Company portrait

Die Pharmbiocon LSE ist Ihr Partner in Pharmaindustrie und Medizintechnik, in den Bereichen Management / Qualitätssicherung / Forschung und Entwicklung / Engineering mit über 15 Jahren Erfahrung in der Pharmaindustrie.

Unser Leistungsspektrum umfasst die Durchführung von Qualitätsprüfungen von Pharmazeutischen Produkten in unserem zertifizierten Prüflabor, die Planung und Überwachung von technischen Transfer Projekten, die Sicherstellung der GMP Richtlinien, die Entwicklung nuer so wie die weiter Entwicklung bzw. die Optimierung von Prozessen wie z.B. Gefriertrocknungsprozessen.

Sprechen Sie uns gerne an, unsere Erfahrenen Mitarbeiter aus den Bereichen der Herstellung und der Forschung und Entwicklung stehen Ihnen gerne zur Verfügung.

Pharmbiocon
Life Science Engineering

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

Process engineering tools (sensor technology)

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

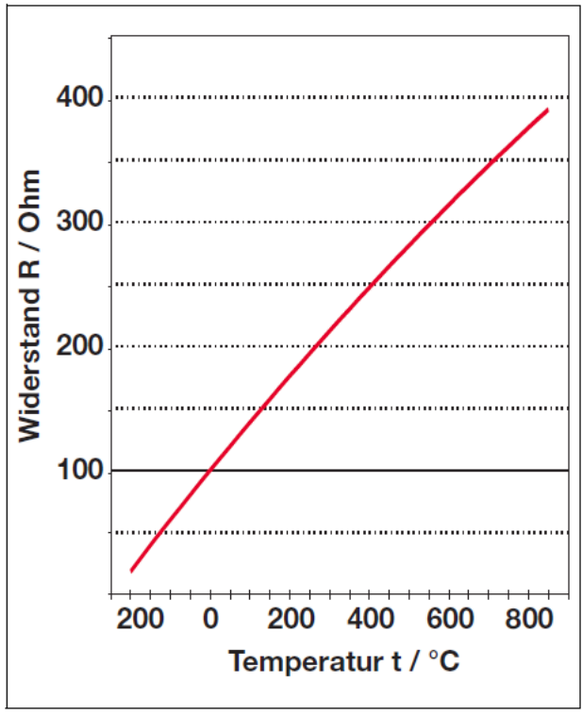


Abbildung 1: Pt100-Kennlinie

Process engineering tools (sensor technology)

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 PT100 temperature sensor
- 2,0Ω /K at PT500 temperature sensor
- 4,0Ω /K at PT1000 temperature sensor

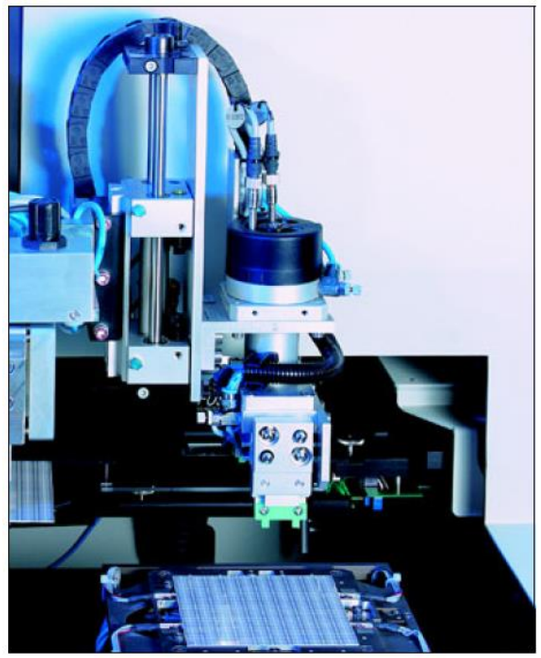


Abbildung 12: Laserabgleich der Platin-Chip-Temperatursensoren

Process engineering tools (sensor technology)

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.

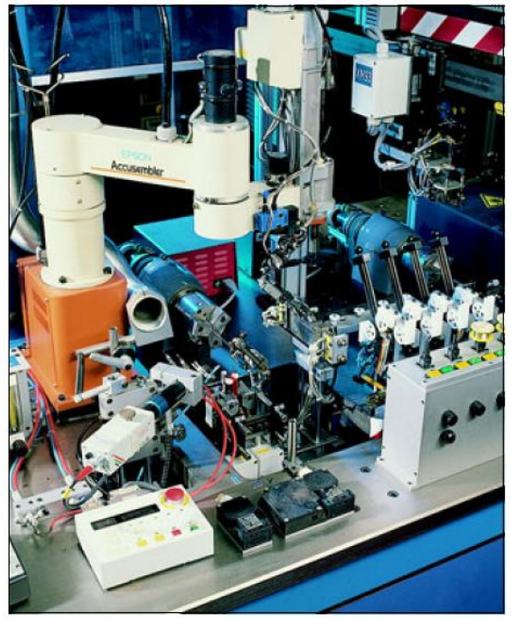


Abbildung 9: Automatisierte Produktion drahtgewickelter Platin-Glas-Temperatur-sensoren

Process engineering tools (sensor technology)

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

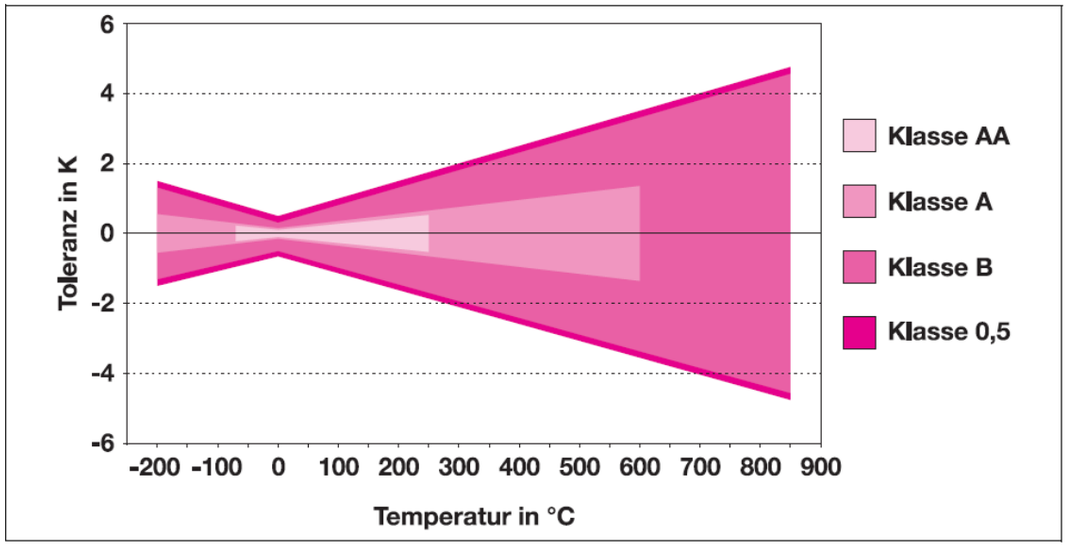


Abbildung 2: Toleranzverlauf in Abhängigkeit von der Temperatur

Process engineering tools (sensor technology)

Thermal resistance measurement (platinum temperature sensor)

Construction PT-sensor

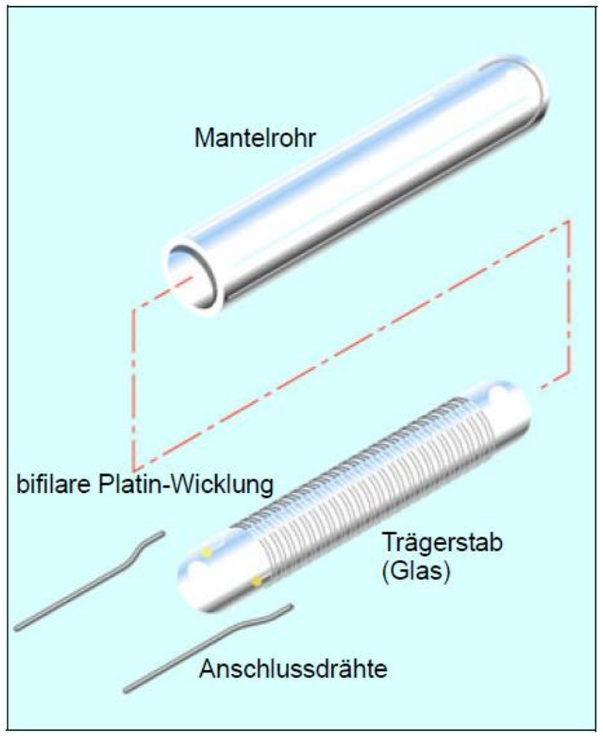


Abbildung 7: Prinzipieller Aufbau von Platin-Glas-Temperatursensoren

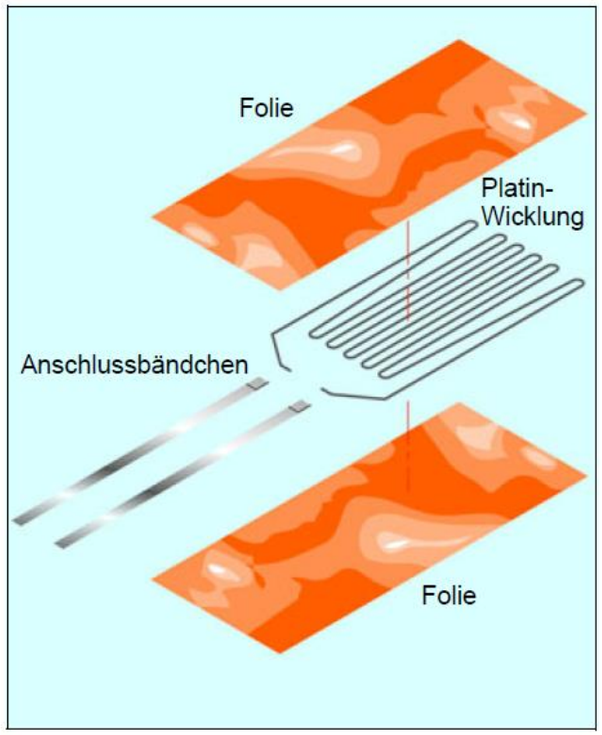


Abbildung 11: Prinzipieller Aufbau von Platin-Folien-Temperatursensoren

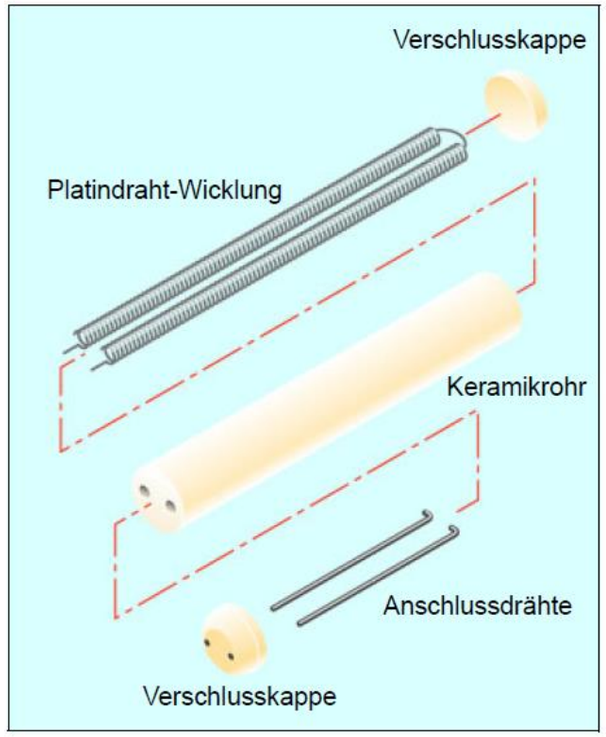


Abbildung 10: Prinzipieller Aufbau von Platin-Keramik-Temperatursensoren

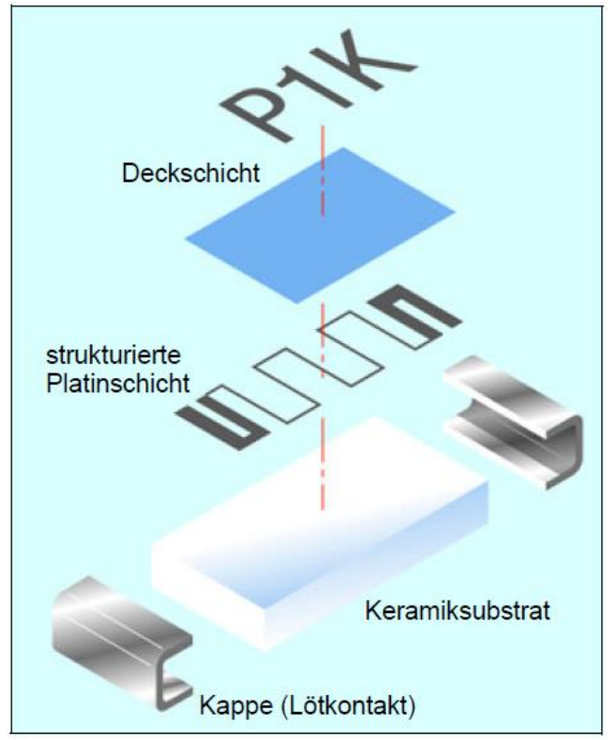


Abbildung 16: Prinzipieller Aufbau von Platin-Chip-Temperatursensoren in SMD-Bauform

