCADA systems, customizable reports and CSV export functions are also available.

- **We execute qualified installation**
  Tempris services include engineering, commissioning, Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), training, system maintenance, calibration and technical support.

- **Available worldwide**
  Tempris has distributors all around the world and is being used in laboratory, pilot and commercial production freeze dryers.

Product development support

Lab Scale Development

Lyo-cycle development in the laboratory establishes the base for the freeze drying cycle and its subsequent optimization.

Tempris captures T_b, the product temperature at the vial bottom, one of the most critical lyo-cycle parameters.

Scale-Up and Transfer

Your product moves to a larger freeze-dryer, to a different type of freeze-dryer or simply to cGMP environment. These activities used to involve a change in Tb measurement technology (e.g., from TCs to RTDs, MTM cannot be used), causing problems or limitations with respect to the comparability of the obtained data (positioning of RTDs in sterile enviroment). With Tempris, the same sensors which are used in lab scale development can also be used in pilot and production scale freeze-dryers at equivalent positions, thus providing directly comparable data.

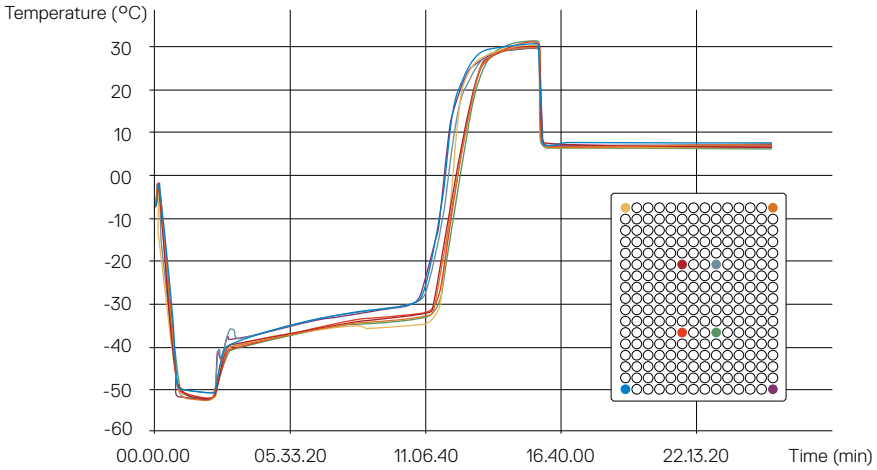
Production

Full production scale lyophilization under cGMP conditions places increased demands on the equipment used. The installation of wired temperature sensors is usually impossible where Automatic Loading and Unloading Systems are in use.
Wireless Tempris sensors, however, can be used in such environments, thus allowing you to capture valuable data in production and to gain more insight and ensure more safety of your production process.

Tempris DataServer Software

Tempris DataServer (TDS):

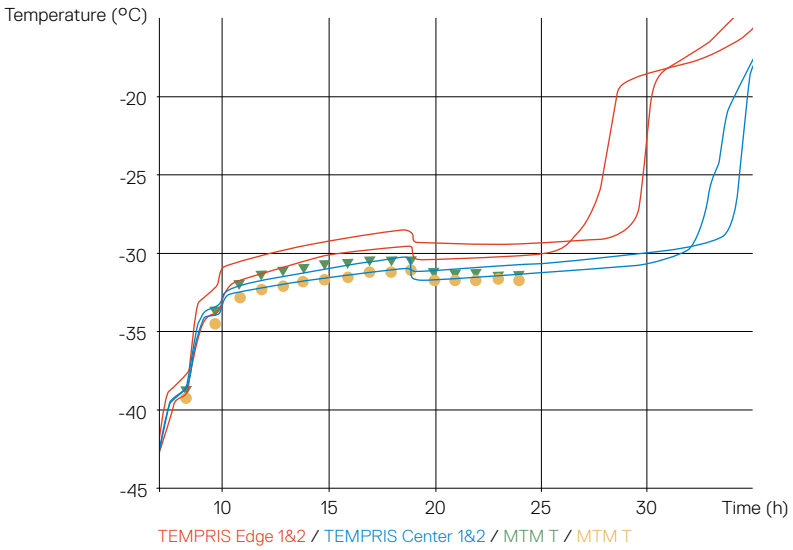
- Data Logging and Data Visualization
- cGMP/GAMP 5 Compliance
- FDR 21 CFR Part 11 Compliance
- User Administration
- Audit Trail
- Backup
- Log File Reports
- CSV Export
- Automation Interfaces to PLC / SCADA



Data Accuracy

Tempris vs. MTM

Compared to MTM (Manometric Temperature Measurement, a batch method for the determination of Tp and T_b), Tempris sensors in center vials show excellent agreement with MTM data all along the run and in the end-point detection of primary drying. Thus Tempris is an important link between “Single Vial” and “Batch” methods.



