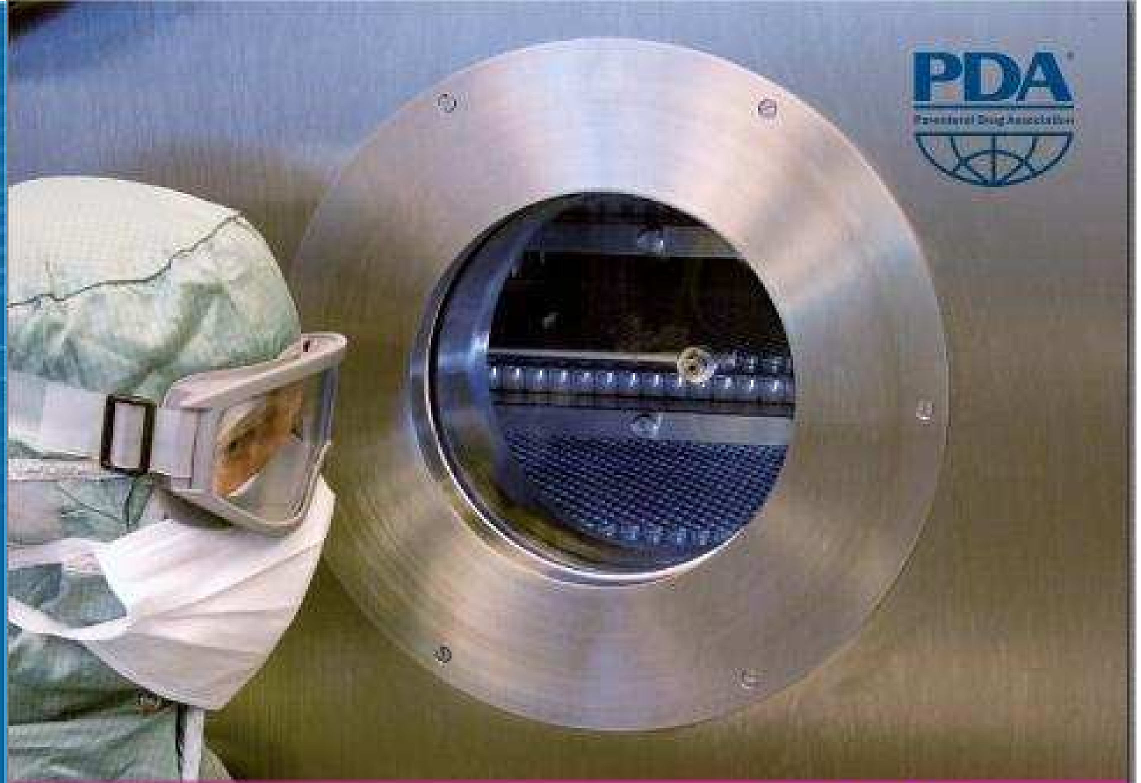
Connecting People, Science and Regulation®



2018 PDA Europe

Freeze Drying in Practice

23–27 April 2018 | Training Course

23–27 April 2018

Martin Christ Gefriertrocknungsanlagen GmbH
Osterode (Harz) | Germany

www.pda.org/URL

Company portrait

Lyo Engineering is your partner in pharmaceutical industry and medical engineering in the areas of management / quality assurance / engineering with more than 10 years of experience in pharmaceutical plant engineering and construction in the fields of project handling and quality assurance.

Among other things our business activities include project management for international freeze drying projects in pharmaceutical industry, planning and monitoring of technical transfer projects of fill- / finish areas and all aspects of GMP quality assurance, for instance classification of equipment components in accordance with GMP risk analysis as qualification basis, GMP-based employee training, performance of external and internal audits, planning and monitoring of acceptance tests (FAT / SAT) and qualification phases (DQ / IQ / OQ / PQ), as well as the creation of the pharmaceutical technical documentation.

We gladly support you in the successful implementation of projects in regulated environments from the URS to the handover to the production.

Lyo Engineering

GMP is our passion!

Theory 4:
Process engineering tools (sensor technology)

- thermal resistance measurement
- pressure and vacuum measurement
- barometric pressure measurement
- metric pressure measurement
- wireless temperature measurement (Amphenol)
- conductometry
- camera systems

Thermal resistance measurement (platinum temperature sensor)

Platinum temperature sensors use the effect of temperature dependence of the electric resistance of the precious metal platinum. The resistance increases at higher temperatures, it is a positive temperature coefficient, such sensors are named PTC (positive temperature coefficient).

Abbildung 6: Temperatursensorproduktion unter Reinraumbedingungen

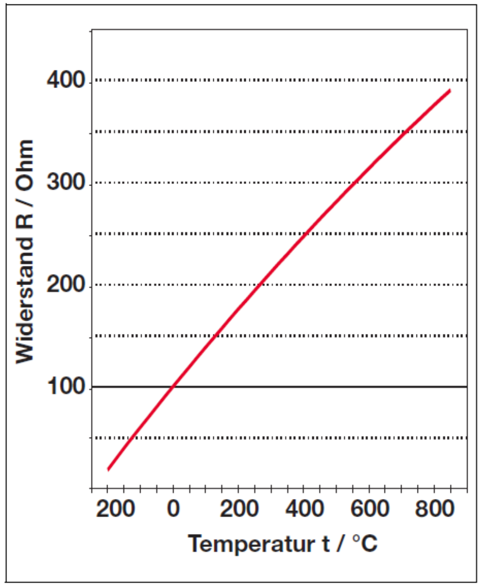


Abbildung 1: Pt100-Kennlinie

Thermal resistance measurement (platinum temperature sensor)

Besides the “standard” PT100 there are temperature sensors with higher nominal values for instance PT500, PT1000.

They have a higher sensitivity, because the increase factor of characteristic curve is directly proportional to the par value R_0.

Their advantage is a larger variation of their resistance depending on the temperature.

Resistance changes (temperature range up to 100 °C)

- 0,4Ω /K at PT00 temperature sensor
- 2,0Ω /K at PT500 temperature sensor
- 4,0Ω /K at PT1000 temperature sensor

Abbildung 12: Laserabgleich der Platin-Chip-Temperatursensoren

Thermal resistance measurement (platinum temperature sensor)

The long-time behavior is another important factor apart from tolerance of temperature sensors. It is responsible for the compliance of measurement uncertainty. The values listed in the data sheets are guide values. They were determined into an oven with normal atmosphere by temperature sensors.

The processing of temperature sensors and the materials with which it comes into contact can influence the long-term stability. In order to determine the long-term stability in each case of the existing construction a regular calibration in their intended conditions of use is necessary.

Abbildung 9: Automatisierte Produktion drahtgewickelter Platin-Glas-Temperatur-sensoren

Thermal resistance measurement (platinum temperature sensor)

Tolerance classes

Toleranzklasse	Sensor-Kategorie	Temperaturbereich in °C	Toleranz in K
Klasse AA	Dünnschicht Draht	-50 ... +200 -70 ... +250	± (0,10 K + 0,0017 × |t|
Klasse A	Dünnschicht Draht	-70 ... +300 -200 ... +600	± (0,15 K + 0,002 × |t|
Klasse B	Dünnschicht Draht	-70 ... +600 -200 ... +850	± (0,30 K + 0,005 × |t|
Klasse 0,5	Dünnschicht Draht	-70 ... +600 -200 ... +850	± (0,50 K + 0,006 × |t|
			|t| = Messtemperatur in °C (ohne Vorzeichen)

Tabelle 1: Toleranzklassen - Temperaturgültigkeitsbereich

Temperatur in °C	Klasse AA in K	Klasse A in K	Klasse B in K	Klasse 0,5 in K
-200		0,55	1,30	1,70
-70	0,22	0,29	0,65	0,92
0	0,10	0,15	0,30	0,50
100	0,27	0,35	0,80	1,10
250	0,53	0,65	1,55	2,00
350		0,85	2,05	2,60
600		1,35	3,30	4,10
850			4,55	5,60