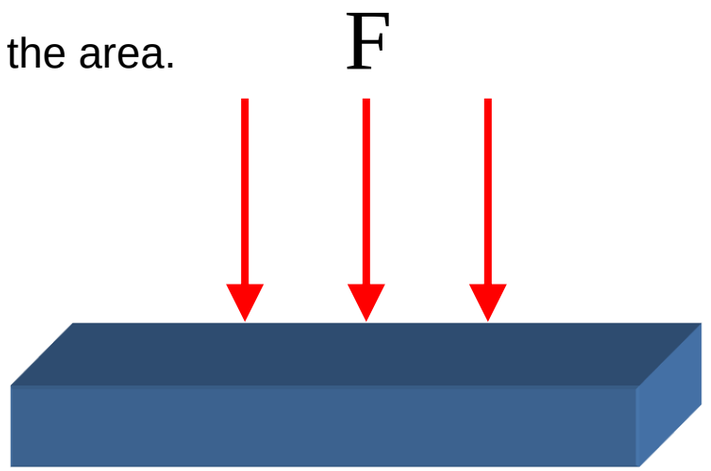
Process engineering tools (sensor technology)

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.**

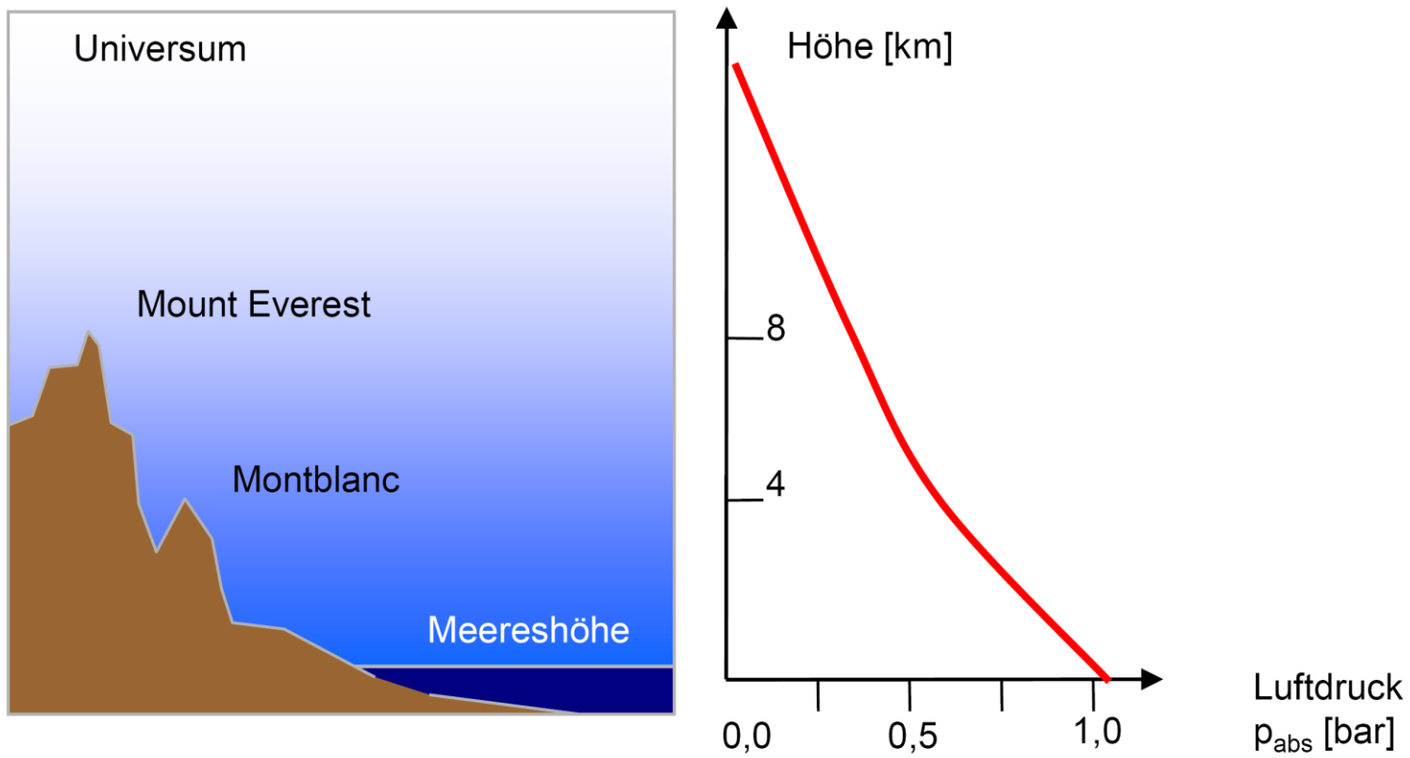
Each unit can be transferred to another:

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

Definition

P_{abs}

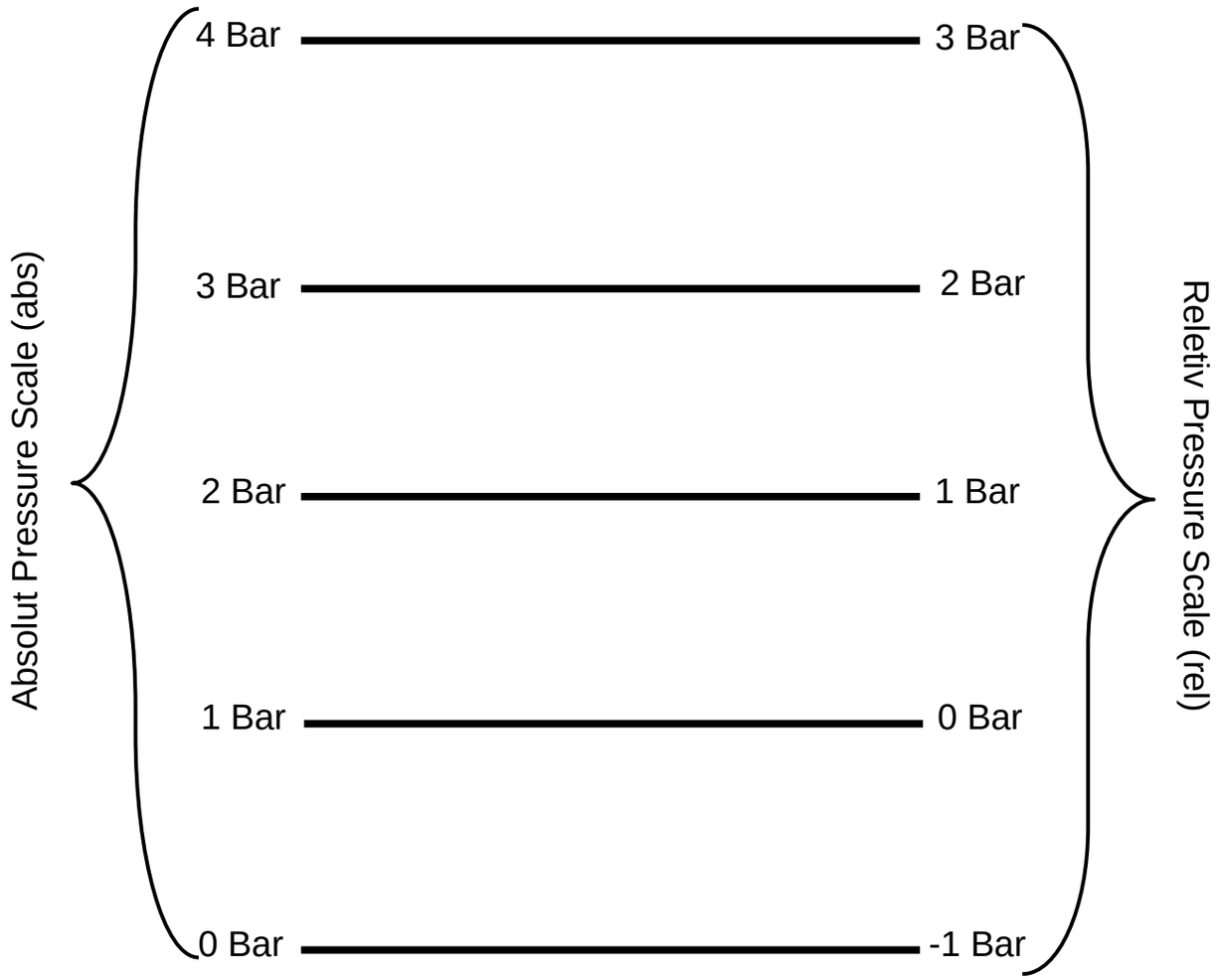
Referenz Pressure (Universe)



The Referenz Pressure will be generaded by Vacuumpumps

Process engineering tools (sensor technology)

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, semiconductor industry

Process engineering tools (sensor technology)

Pressure measurement (vacuum and overpressure)

One of the most important parameters is the pressure measurement

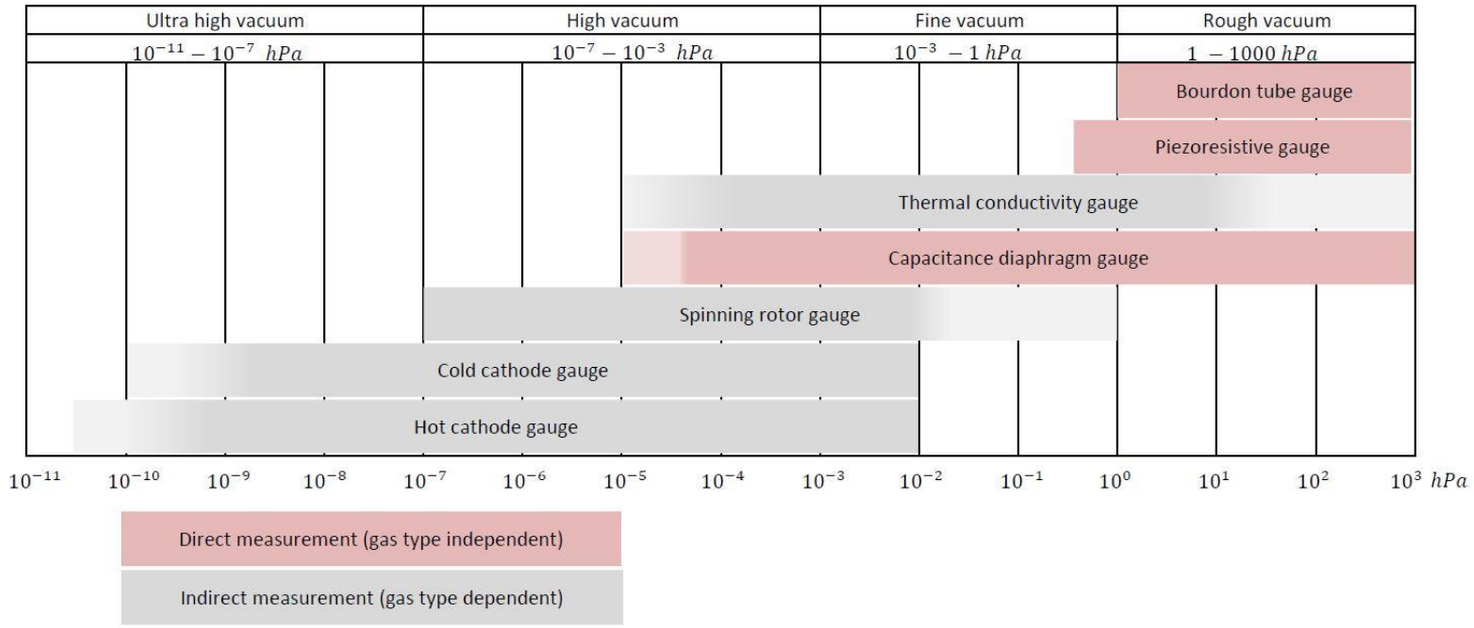
- during a running process the pressure measuring device must have a high accuracy (freeze-drying and sterilisation)
- during a freeze-drying the pressure measurement may be used for comparative pressure measurement (capacitive sensor / Pirani)
- during a sterilisation process the pressure measurement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