Tempris vs. TC

At the CHI-Pep Talk held in 2012 in San Diego, Pfizer made a presentation on an investigation conducted on several temperature sensor types for bringing a dual chambered syringe (DCS) from development to production.

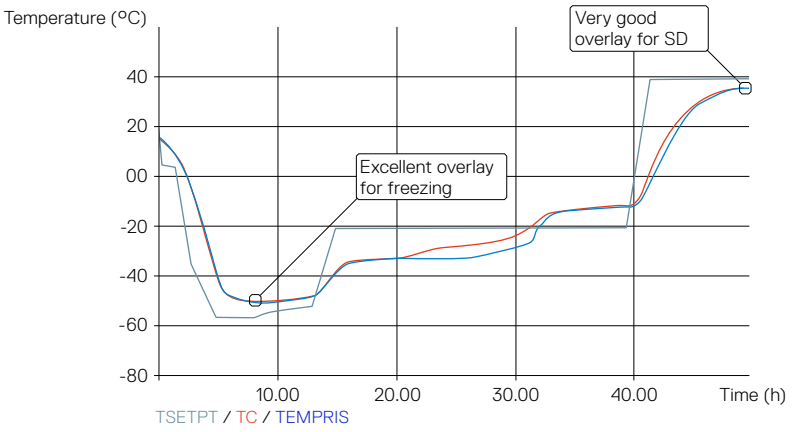
Pfizer’s investigation concludes the following:

1. Excellent correlation of Tempris with TC for freezing and early primary drying.
2. Tempris profiles maintained better contact with ice than TCs during primary drying.
3. Tempris sensors are very good at monitoring the ice nucleation process during freezing

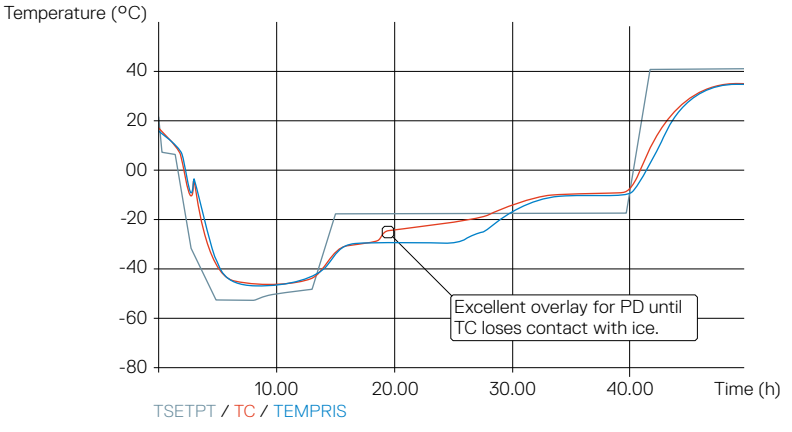
Dual chambered syringe

Chamber 1: freeze-dried therapeutic =protein (1ml).
Chamber 2: reconstitution diluent (4ml).
Low filling height of ~ 0.7 cm in 1 ml.