Tabelle 2: ±-Toleranz in K je Klasse

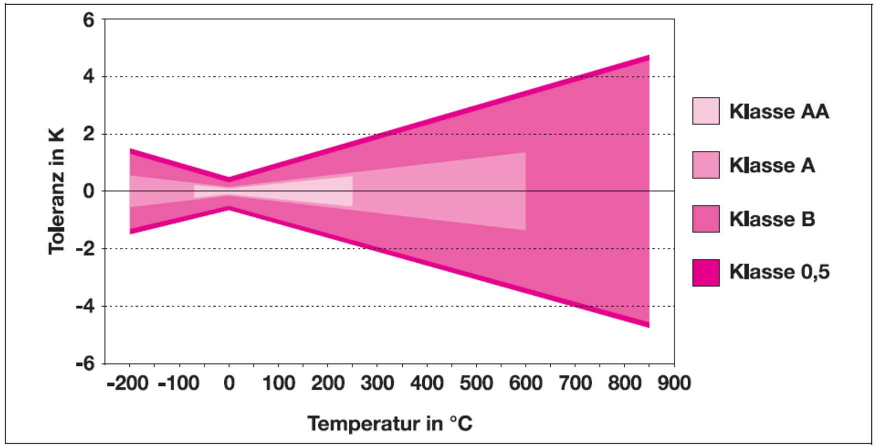


Abbildung 2: Toleranzverlauf in Abhängigkeit von der Temperatur

Thermal resistance measurement (platinum temperature sensor)

Construction PT-sensor

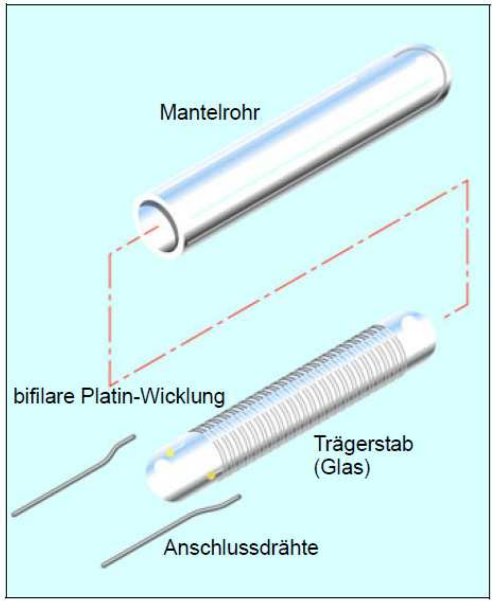


Abbildung 7: Prinzipieller Aufbau von Platin-Glas-Temperatursensoren

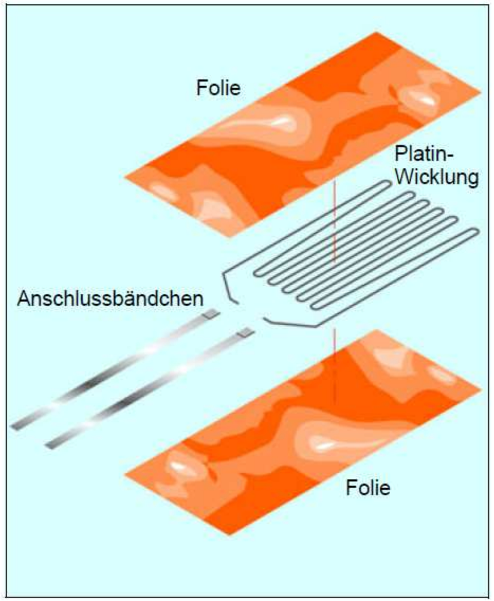


Abbildung 11: Prinzipieller Aufbau von Platin-Folien-Temperatursensoren

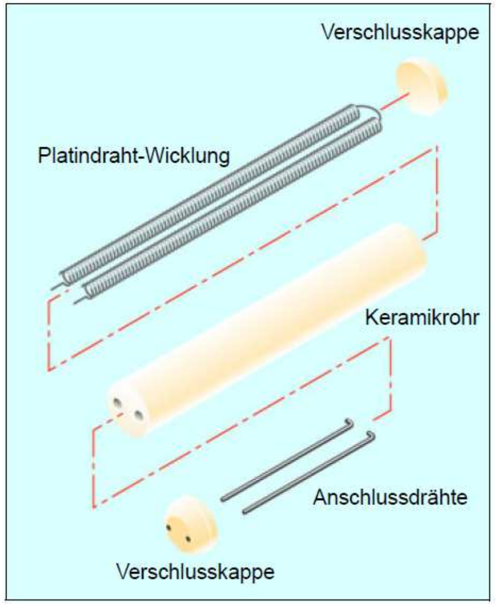


Abbildung 10: Prinzipieller Aufbau von Platin-Keramik-Temperatursensoren

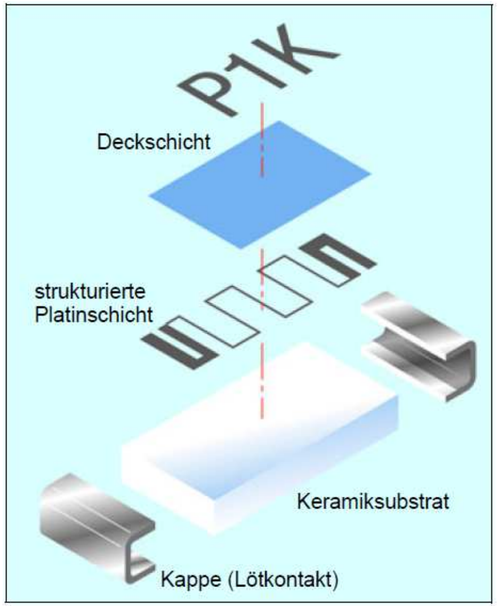


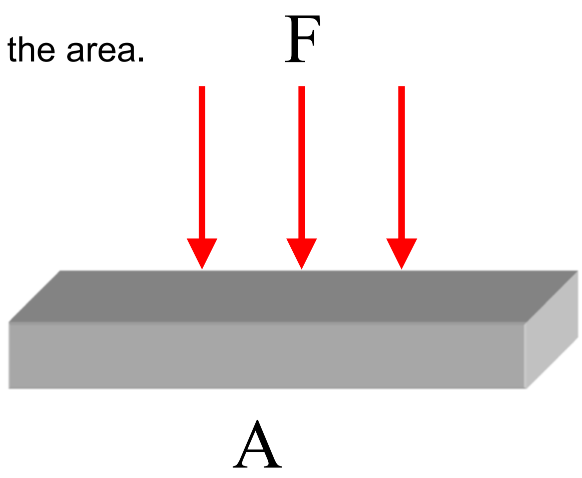
Abbildung 16: Prinzipieller Aufbau von Platin-Chip-Temperatursensoren in SMD-Bauform

Definition

How is pressure defined?

Pressure p is defined as the **force F** exerted on an **area A** divided by the size of the area.

$$p = \frac{F}{A}$$



Separate technical units of pressure:

newtons per square (*n/m2*), **Pascal** (*Pa*), **bar** (*bar*) und **Pound-Force per square inch** (*Psi*).

Furthermore **outdated units** are still in use: **technical atmosphere** (at) and **physical atmosphere** (atm) and **Torr.**

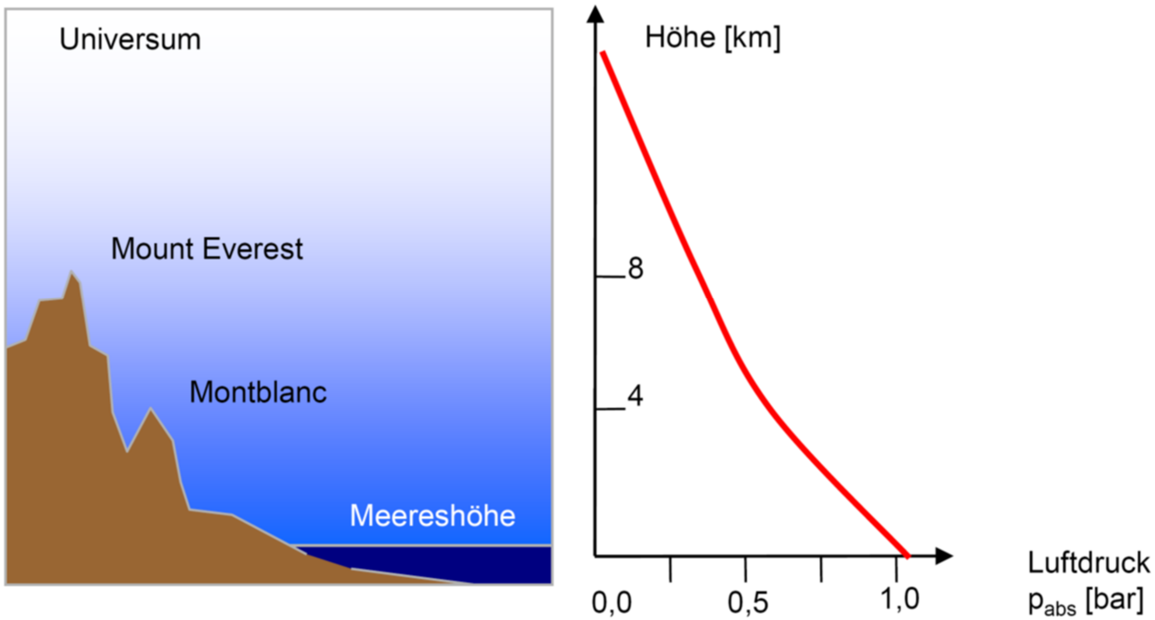
Each unit can be transferred to another:

1 bar = 100 000 pa ~ 14,504 psi ~ 1,0197 at ~ 0,98692 atm ~ 750,06 Torr.