Process engineering tools (sensor technology)

Pressure measurement (vacuum and overpressure)

The most common vacuum sensors at freeze-drying are:

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

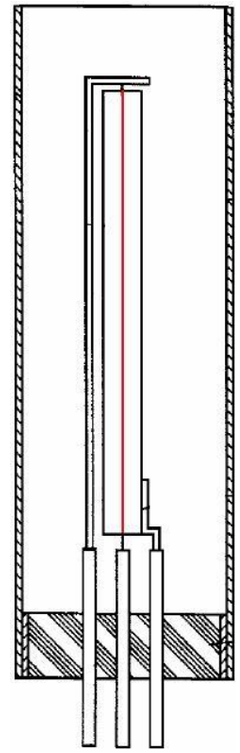


Process engineering tools (sensor technology)

Pressure measurement (vacuum and overpressure)

Construction of conductive pressure measurement systems (Pirani)

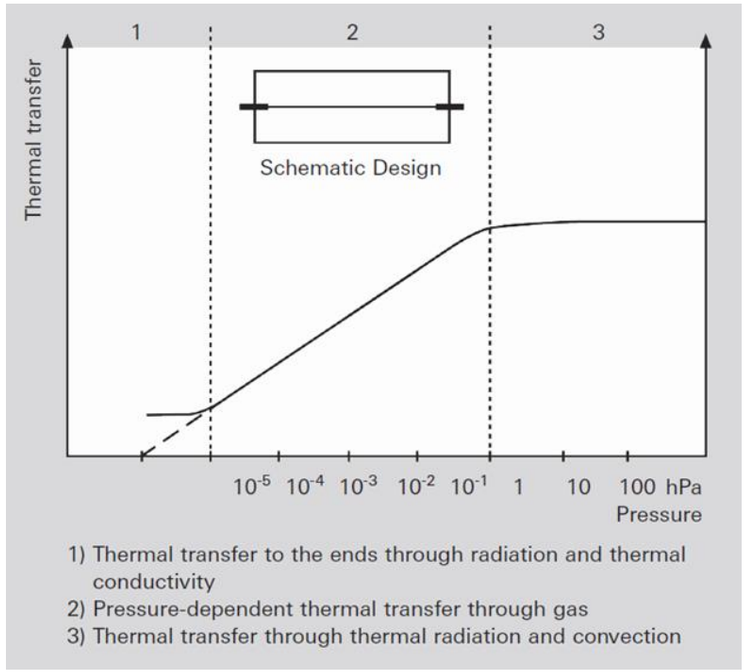
Heat up the wire approximately at a temperature of 110°C to 130°C. The heated wire forms a part of a Wheatstone bridge.



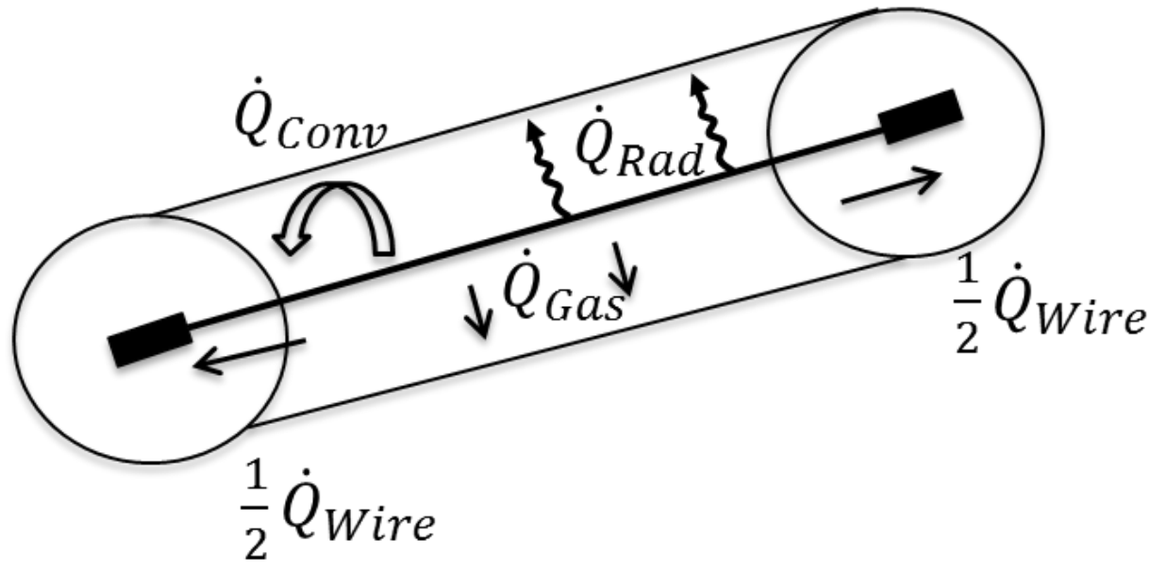
Process engineering tools (sensor technology)

Pressure measurement (vacuum and overpressure)

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



1) Thermal transfer to the ends through radiation and thermal conductivity
2) Pressure-dependent thermal transfer through gas
3) Thermal transfer through thermal radiation and convection



Process engineering tools (sensor technology)

Pressure measurement (vacuum and overpressure)

Adjustment of Pirani:

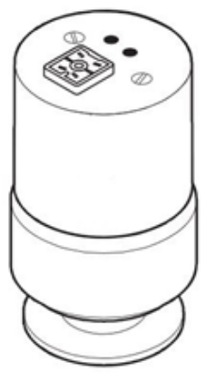
- adjustment of Pirani takes place under real installation conditions
- depending on the age and usage of the Pirani sensor it is necessary to do a zero point calibration (offset)

Process engineering tools (sensor technology)

Pressure measurement (vacuum and overpressure)

When using a Pirani you must think about the following:

- vertical installation of the Pirani
- Regular Changing of the Pirani depending on Life Time and Process Turnaround
- depending on the age and usage of the Pirani it is necessary to do a zero point adjustment (offset)
- the accuracy of the Pirani sensor depends on the measured gas

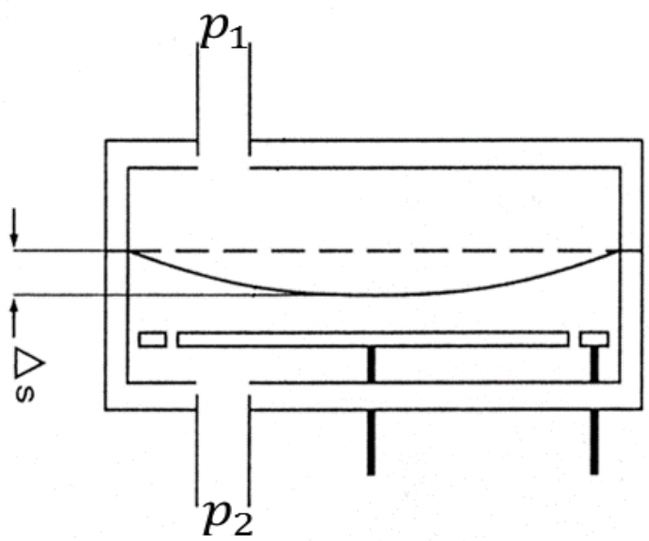


Process engineering tools (sensor technology)

Pressure measurement (vacuum and overpressure)

Construction of a capacitive pressure measurement system:

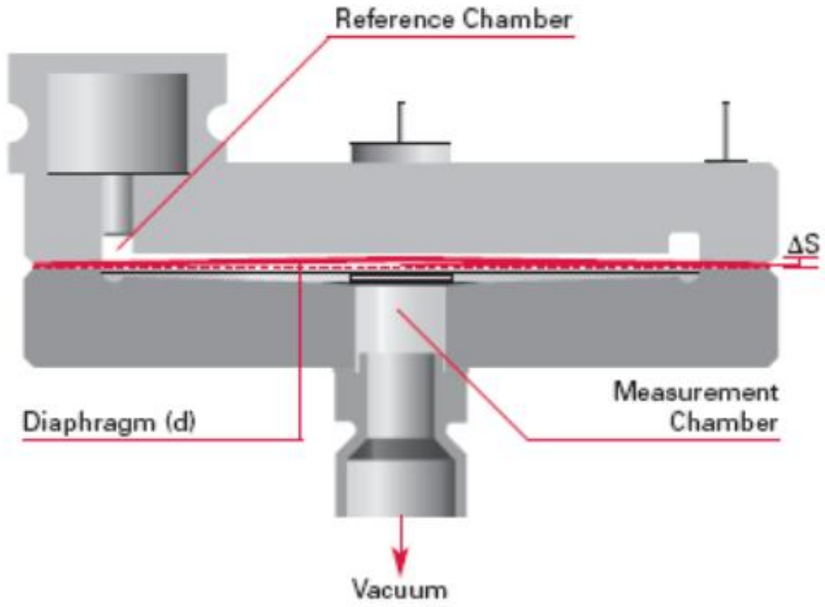
- a capacitive pressure measurement system is independent of the measured gas
- a flexible membrane is mounted inside the Sensor



Process engineering tools (sensor technology)

Pressure measurement (vacuum and overpressure)

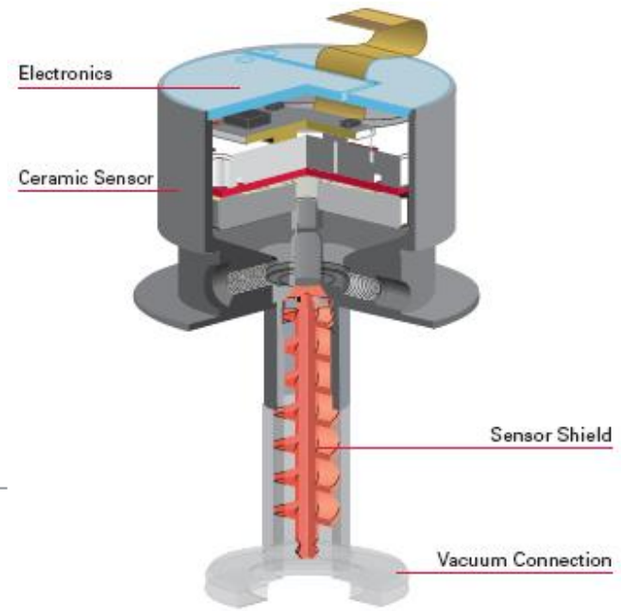
Construction of a capacitive pressure measurement system:



Pressure measurement (vacuum and overpressure)

Construction of a capacitive pressure measurement system:

- To avoid a risk of an influence from Temperatures, the capacitive measurement sensors is heated. The temperature of the Sensor is between 45 °C and 200 °C depends on the type of the sensor.
- a freeze dryer which can be sterilized, the capacitive sensors should be heated higher than 150 °C because of the wet sterilisation (Clean Steam).