Center



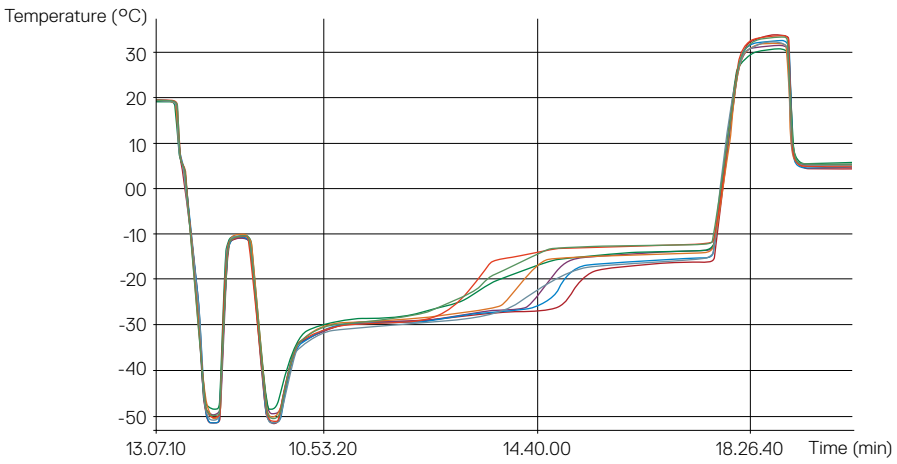
Edge

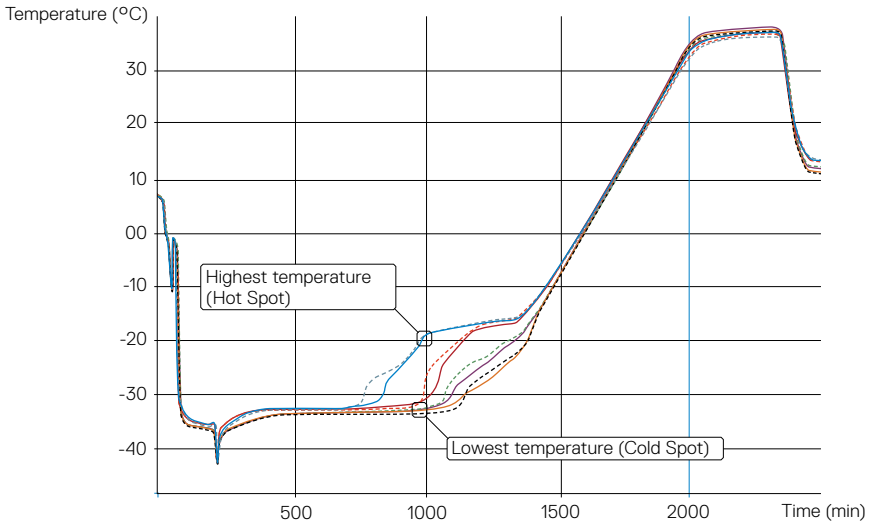


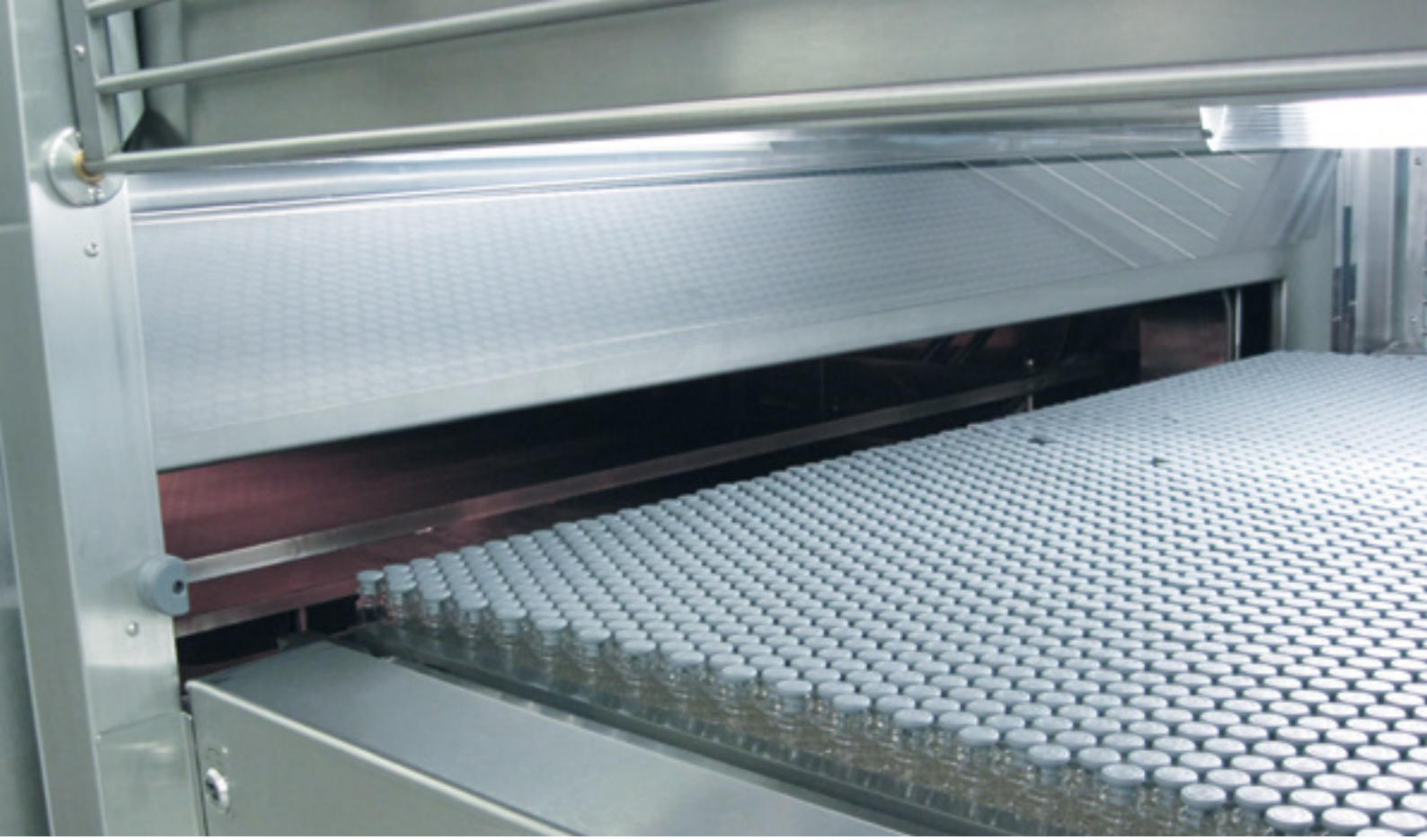
Performance Qualification (PQ): Mapping & Monitoring of Hot and Cold Spots (HCS) with Tempris