Definition

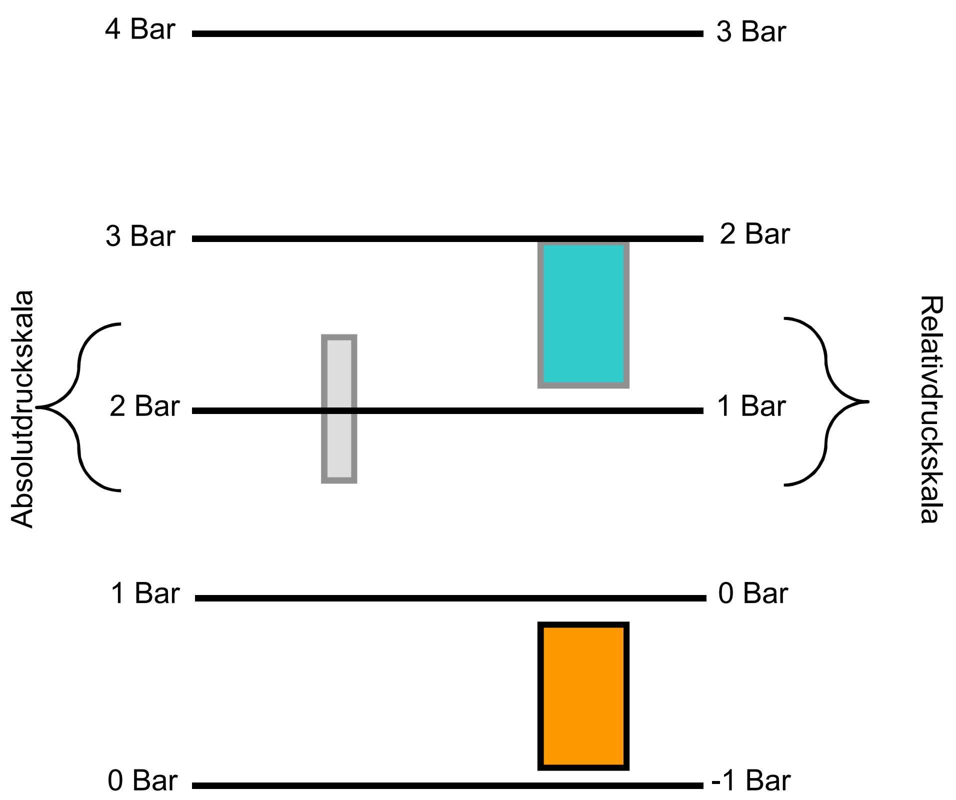
P_{abs}

Ein Druck, der auf den luftleeren Raum des Universums bezogen ist



Der Bezugspunkt wird in der Praxis mit einer Vakuumpumpe erzeugt.

Pressure scale



Process engineering tools (sensor technology)

Druckbereich	Druck in hPa (mbar)	Moleküle pro cm^3	mittlere freie Weglänge
Umgebungsdruck	1013,25	$2{,}7 \times 10^{19}$	68 nm
Grobvakuum	300…1	$10^{19}…10^{16}$	0,01…100 µm
Feinvakuum	$1…10^{-3}$	$10^{16}…10^{13}$	0,1…100 mm
Hochvakuum (HV)	$10^{-3}…10^{-7}$	$10^{13}…10^{9}$	100 mm…1 km
Ultrahochvakuum (UHV)	$10^{-7}…10^{-12}$	$10^{9}…10^{4}$	$1…10^{5}$ km
extrem hohes Vakuum (XHV)	$<10^{-12}$	$<10^{4}$	$>10^{5}$ km

- rough vacuum: vacuum cleaner (> 0,5 bar)
- fine vacuum: low-pressure gas discharge lamps
- high vacuum: electron tubes, particle accelerator
- ultra-high vacuum: particle accelerator, near-earth space, frequent at equipment in the semiconductor industry
- extremely high vacuum: space, rarely at semiconductor industry

Pressure measurement (vacuum and overpressure)

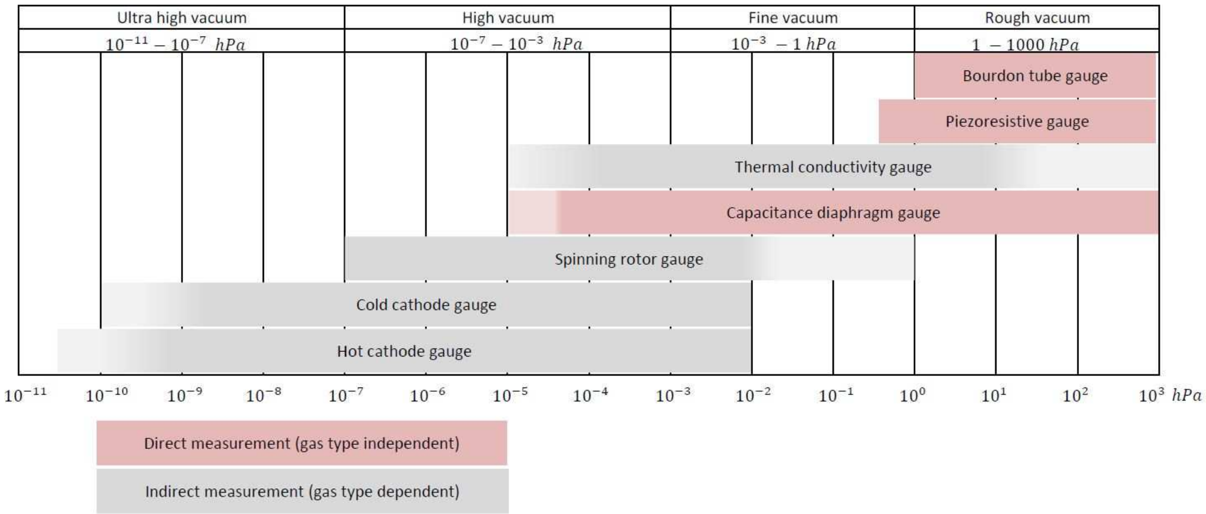
One of the most important parameters is the pressure measurement

- during a running process the pressure measuring device must have a high accuracy (freeze-drying and sterilisation)
- during a freeze-drying the pressure measurement may be used for comparative pressure measurement (capacitive sensor / Pirani)
- during a sterilisation process the pressure measurement may be used for determining saturated steam conditions

Pressure measurement (vacuum and overpressure)

The most common vacuum sensors at freeze-drying are:

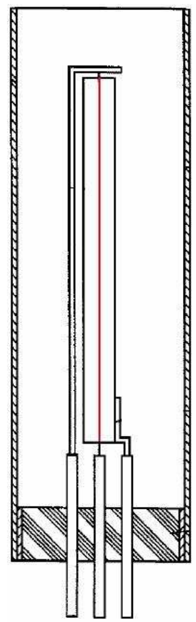
- conductive pressure measurement systems (Pirani)
- capacitive pressure measurement systems



Pressure measurement (vacuum and overpressure)

Construction of conductive pressure measurement systems (Pirani)

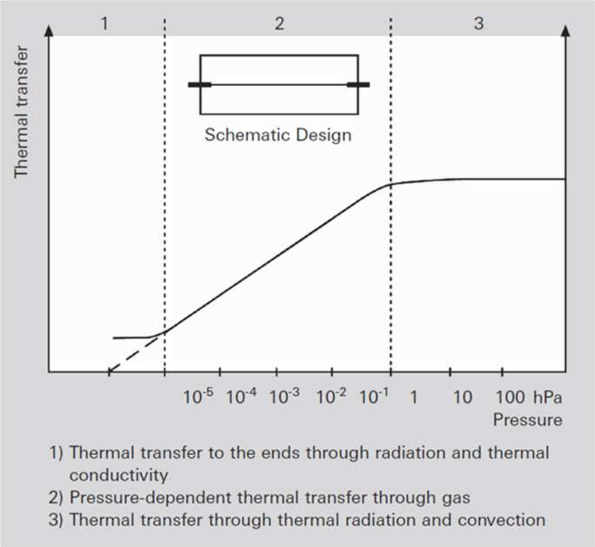
Heat up the wire approximately at a temperature of 110°C to 130°C. The heated wire forms a part of a Wheatstone bridge.