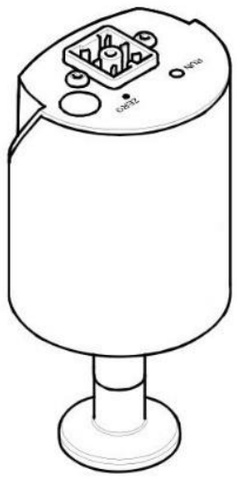


Process engineering tools (sensor technology)

Pressure measurement (vacuum and overpressure)

When using a capacitive measurement sensor it should be remembered:

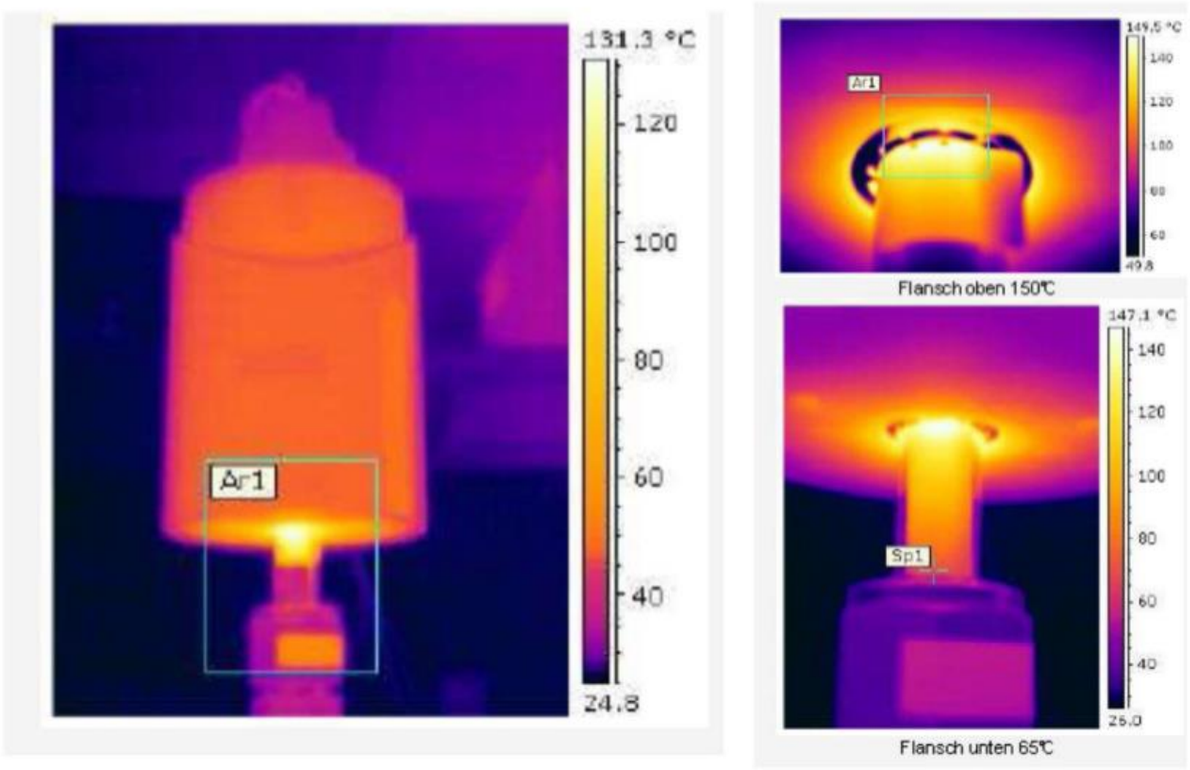
- measurement sensor have a heating up Time (some Sensors around 9h)
- a contaminated membrane have an influence to the accuracy of the Sensor
- Because of the mounted flexible Membrane the installation position is important



Process engineering tools (sensor technology)

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:

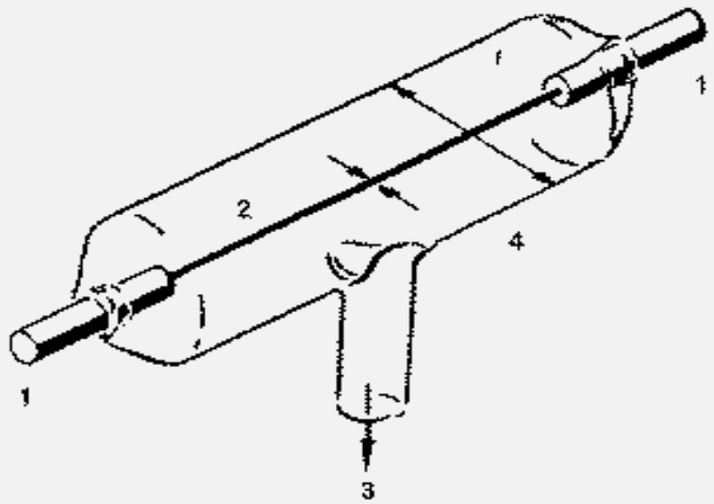
pressure measurement for determining the end of main drying

Measurement of camber pressure with Pirani sensor

based on radiation of heatwire;

depends on the gas inside the Freeze Dryer

Pirani sonde



Comparative pressure measurement

(Pirani / capacitive pressure measurement)

Pressure measurement

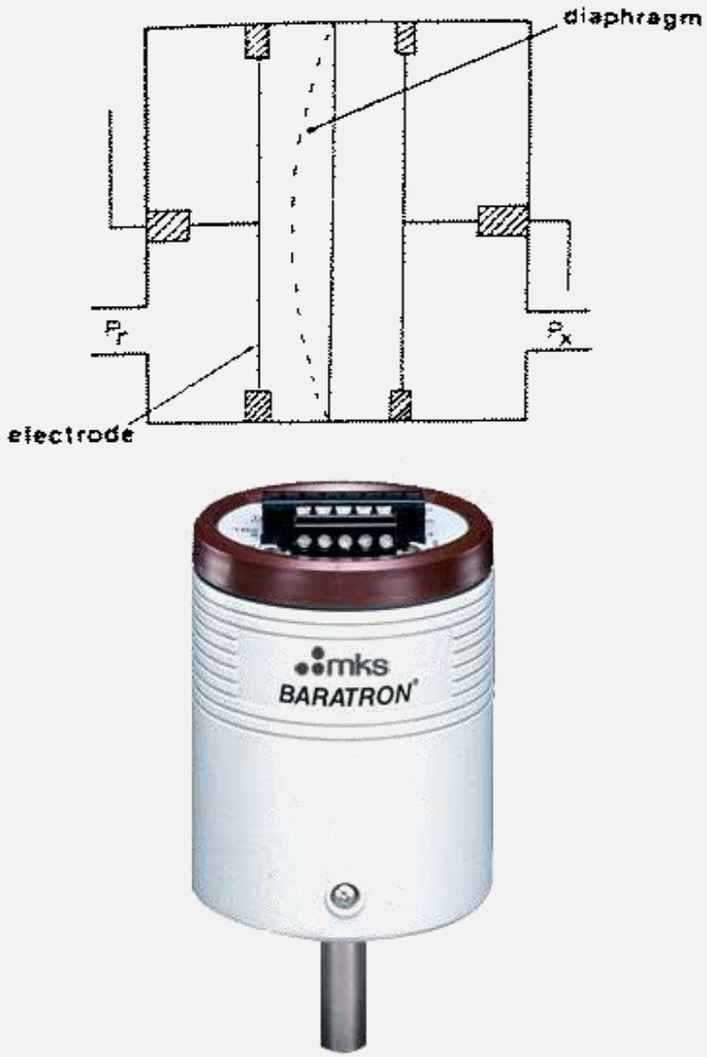
Measurement of camber pressure with

capacitive sensor

Based on a electrical measurement (Piezo),

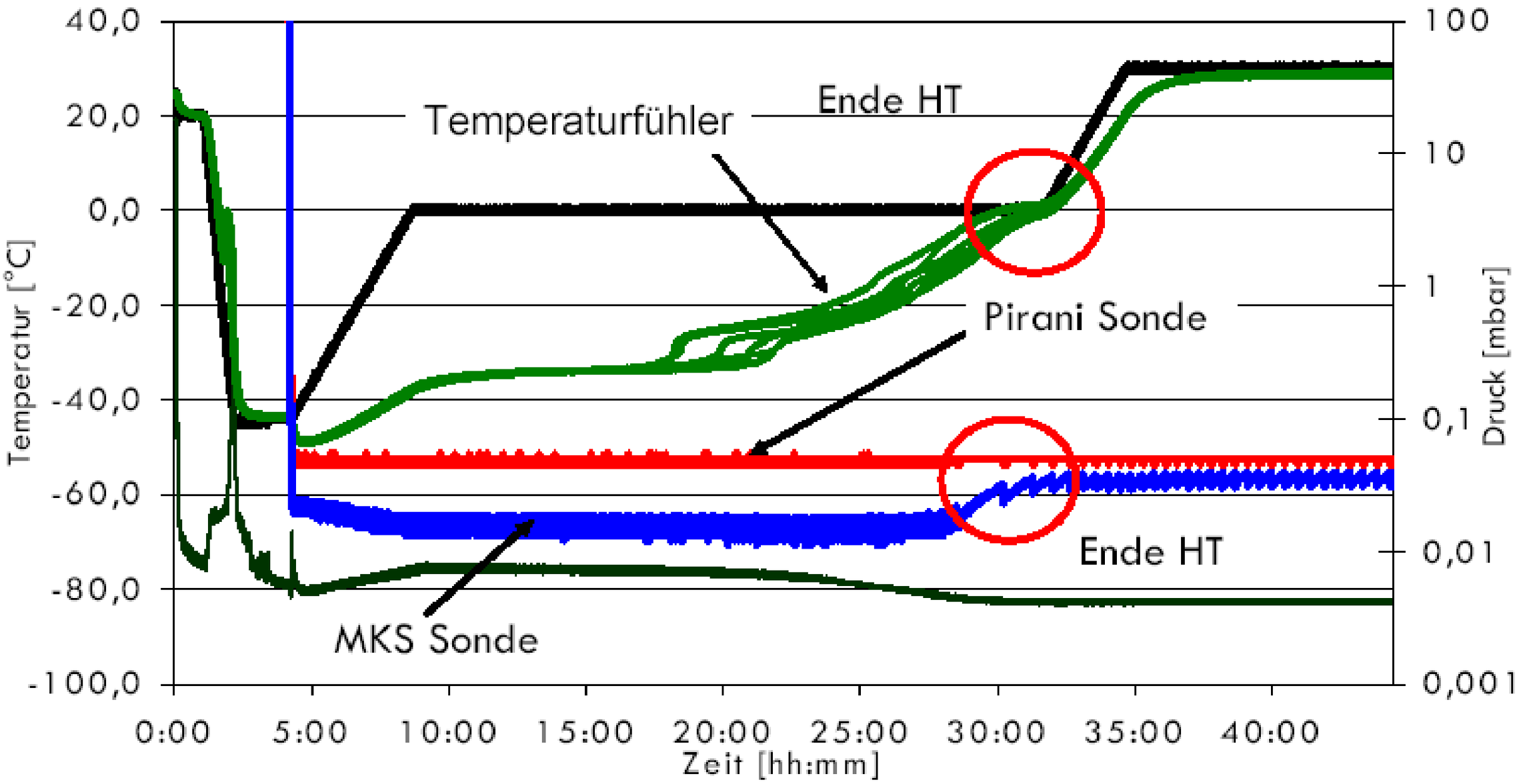
independent from gas inside the Freeze Dryer

capacitive manometer



Comparative pressure measurement

(Pirani / capacitive pressure measurement)



Comparative pressure measurement

(Pirani / capacitive pressure measurement)