Performance Qualification (PQ) plays an important role in modern approaches towards process validation from as early as lab scale development up to routine manufacture, particularly in aseptic lyophilization technology.

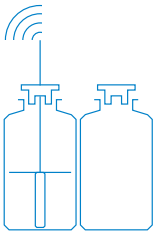
Case studies showed relevant temperature differences between single vial positions (center vs. edge) and across different shelves (depending on the distance to the condenser) within commercial scale lyophilization. Standard lyo-cycles had been instrumented with Tempris.
With the definition of hot and cold spots (HCS) during Performance Qualification (PQ), employing a single-vial method proved to be practical and reliable during routine use, particularly for freezing step optimization and primary drying end-point determination.

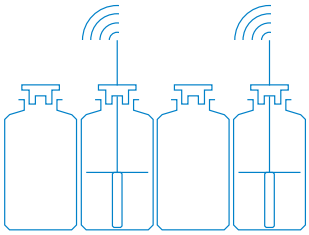


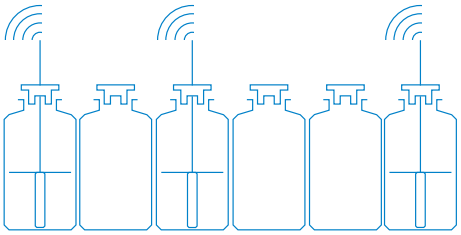




Scale-Up







Tempris Scale-Up and Transfer

For successful lyo-cycle transfer during scale-up to a larger batch size or change of the freeze-drying equipment, data needs to be provided to the regulatory body to prove the successful transfer due to necessary change in the production equipment or production site. This is to demonstrate that the transfer does not have any effect on the end product quality, by comparing the freeze-drying runs.

Tempris can help you

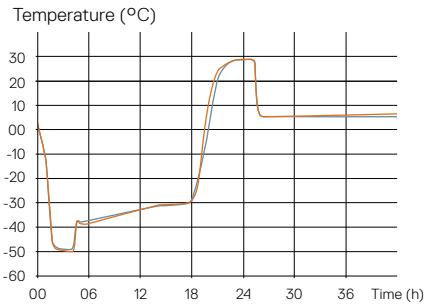
- Tempris is easy to install in any freeze-dryer
- Tempris provides the data required for successful lyo-cycle transfers

Tempris measurement data can be used for lyo-cycle validation and saved and archived for regulatory purposes.

Tempris supports continuous monitoring in routine manufacturing, thus providing easy access to supportive data.