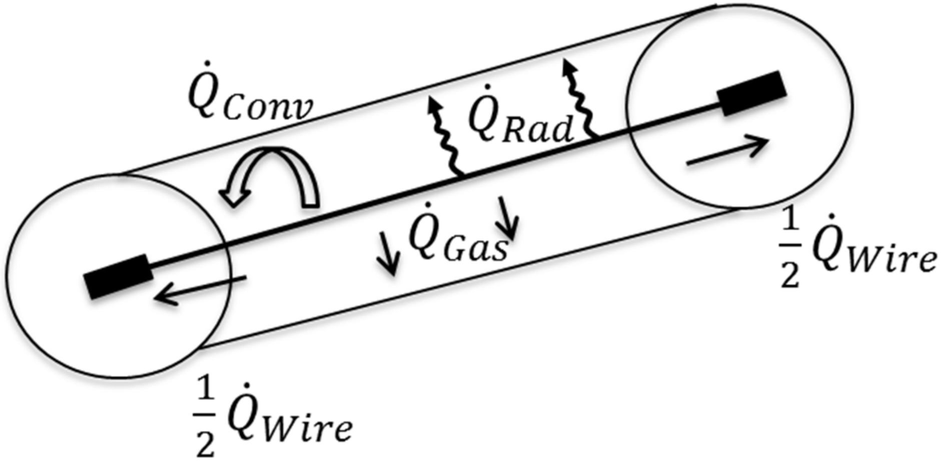


Pressure measurement (vacuum and overpressure)

Construction of conductive pressure measurement systems (Pirani)

The Pirani sensor works with radiation which changes depending on the available pressure.





Pressure measurement (vacuum and overpressure)

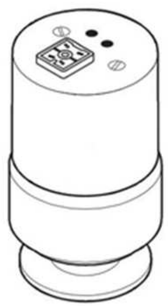
Adjustment of Pirani tube:

- adjustment of Pirani tube takes place under real installation conditions
- depending on the age and usage of the Pirani sensor it is necessary to subject a zero point calibration (offset)

Pressure measurement (vacuum and overpressure)

When using a Pirani tube it should be remembered:

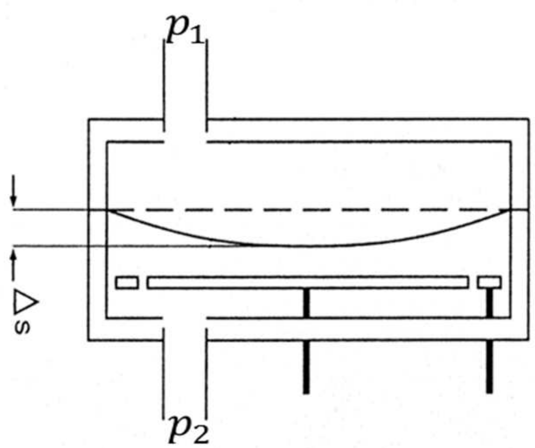
- vertical installation position
- using a Pirani sensor for a long period it can be necessary to change those, because the device closes
- depending on the age and usage of the Pirani sensor it is necessary to subject a zero point calibration (offset)
- the accuracy of the Pirani sensor depends on the measured gas due



Pressure measurement (vacuum and overpressure)

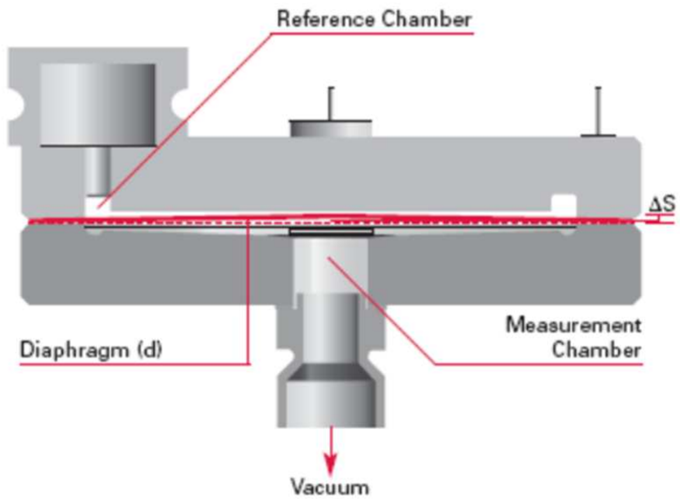
Construction of a capacitive pressure measurement system:

- a capacitive pressure measurement system is independent of the measured gas due
- a flexible membrane represents the measurement equipment



Pressure measurement (vacuum and overpressure)

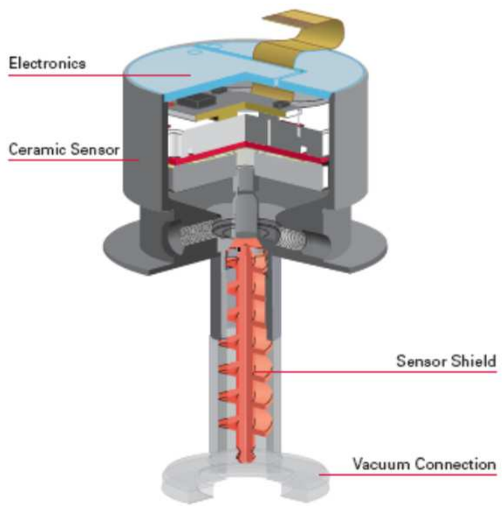
Construction of a capacitive pressure measurement system:



Pressure measurement (vacuum and overpressure)

Construction of a capacitive pressure measurement system:

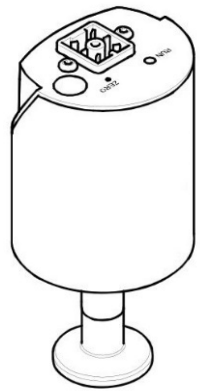
- To avoid risk within the measurement sensor, capacitive measurement sensors are heated. The temperature between 45 °C and 200 °C depends on the type of the sensor.
- At a freeze dryer which can be sterilized, measurements sensors should be used which have a higher temperature above 150 °C.



Pressure measurement (vacuum and overpressure)

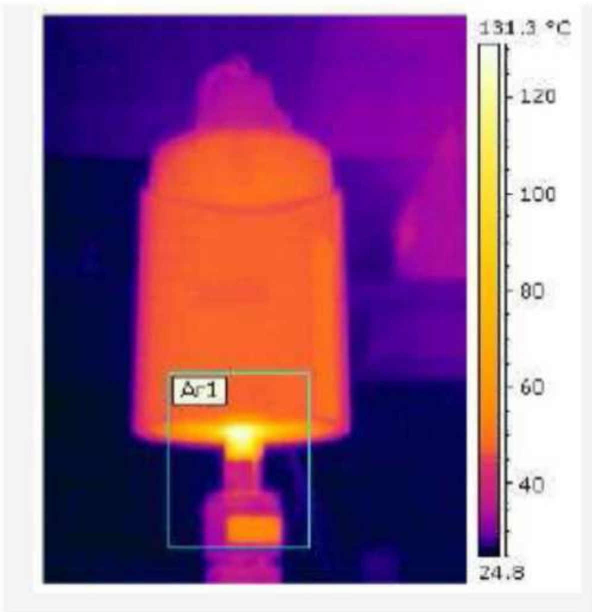
When using a capacitive measurement sensor it should be remembered:

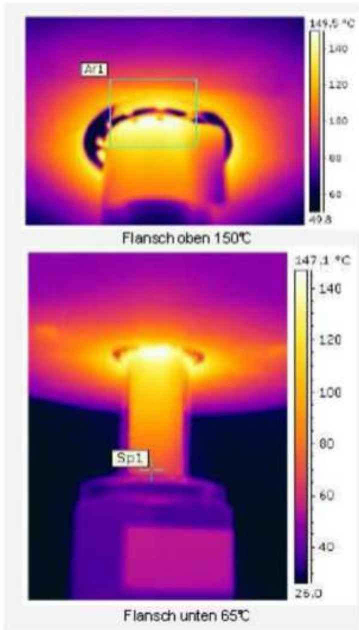
- measurement sensor have a heating up
- a contaminated membrane leads to an inaccurate measurement result
- note the installation position!