Comparing pressure measurement

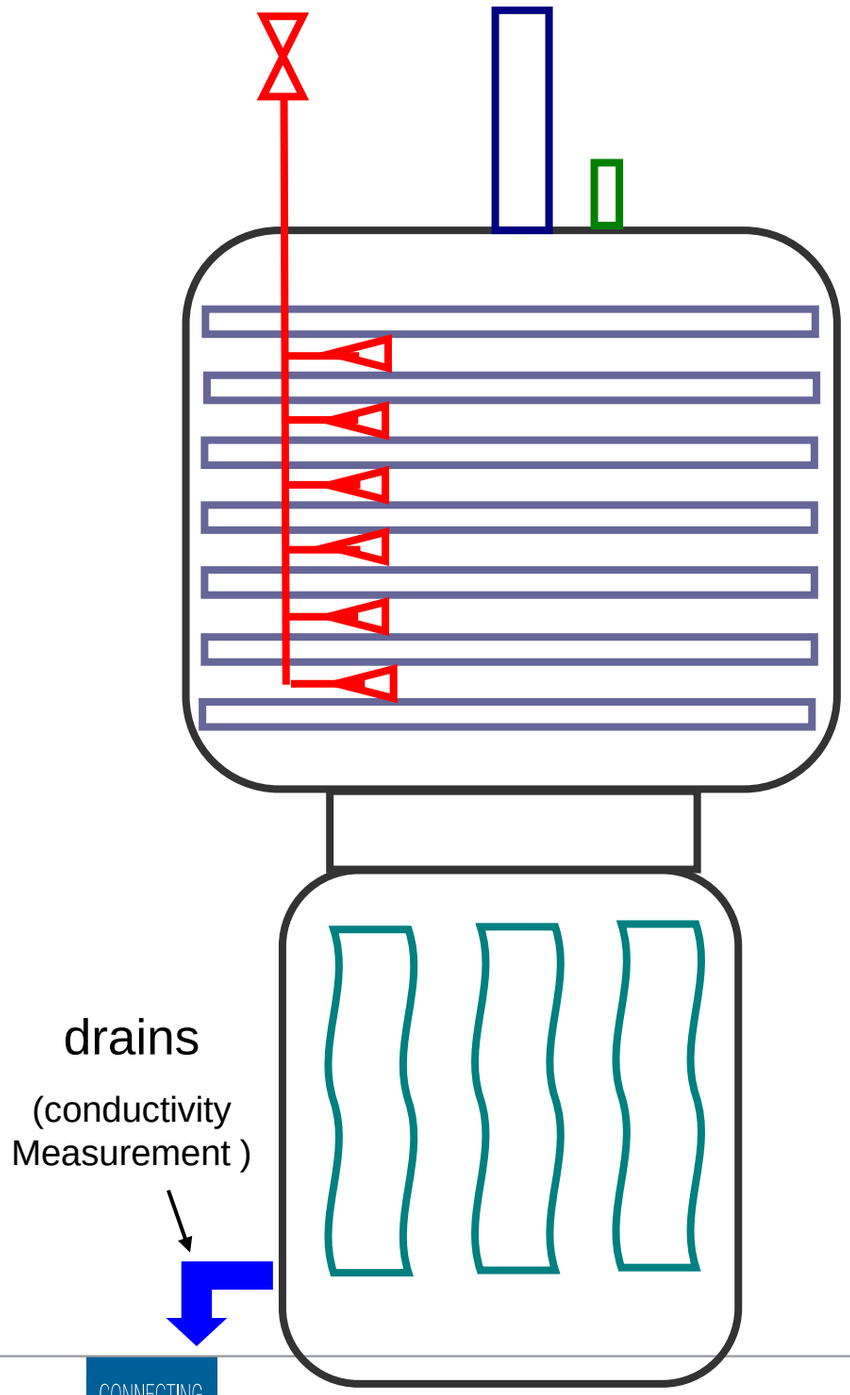
- simultaneous measurement of camber pressure with Pirani and capacitive sensor
- in the beginning the Pirani sensor shows a pressure which is higher than the pressure of the capacitive sensor

(high content of water vapor inside the Freeze Dryer)

- at the end of main drying the measured values of the two sensors approach each other this is an indicator for the end of main drying

(less content of water vapor inside the Freeze Dryer)

Process control tools (sensor technology)



Conductivity Measurement

to check the efficiency of a CIP Cycle a conductivity sensor is usually used.

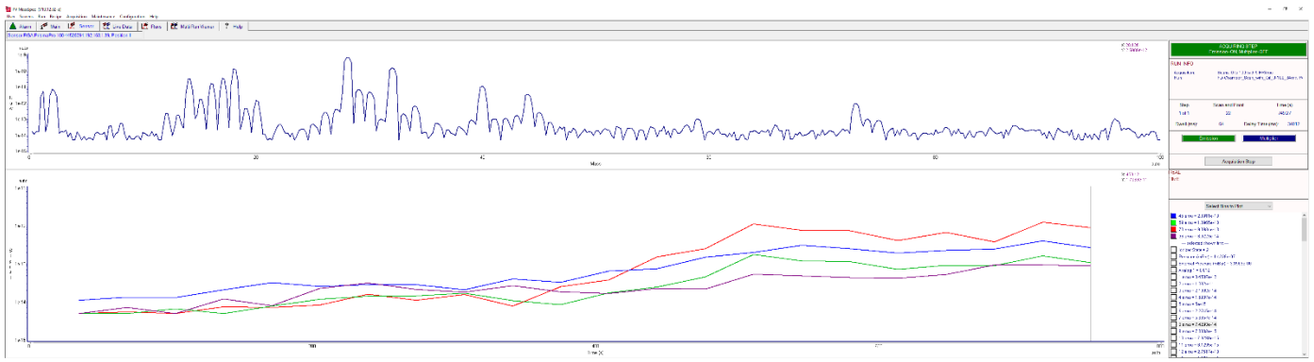
the conductivity sensor should be fit to the relevant requirements e.g. WFI.

the Sensor 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).

Mass Spectrometer

Content of the training:

- Basics mass spectrometer
- Chemical background
- Interpretation of the measurement result
- Hands-On Part



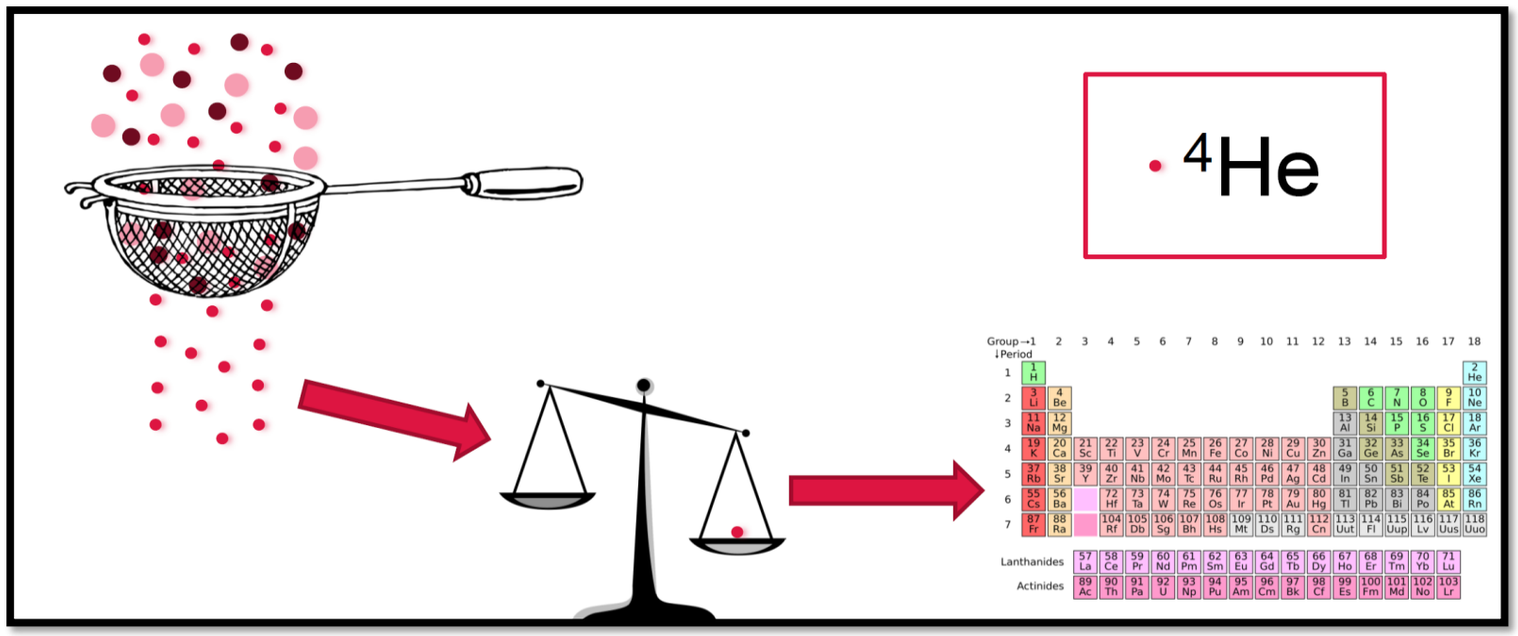
Mass Spectrometer

Applications of mass spectrometry:

- For analysis of chemical products in laboratories
- Process analysis in combustion processes, power plant processes, exhaust gas analysis
- Quality control/Vacuumsystems (outgassing, **leak detection**)
- Surface analysis

Mass Spectrometer

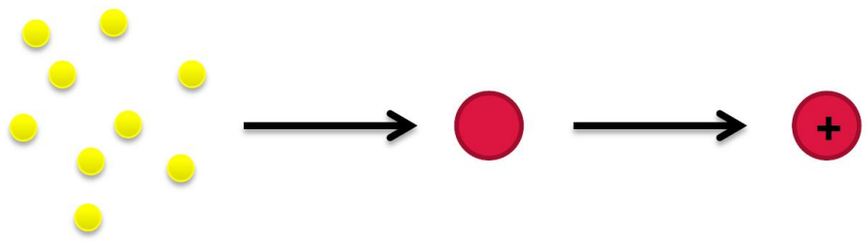
Basic principle of mass spectrometry:



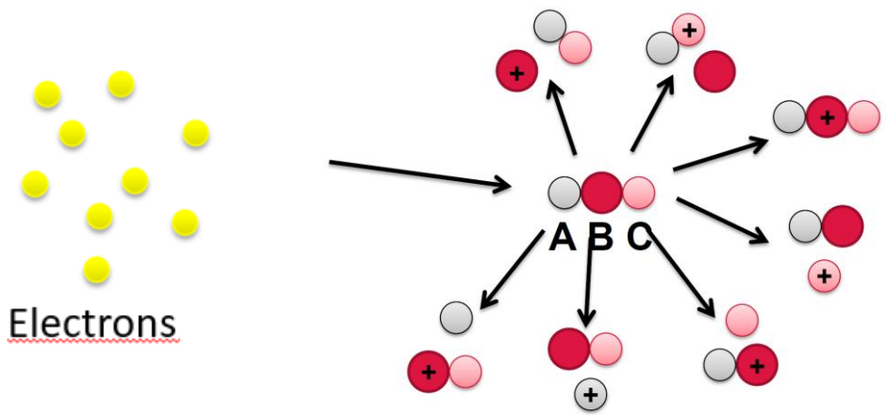
The individual atoms or molecules are separated, the mass/charge ratio is determined and the chemical product is assigned to a specific mass spectrum (fingerprint).

Mass Spectrometer

Ionization of the gases:

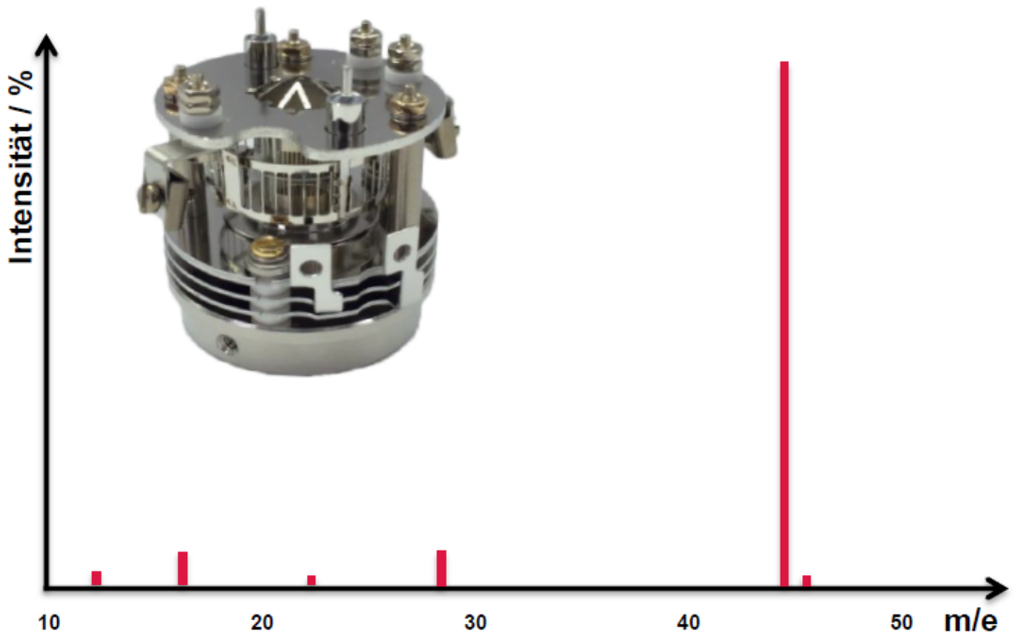


In the ionization process, different fragments are created. Some fragments with high and others with low probability.