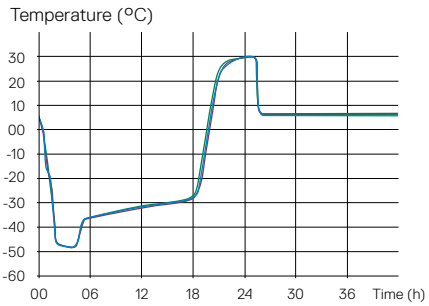
Lyo-Cycle Transfer with Tempris

Freeze dryer A



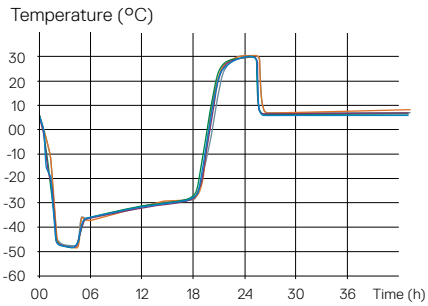
Example: Transfer of lyo-cycle from freeze-dryer A (24 m² / 258 sqft without ALUS®) to freeze-dryer B (33 m² / 355 sqft with ALUS®)

Freeze dryer B



Lyo-cycle temperature profiles from different runs on both freeze-dryers are superimposed to demonstrate that the lyo-cycles are equivalent.

Overlay Freeze dryer A+B



No further assessment of upper and lower temperature limits is required.

Tempris Services

Our Tempris team has years of experience in system installation and Performance Qualification (PQ) of freeze dryers along with assisting our customers using Tempris for production transfer and scale-up.

Pharmaceutical companies are currently experiencing skill shortages in the following areas:

- Operating Tempris systems for best results.
- Using Tempris for freeze-dryer Peformance Qualification (PQ).
- Using PQ data for lyo-cycle optimization during scale-up & transfer.
- Statistical analysis of data obtained.
- Preparation of validation reports for submission to regulatory bodies such as FDA and EMA.

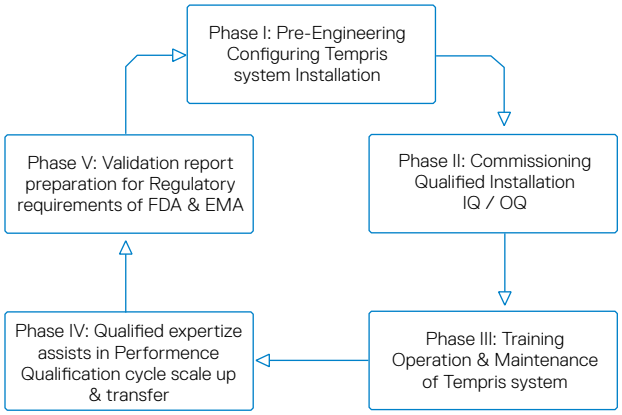
As a result of skill shortages, pharmaceutical companies are facing increasing costs and less productivity. To address these issues, the Tempris team together with FD experts from reputed contract research organizations (CROs) designed a complete service for modern process validation to be carried out in agreement and close cooperation with our customers.

This service is most beneficial for pharmaceutical companies as it reduces the number of lyo-cycles and process time required for cycle-development and cycle optimization significantly.

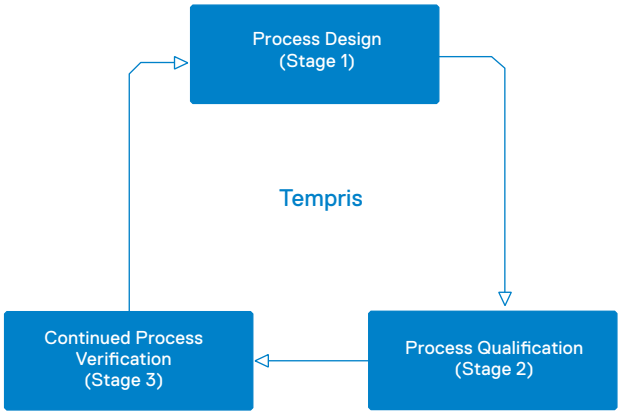
The Tempris Modern Process Validation service includes:

- provision of qualified personnel
- freeze dryer performance qualification (PQ)
- hot and cold spot (HCS) detection
- lyo-cycle scale-up and transfer using Tempris
- development of optimized and reproducible lyo-cycles
- preparation of validation reports containing data for regulatory requirements such as Common Technical Document (CTD), section 32P3