Pressure measurement (vacuum and overpressure)

Temperaturverteilung Anschlussrohr der 160°C beheizten CLR 39x





Temperatur in der Nähe der Bodenplatte des Gehäuses: ~ 150°C

Im Inneren der Messröhre sind alle prozessgasführenden Bereiche oberhalb 150°C

Comparative pressure measurement (Pirani / capacitive pressure measurement)

Pressure measurement

Principle:

pressure measurement for determining the end of main drying

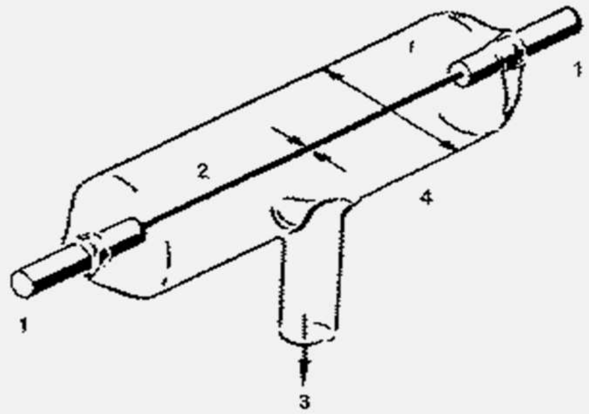
End of main drying

- no steam development
- pressure increase test

Measurement of camber pressure with

1. Pirani sensor (based on pressure dependence of heat dissipation to the environment of the hot wire placed inside; **depends on the type of gas**)

Pirani sonde



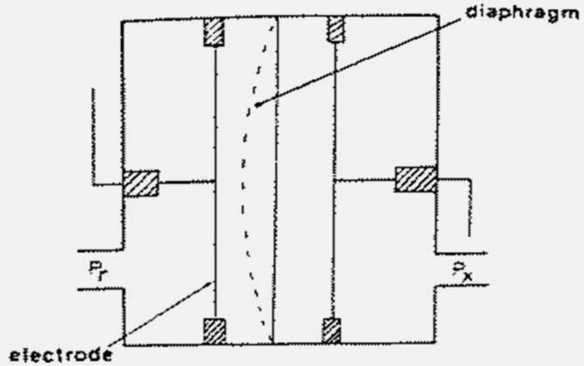
Comparative pressure measurement
(Pirani / capacitive pressure measurement)

Pressure measurement

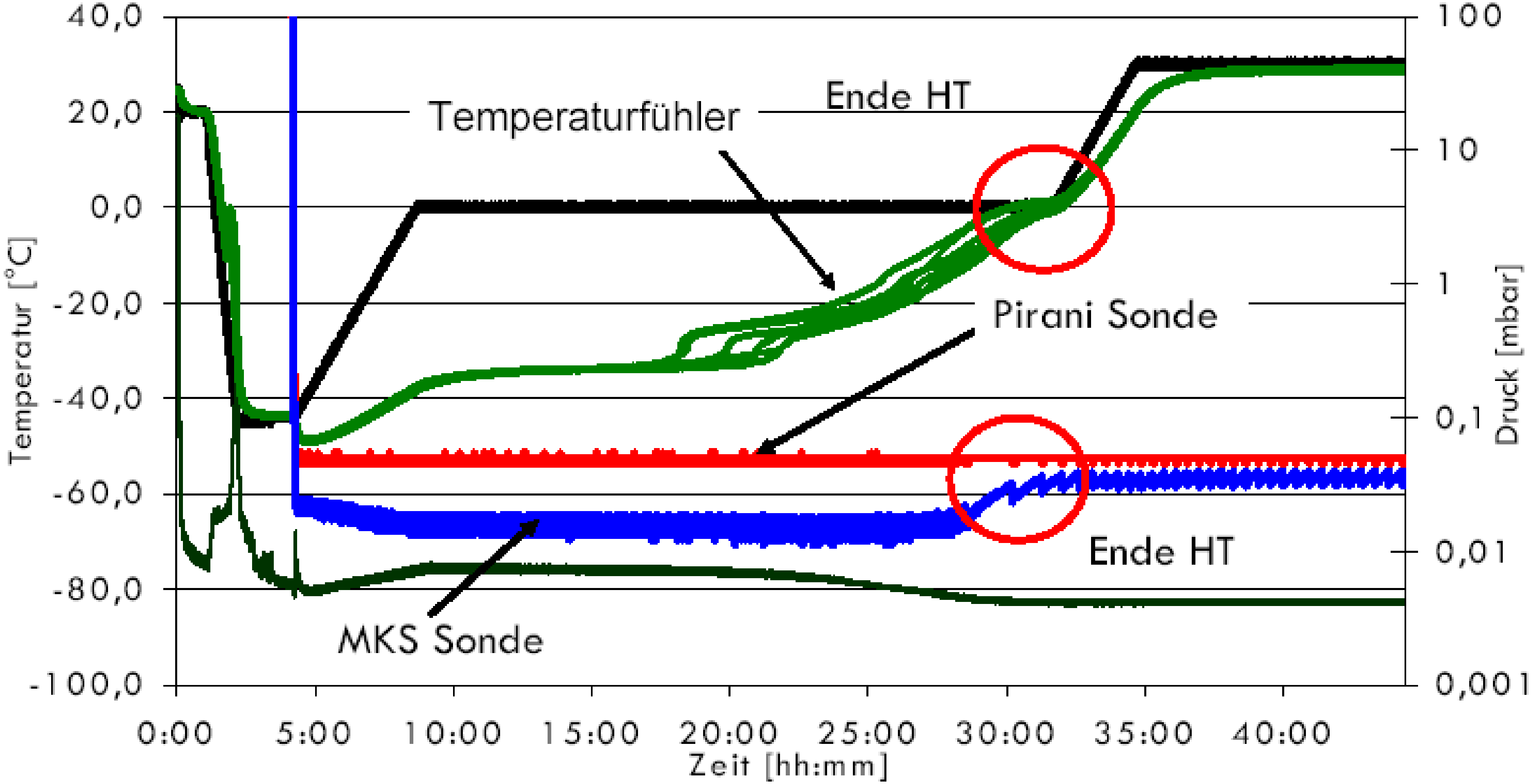
Measurement of camber pressure with

2. capacitive sensor (based on pressure-dependent of the membrane of electrical capacitor, **independent of the type of gas**)

capacitive manometer

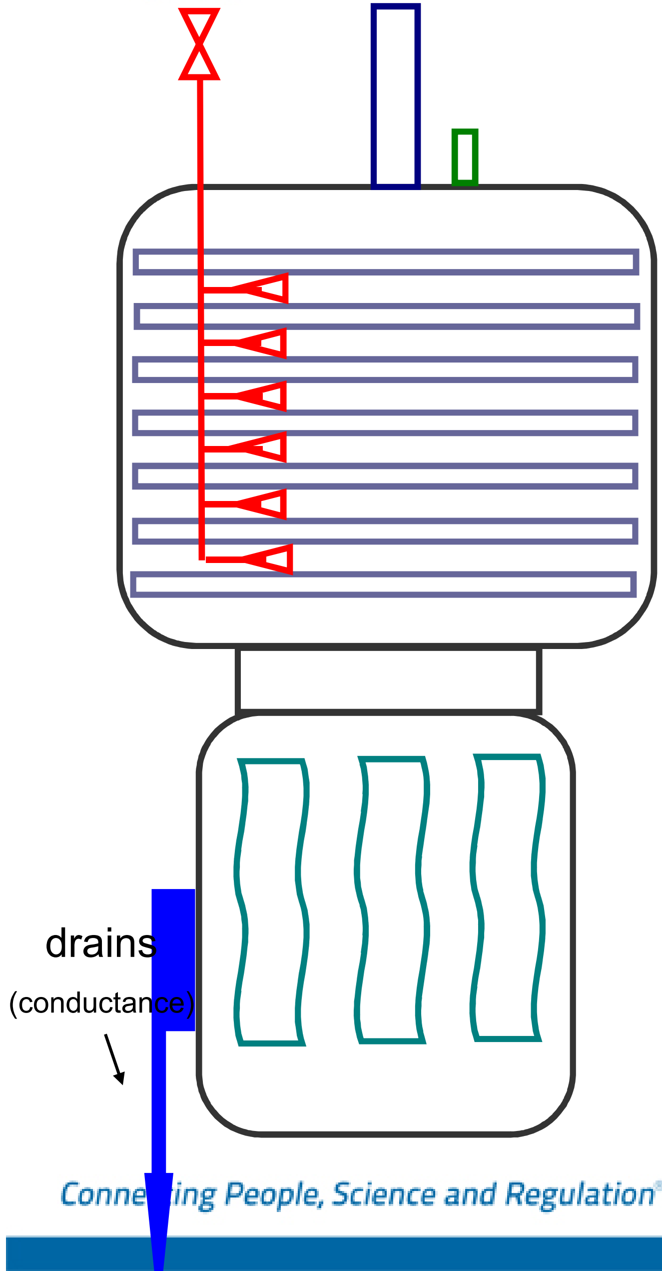


Comparative pressure measurement (Pirani / capacitive pressure measurement)



Comparing pressure measurement

- simultaneous measurement of camber pressure with a Pirani sensor and a capacitive sensor
- at the beginning shows the Pirani sensor a pressure which is higher than the pressure of the capacitive sensor (high content of water vapor)
- at the end of main drying the measured values of the two sensors approach each other
- the approach of the measured values shows a lower content of water vapor at the camber and it is an indicator for the end of main drying



Conductometry

In order to make the cleaning result of a CIP processes measurable a conductivity sensor is usually used.