Mass Spectrometer

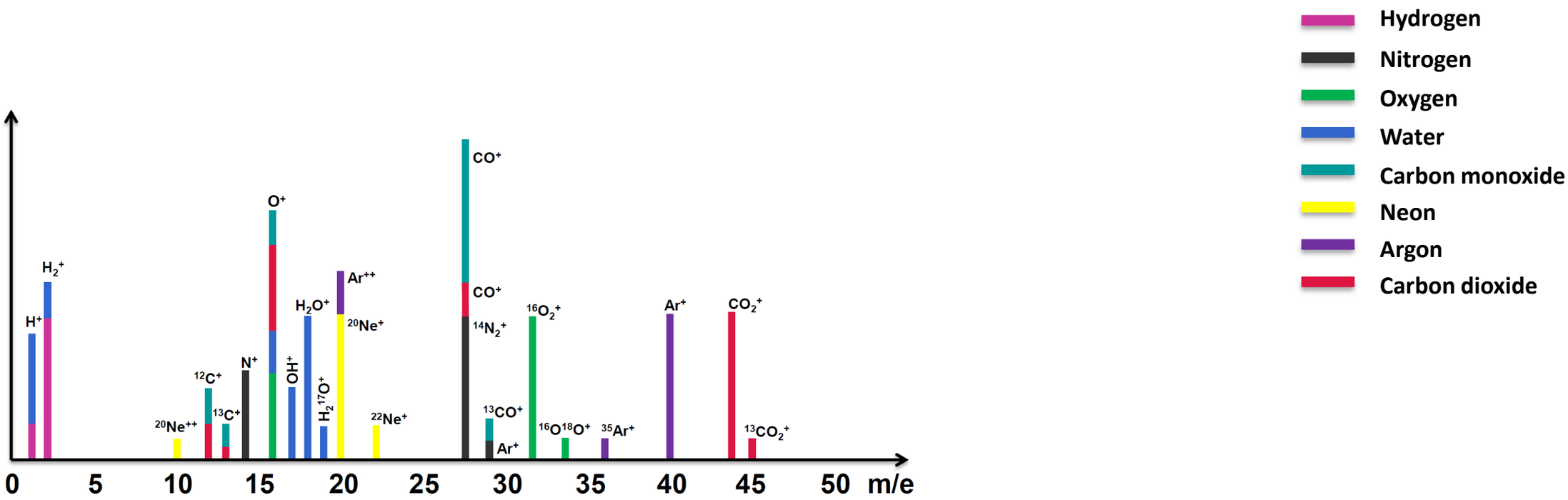
CO2 fragmentation



m/e	Intensität	Ion
12	2,46	$^{12}C^{+}$
16	6,24	$^{16}O^{+}$
22	1,78	$^{12}C^{16}O_2^{++}$
28	6,55	$^{12}C^{16}O^{+}$
29	0,06	$^{13}C^{16}O^{+}$
44	**100,00**	**$^{12}C^{16}O_2^{+}$**
45	1,16	$^{13}C^{16}O_2^{+}$
46	0,41	$^{12}C^{16}O^{18}O^{+}$

Mass Spectrometer

Applications of mass spectrometry:

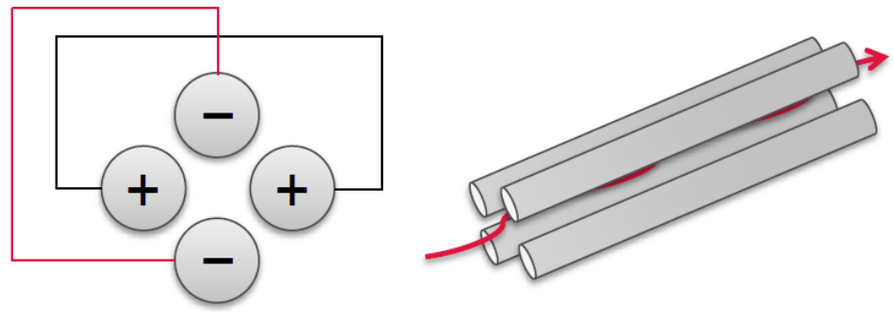


Due to the Gaussian normal distribution, a unique mass spectrum is created for each molecule

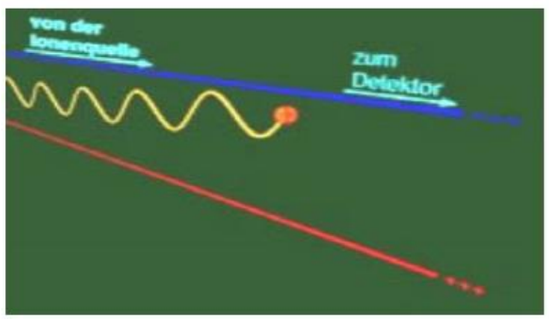
Mass Spectrometer

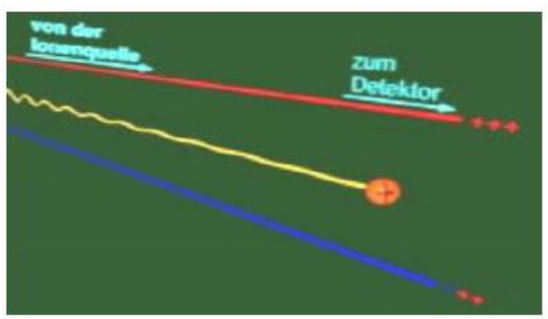
Separation of masses:

- 4 cylindrical metal bars
- opposite bars are electrically connected
- an AC voltage field is applied to a DC voltage field
- stable flight paths for certain ions
- with a suitable m/e- relation, the ion reaches the detector



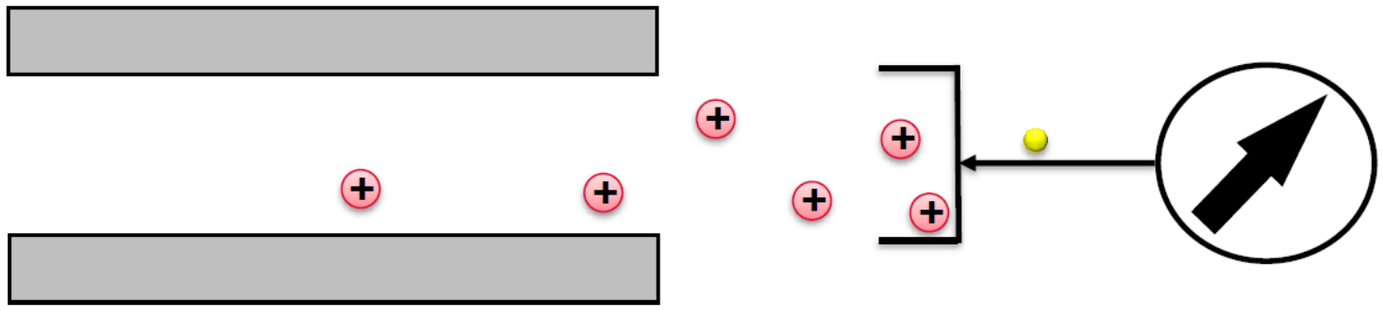
- if the relation does not fit, the ion is deflected before it hits the detector





Mass Spectrometer

Detector:

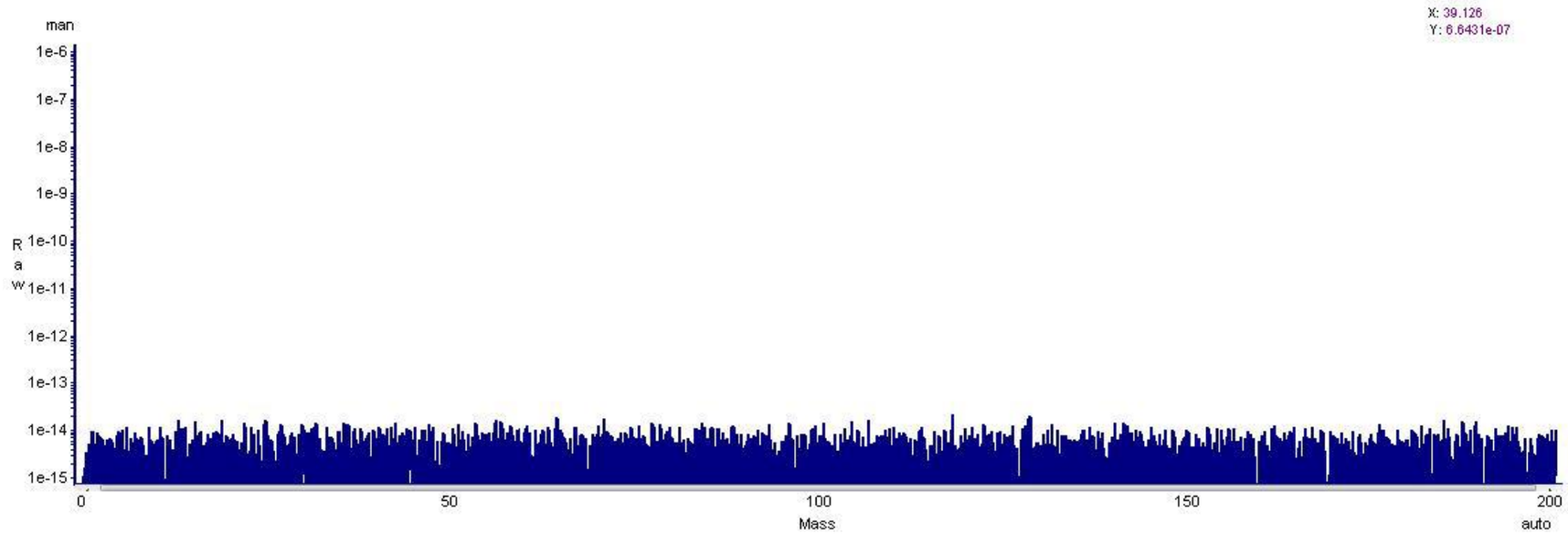


- If the m/e- relation is correct, the corresponding ion flies through the magnetic field and hits the detector.
- The relation m/e- is adjusted for each mass, so that only the corresponding mass crosses the path.

Mass Spectrometer

Detector:

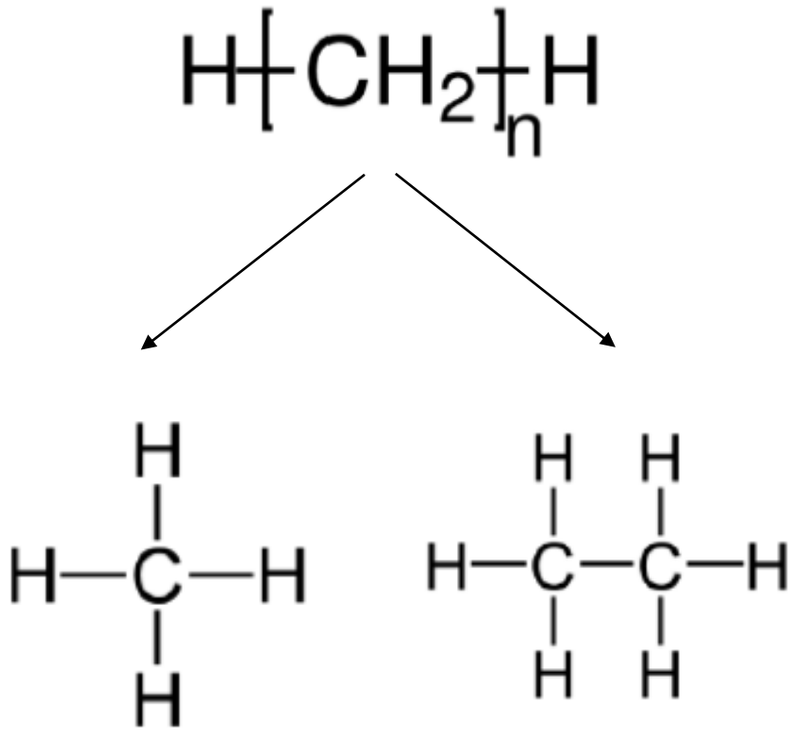
Background signal of the detector



- The detector outputs a minimum intensity independent of the gas analysis
- This signal is called “ground” and results from minimal voltage changes

Mass Spectrometer

Alkanes (hydrocarbons)

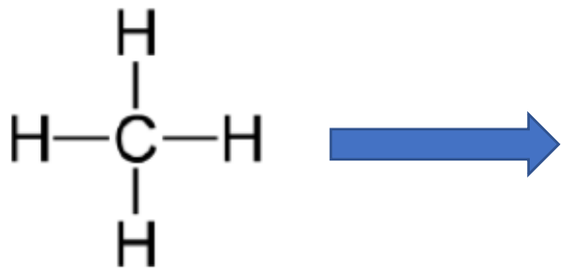


In the following we will have a look at which fragments are produced during ionization and which mass spectrum results from it