Complete Tempris Service



Modern Process Validation Approach

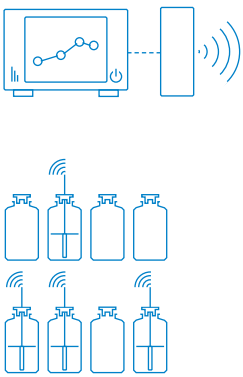


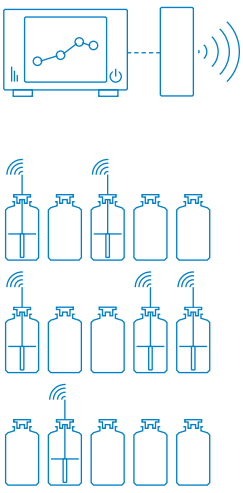
Easy to Retrofit

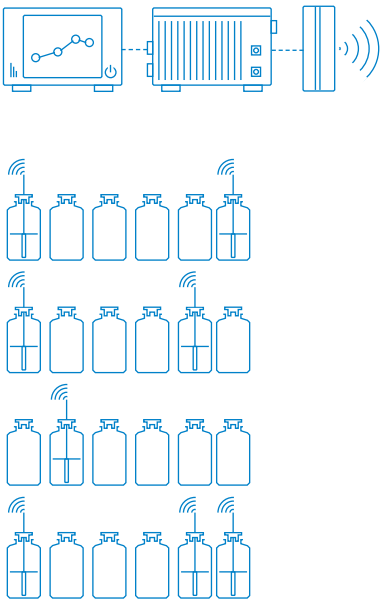
Tempris is a modular system which can be retrofitted easily to any type of laboratory, pilot and production freeze dryer, regardless of freeze-dryer dimension, shape and design.

Our Tempris engineering team makes sure that your Tempris system is configured exactly according to your User Requirement Specifications (URS).

Our services include engineering, commissioning, Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), training, system maintenance, calibration and technical support.





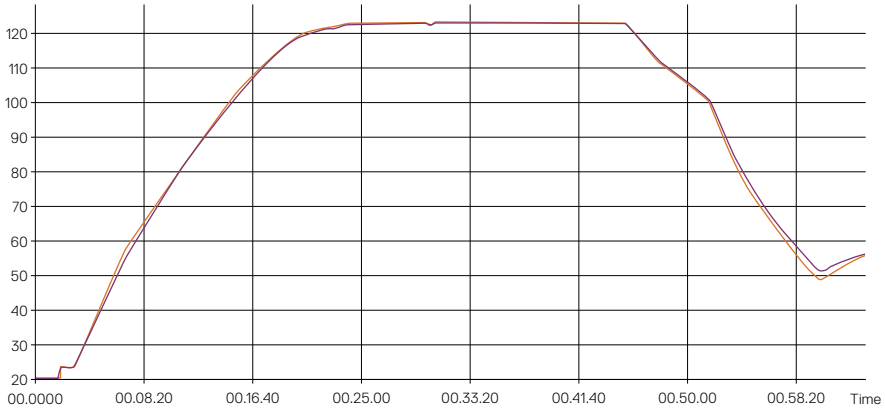


Other Applications

Tempris-4-S Applications.

Terminal sterilization of parenteral drugs and products is an important requirement for Biotechnology and Pharmaceutical companies in order to meet regulatory requirements. These industries are striving very hard to achieve the requirements while continuing to make improvements to their manufacturing standards and increase productivity, with the introduction of automatic loading and handling systems. However, these systems limit the manufacturer's ability to measure the product temperature (Tp) accurately. Wired temperature sensors are not compatible with the automated systems. Therefore they have to measure the Tp with reference bottles which are placed at a distance from the commercial product, increasing the risk of temperature difference between the commercial product and reference bottles. The introduction of Tempris-4-S, a real-time Tp monitoring system will overcome all the limitations of wired sensors and reference bottles and offers the following:

- Real-time Tp data to PLC / SCADA
- More representative and highly reliable Tp data
- Detection and monitoring of extreme hot and cold spots (HCS) inside the sterilizer
- Tempris as a PAT tool for implementing modern process validation for "Parametric Release" of parenteral products especially as a process control to justify release for sterility without pharmacopoeial sterility testing (parametric).



Sterilizing equipment:

- Hot water shower process
- Steam air mixture process
- Saturated steam process

Products to be sterilized and of special interest due to physical and chemical instability (i.e., F0 concept to be applied):

- Oncology drugs
- Albumin and plasmaproteins derived from blood
- Immunoglobulins
- Thrombolytics
- Parenteral nutrition products such as lipid emulsions

Primary packaging:

- Infusion bottles
- Vials
- Single-chamber bags
- Multi-chamber bags
- Syringes

System accuracy:

± 0.3°C @ 0°C to 140°C

tempris sensor technology

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