The conductivity sensor should be adapted to the relevant requirements.

It should be designed for the expected temperatures of the measuring point (usually the sensor is located inside of the sterile boundary and will be charge with clean steam).

In order to validate the dosage and effectiveness of CIP, viz. also product and rinsing medium are (acids, alkalis) washed out

- The Fluids (e.g. sodium hydroxide, acetic acid) are injected with dosing valves into the suction line of the CIP-circulation pump. A conductivity sensor is required in circulation system to monitor the dosing.
- After cleaning the dosing fluids must be completely removed from the chamber. These include that the complete system must be rinsed with WFI The rinsing process is controlled with a second conductivity sensor at drain.

Condumax Indumax (both Endress+Hauser)

Wireless temperature measurement

These sensors are used for:

- temperature measurement
- determining relative humidity
- pressure measurement

Process control tools (sensor technology)

Wireless temperature measurement

Freeze Dryer Logger -
85C to +140C

Cryologger

-85C to +140C

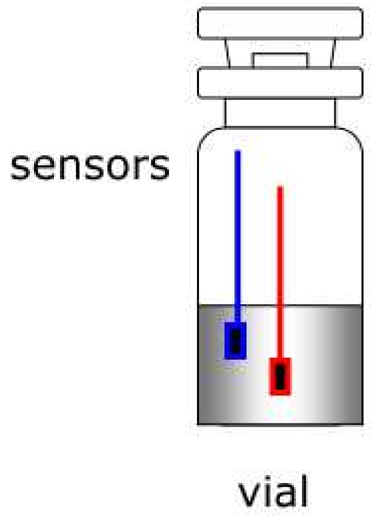
Process control tools (sensor technology)

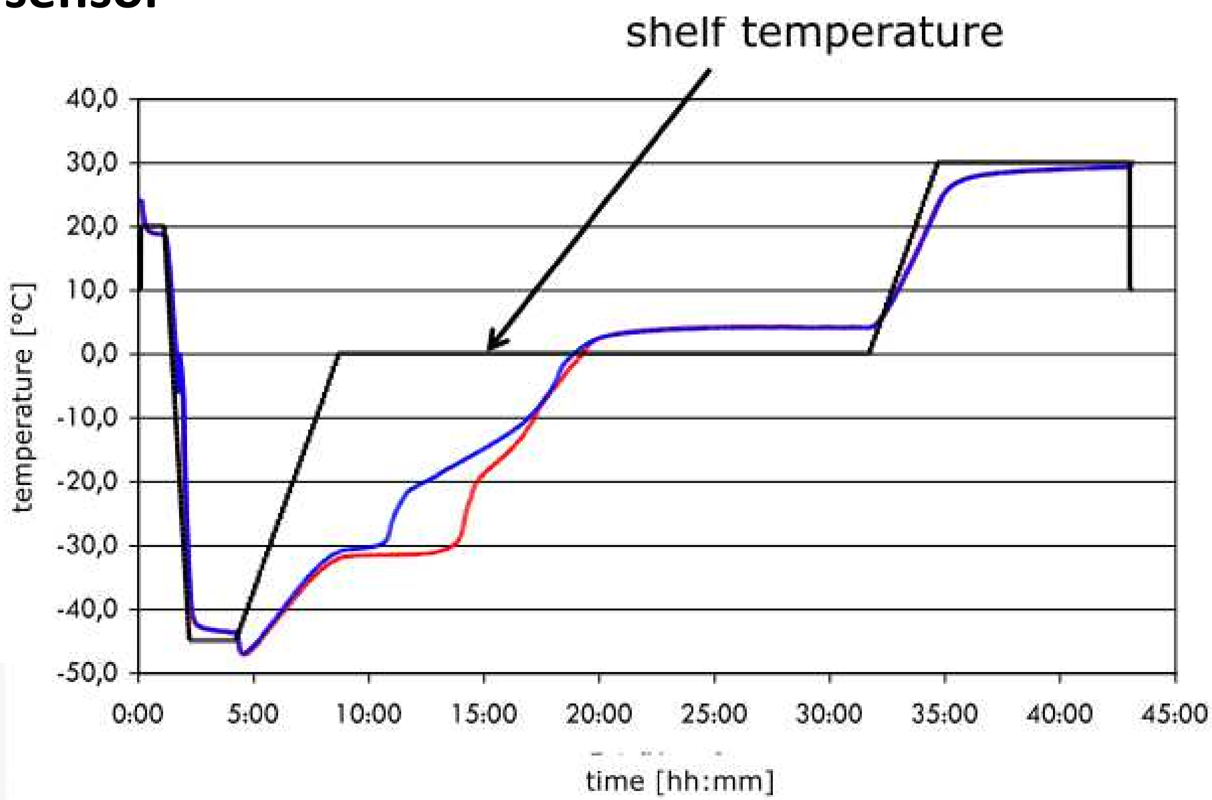
Wireless temperature measurement

positioning equipment

Process control tools (sensor technology)