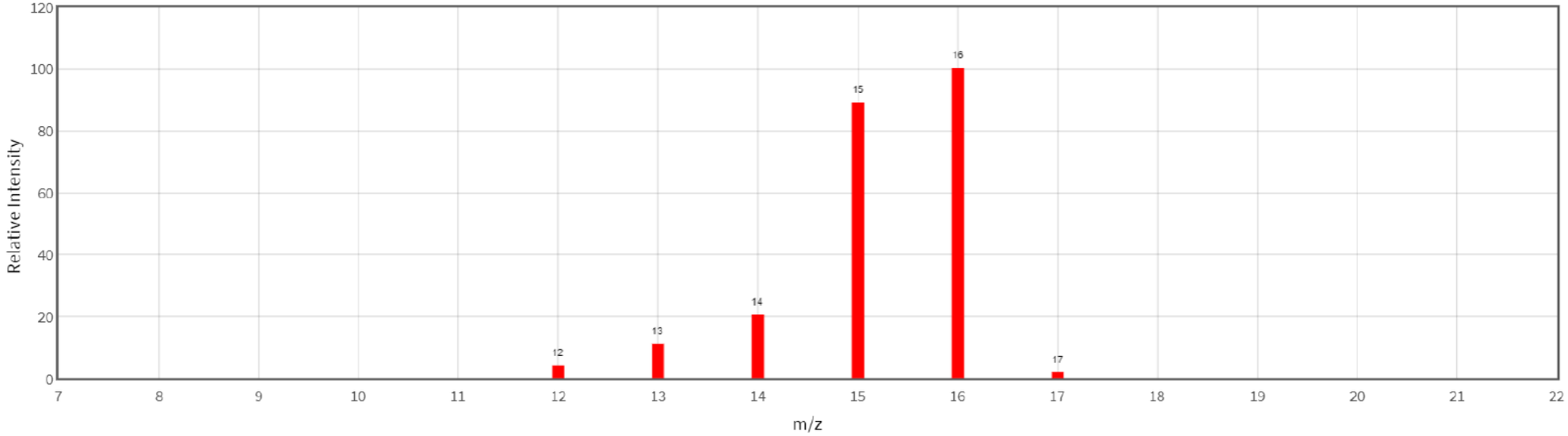
The fragments occur with different probabilities, the most frequently occurring fragment is set to intensity 100% and the others are set in relation to it

Mass Spectrometer

Methan



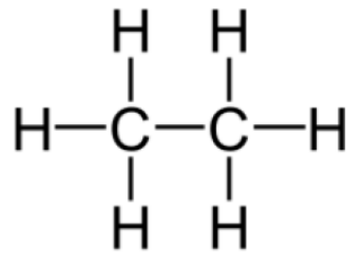
CH_4^+ → 17 amu
CH_4 → 16 amu
CH_3 → 15 amu
CH_2 → 14 amu
CH → 13 amu
C → 12 amu
H_2 → 2 amu
H → 1 amu

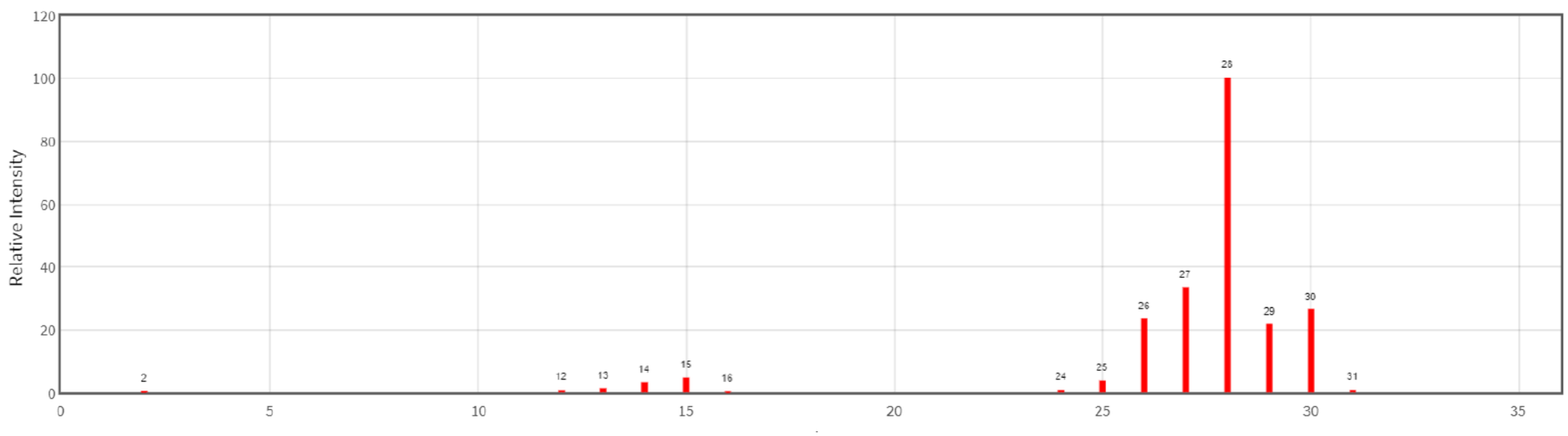


Due to the different probability of the resulting fragments, a unique mass spectrum results like a fingerprint

Mass Spectrometer

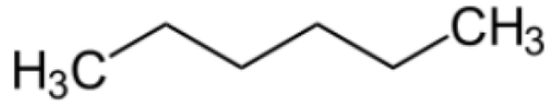
Ethan

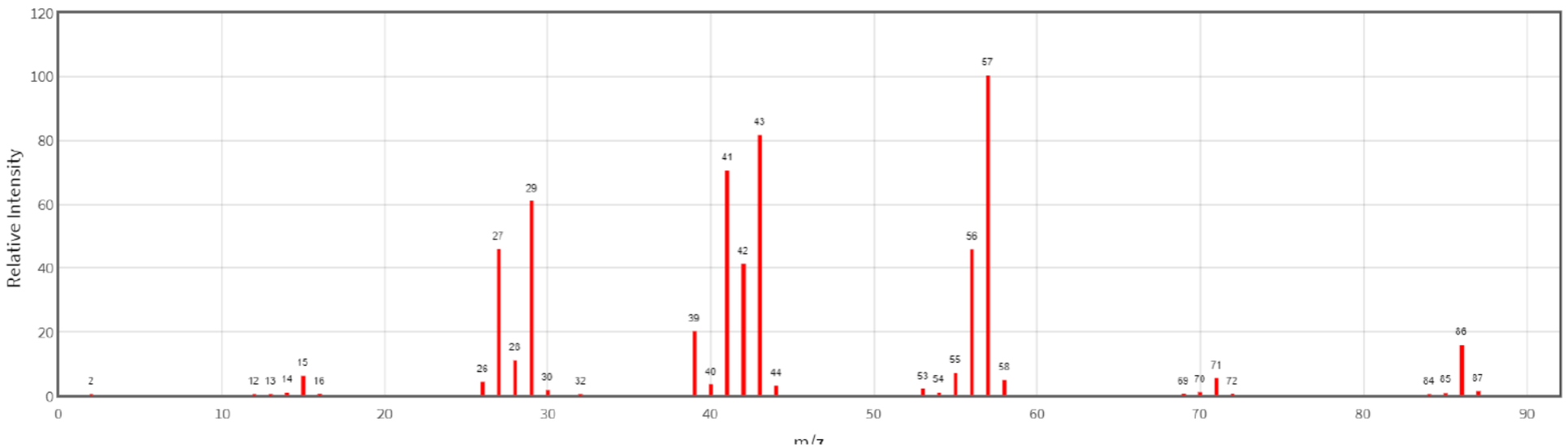




Mass Spectrometer

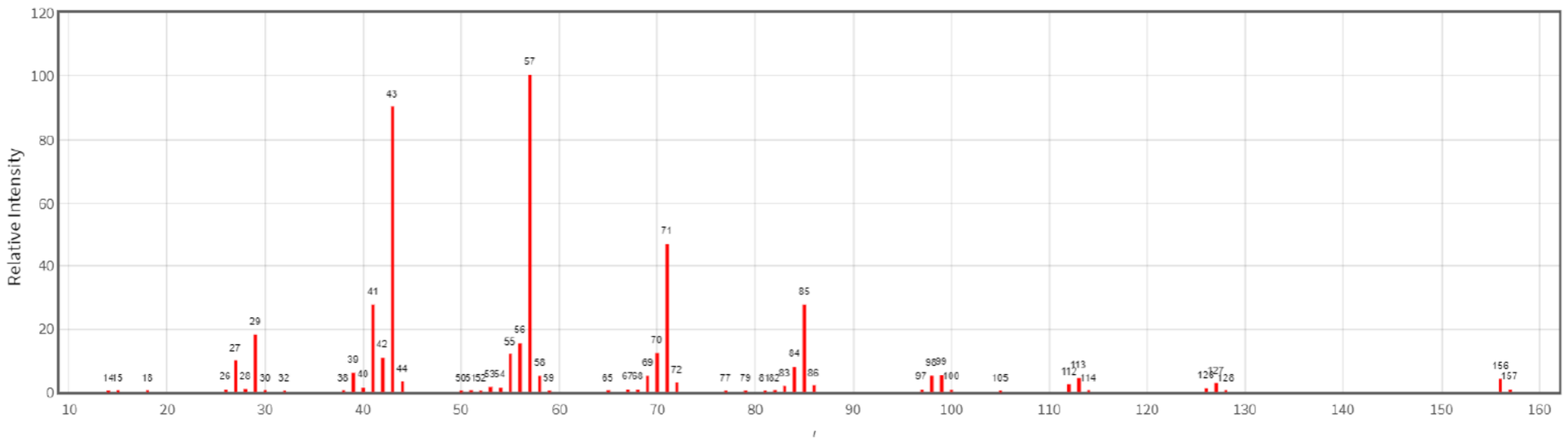
n-Hexan



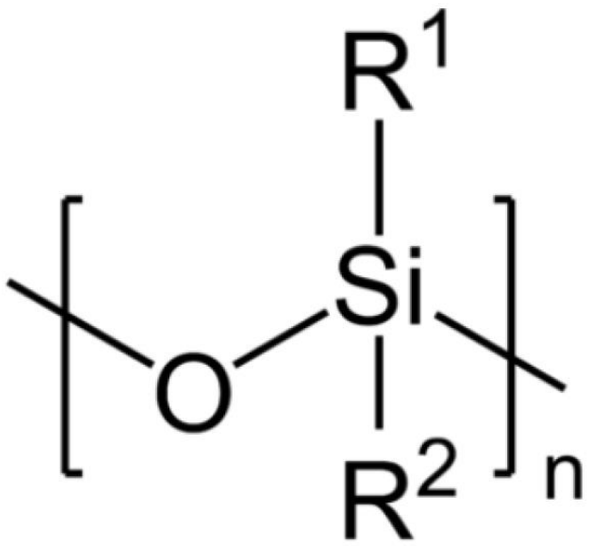


Mass Spectrometer

n-Hexan



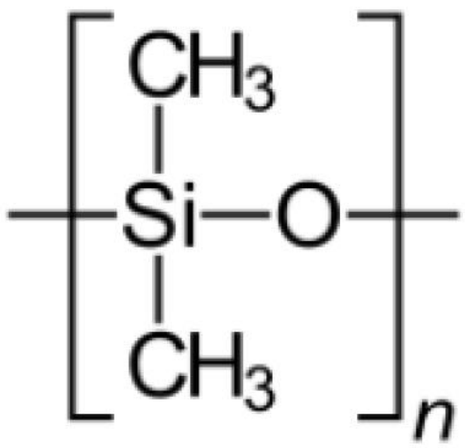
Silicone oils



The repeating unit of the siloxane polymer

- Siloxane Polymer
- Silicone oils are clear, colorless, nontoxic, neutral, odorless, tasteless, chemically inert, temperature-stable over a wide range, hydrophobic liquids with a molecular mass of 162 to 150,000 g/mol

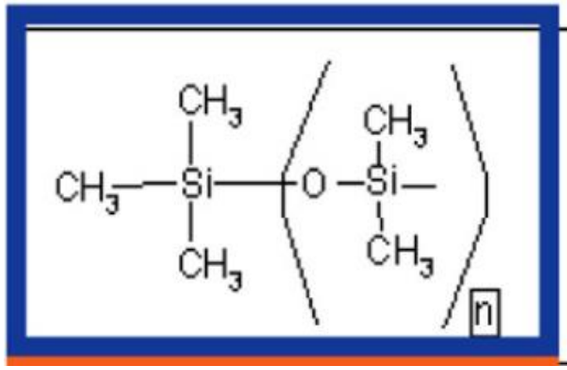
Polydimethylsiloxane (C2H6OSi)