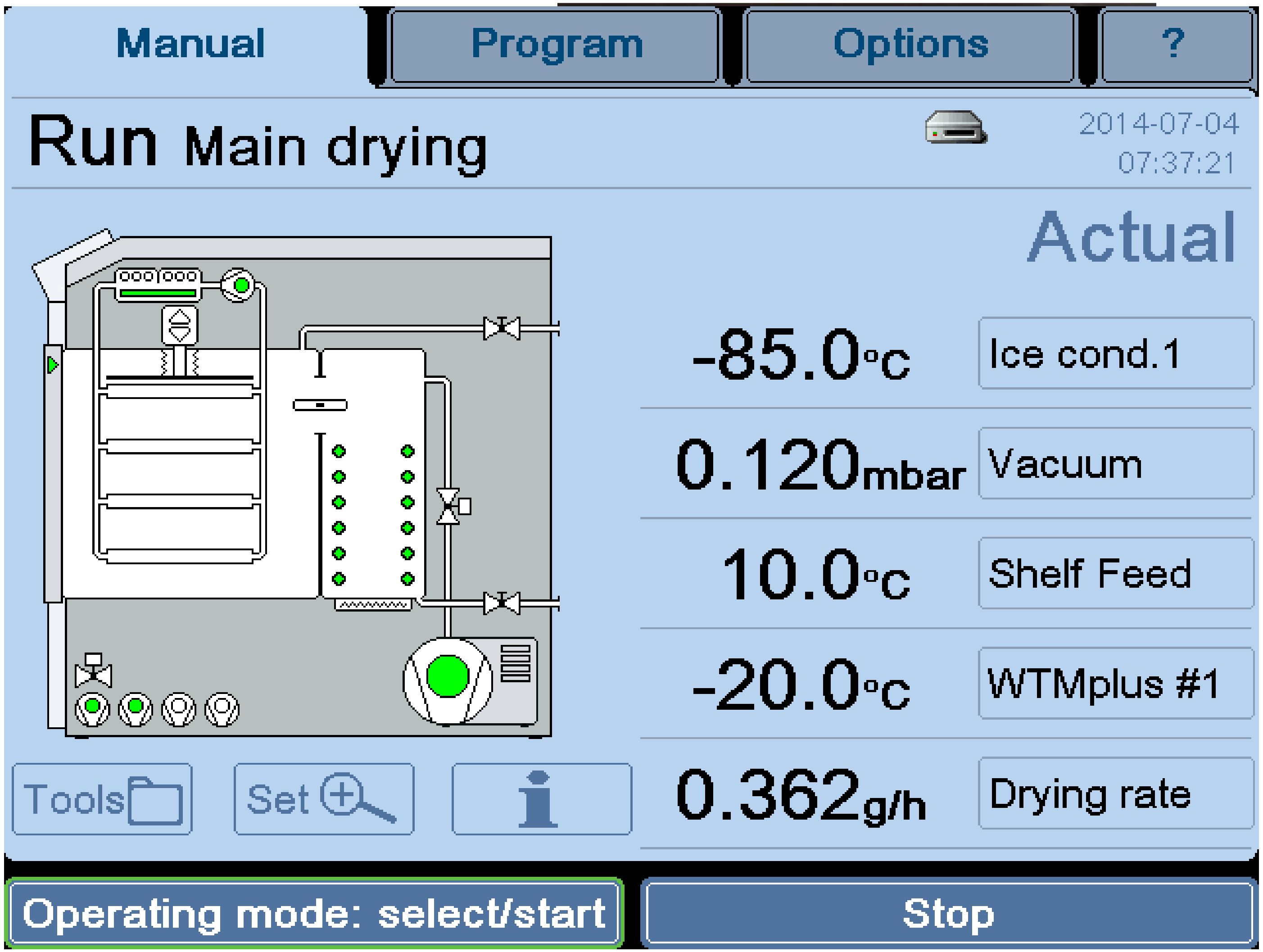
Principle: temperature sensor

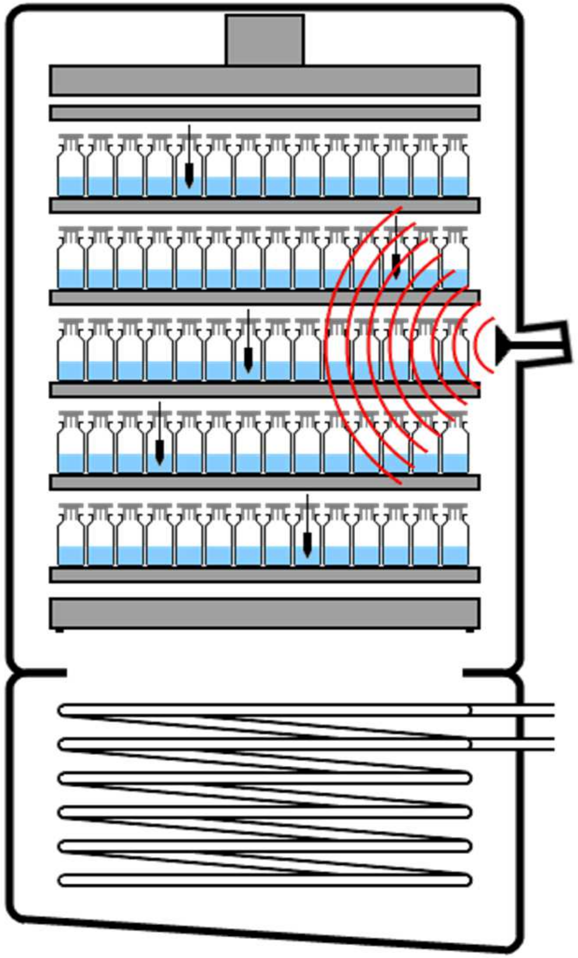




WTMplus „wireless“

Process control tools (sensor technology)





Functional principle WTMplus

- energy supply of the sensors by means of a radio frequency within in the 2.4 GHz range, i.e. no battery or other energy storing device necessary
- intermediate storage of energy by stimulation of a quartz crystal
- high precision temperature-dependent detuning of quartz-oscillation frequency
- transmission of frequency modulation via an antenna to the evaluation electronics for temperature determination

WTMplus

easy sensor positioning

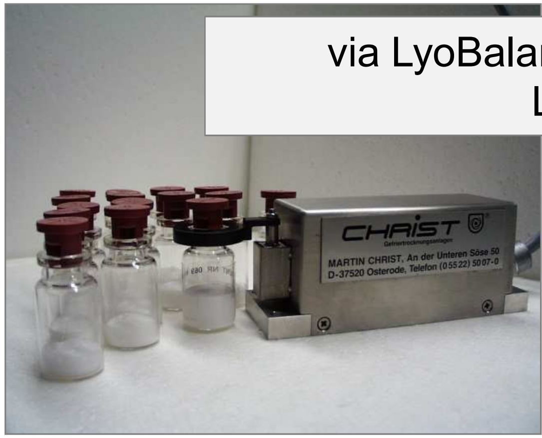
small, robust sensors

Process control tools (sensor technology)

Features
small and robust, also for 2R vials and bulk
no plugs and wires with cleaning and contact problems, GMP-design
small and robust, also for 2R vials and bulk
product temperature in the vial not influenced by energy input of conventional sensors
high accuracy ± 0.5 K , resolution 0.1 K
covers the entire lyophilization cycle (liquid, solid/frozen and dry)
free sensor positioning on shelves or in pre-defined grid square
fully integrated in system controller and process documentation

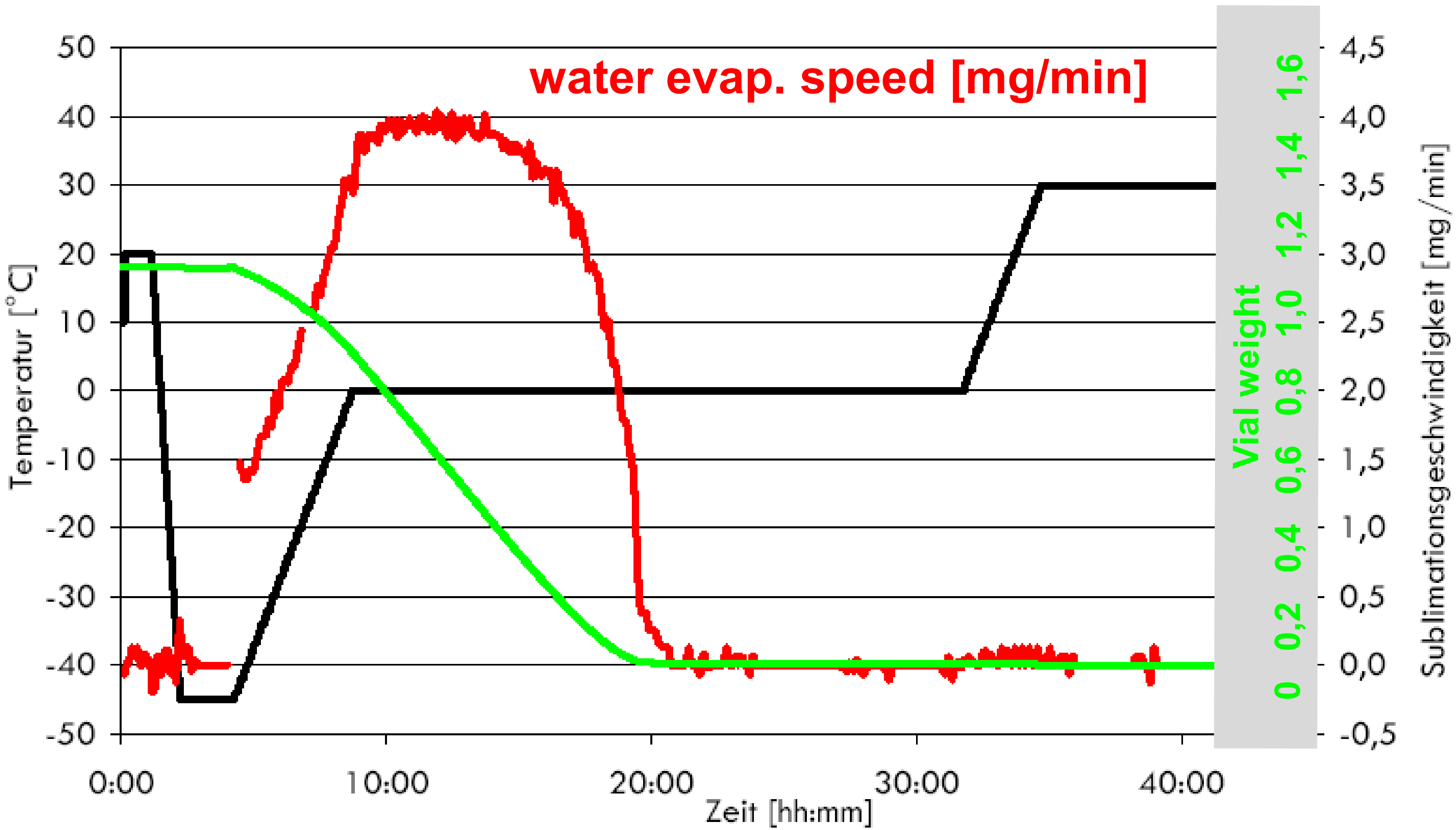
Measurement of drying rates

via LyoBalance (can be integrated in LSCplus units)

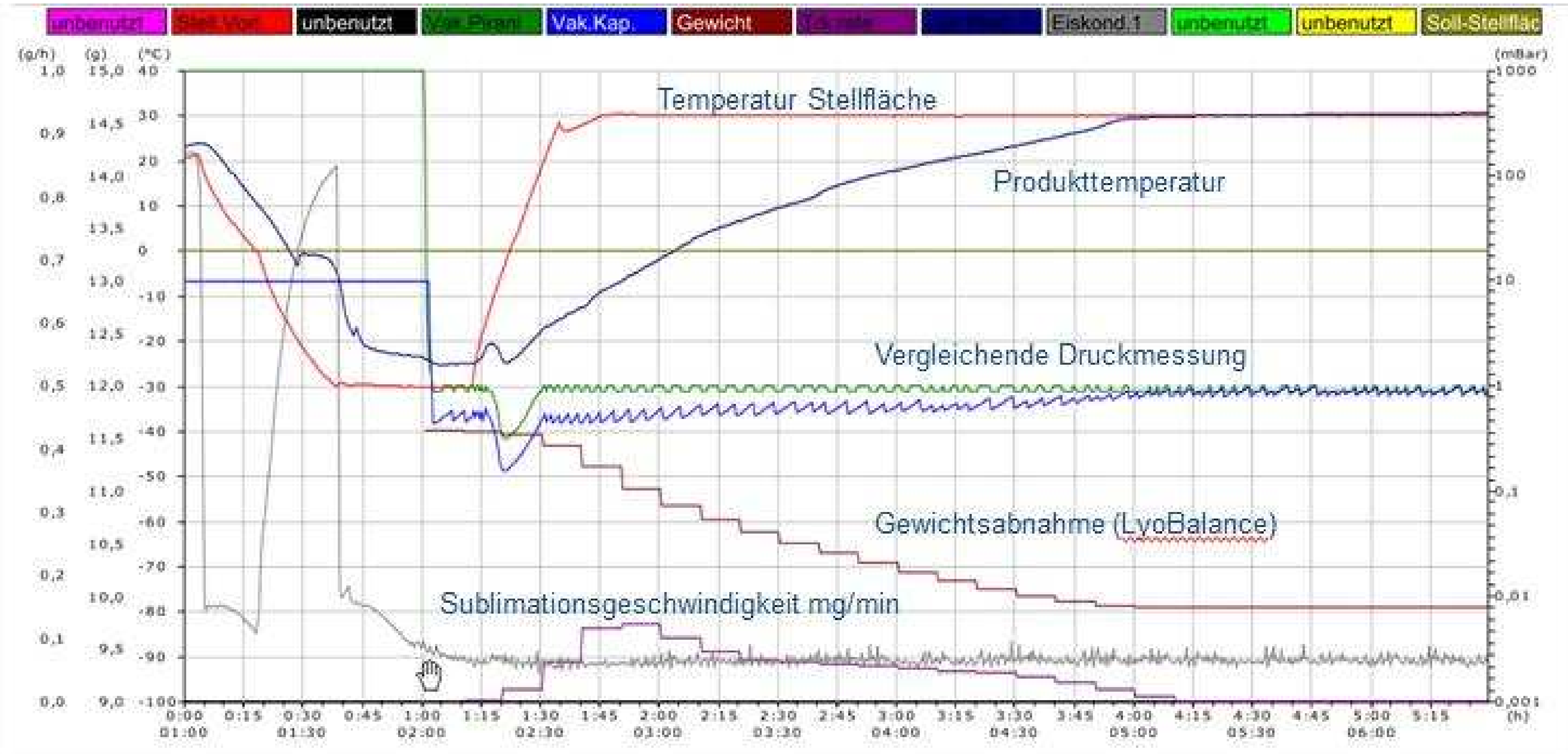


function principle	electromagnetic force compensation
weight determination	▪ via gripping arm, which can be lifted/unlifted in certain - customer defined - time cycles ▪ the weight of the vial is therefore detected periodically
application range	▪ temperatures of -40°C to +40°C ▪ resolution up to 30g vial weight: 0,001g
advantages	▪ can be placed onto every shelve position in the drying chamber ▪ drying process is not disturbed ▪ automatic documentation of the data ▪ can be used as controlling parameter for the process (main drying - final drying)

Speed of the sublimation from analysis with weight cell



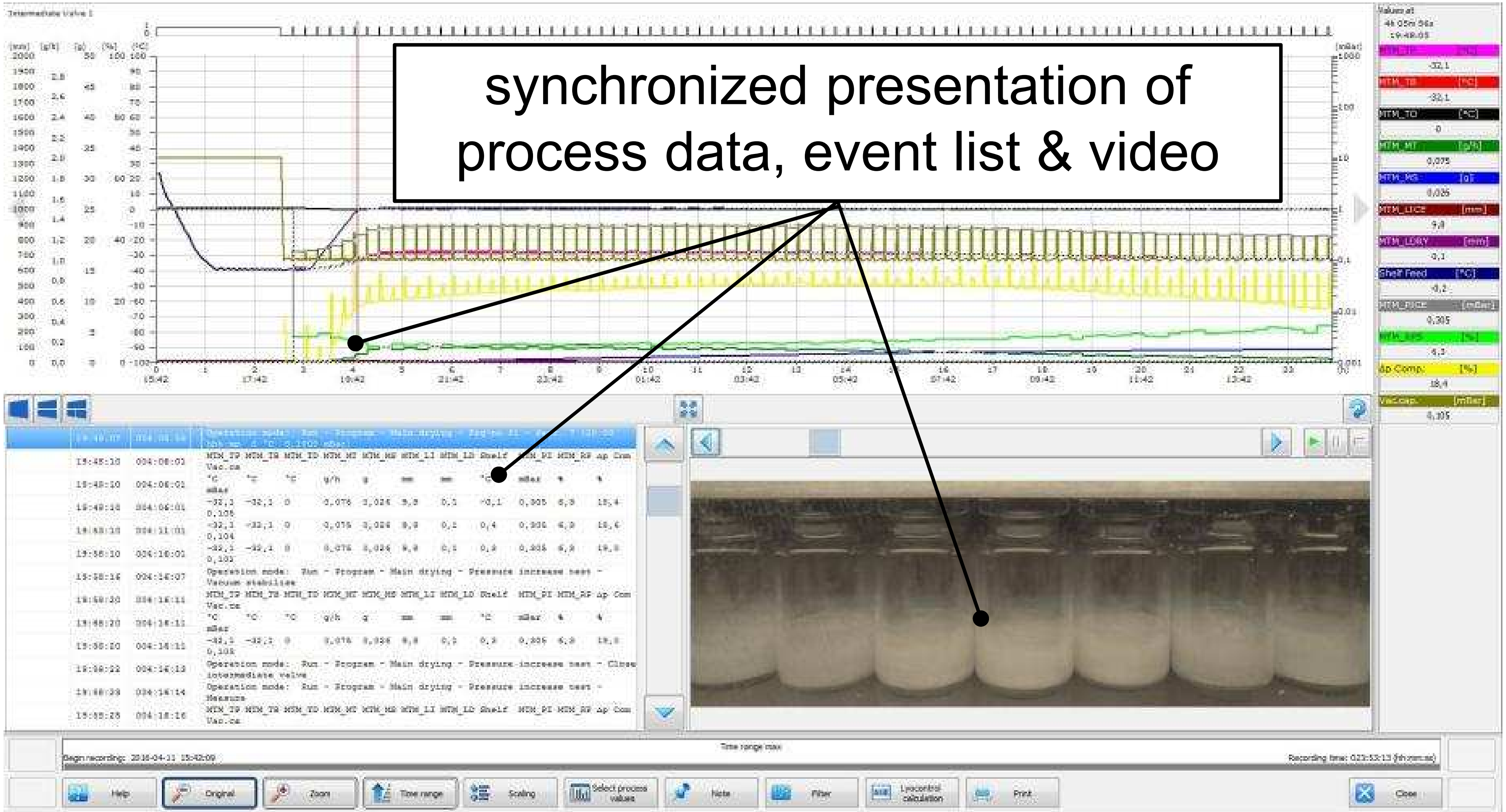
Idealized determination of end drying



Inline camera LyoCam

- monitor and analyze freeze drying processes
- intelligent data storage based on
  - process steps
  - process data (limits, alarms, …)
- fully integrated in process visualization LPCplus
- integrated in process data base (identical time stamp)
- equipped with LED lamps for low energy impact into the product
- up to 4 cameras in LPCplus
- standard sight glasses useable

Inline camera LyoCam



Lyo Engineering

GMP is our passion!