Masses

- H – 1
- C – 12
- O – 16
- Si – 28

Sum formula: $SiOC_2H_6$

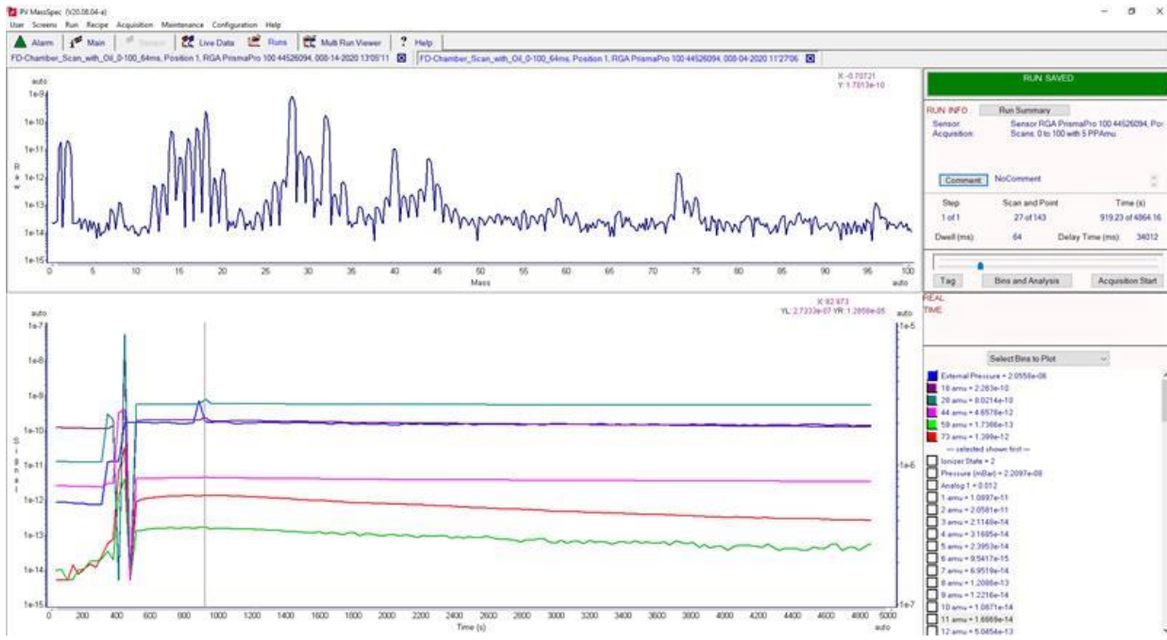


n=0	n=1	n=2
73amu	147amu	221amu
SiC_3H_9	$Si_2OC_5H_{15}$	$Si_3O_2C_7H_{21}$

Mass Spectrometer

Scan of the chamber with silicone oil

- During the scan over all masses, all fragments are detected which are created during the ionization of the air molecules
- If there are traces of evaporated silicone oil in the atmosphere, these fragments are also detected
- The indicators for silicone oil are mainly 45 amu, 59 amu and 73,74,75 amu
- During the scan over all masses, each mass is sampled several times, resulting in parabolic peaks
- The intensity is always relative to the main peak N_2 Intesity = 10
- If the limited sample of silicone oil evaporates, the intensity decreases over time until finally all the oil has evaporated
- In the case of a leak, no decrease in intensity will be seen, as it is not a limited quantity here
- When the chamber is clean, only the fragments of air can be seen



Process control tools (sensor technology)

Wireless temperature measurement

These sensors are used for:

- temperature measurement
- relative humidity
- pressure measurement

Process control tools (sensor technology)

Wireless temperature measurement

Freeze Dryer Logger -
85C to +140C

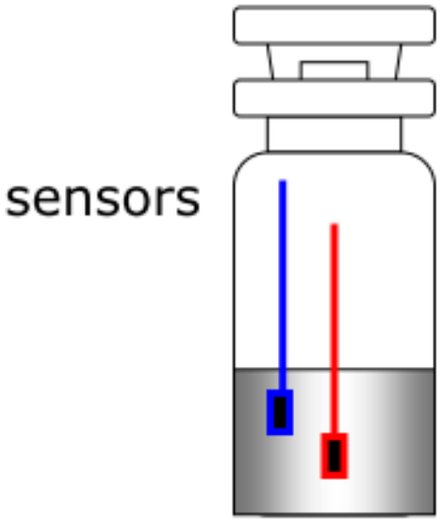
Cryologger

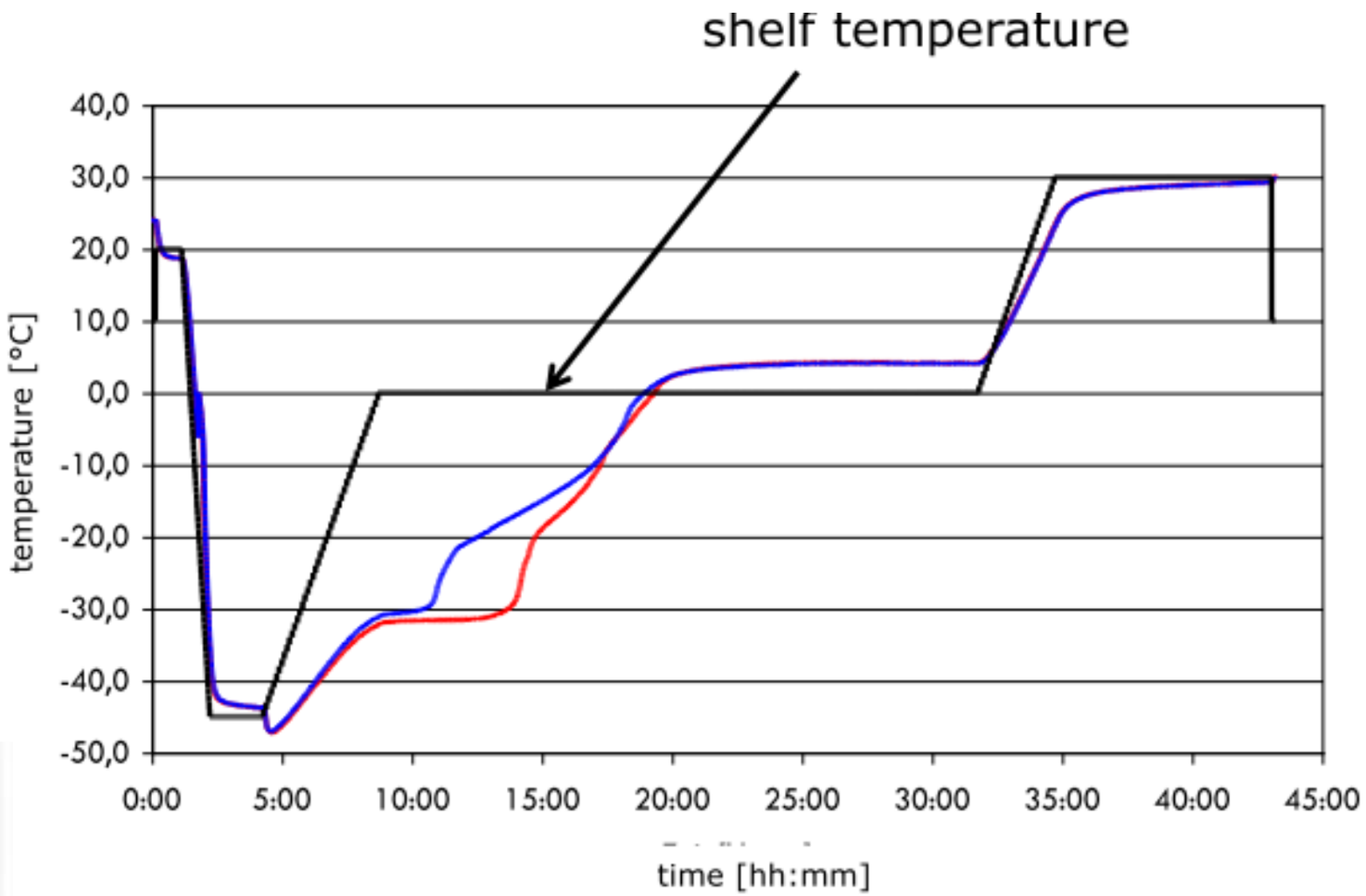
-85C to +140C

Process control tools (sensor technology)

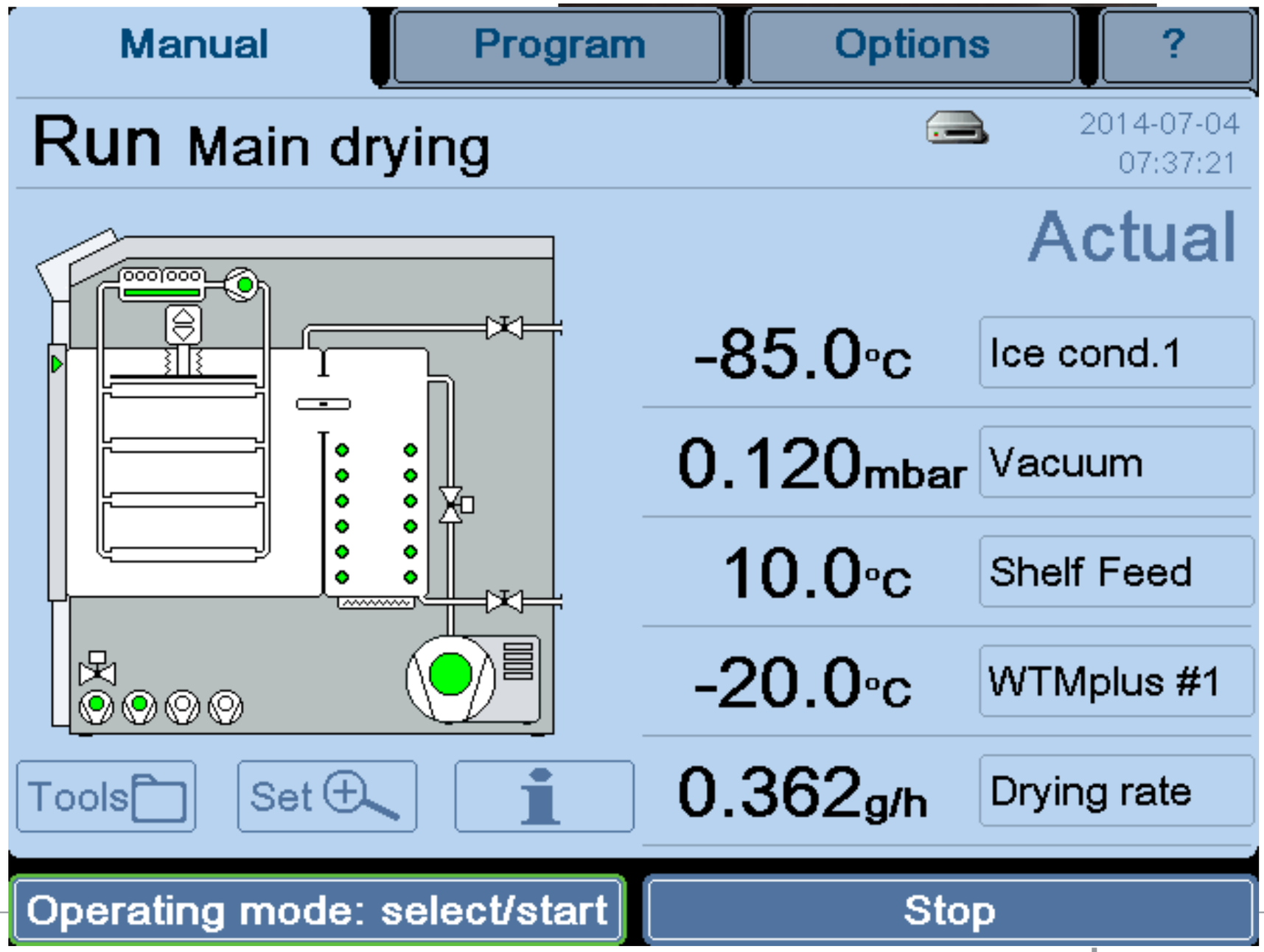
Wireless temperature measurement

positioning equipment

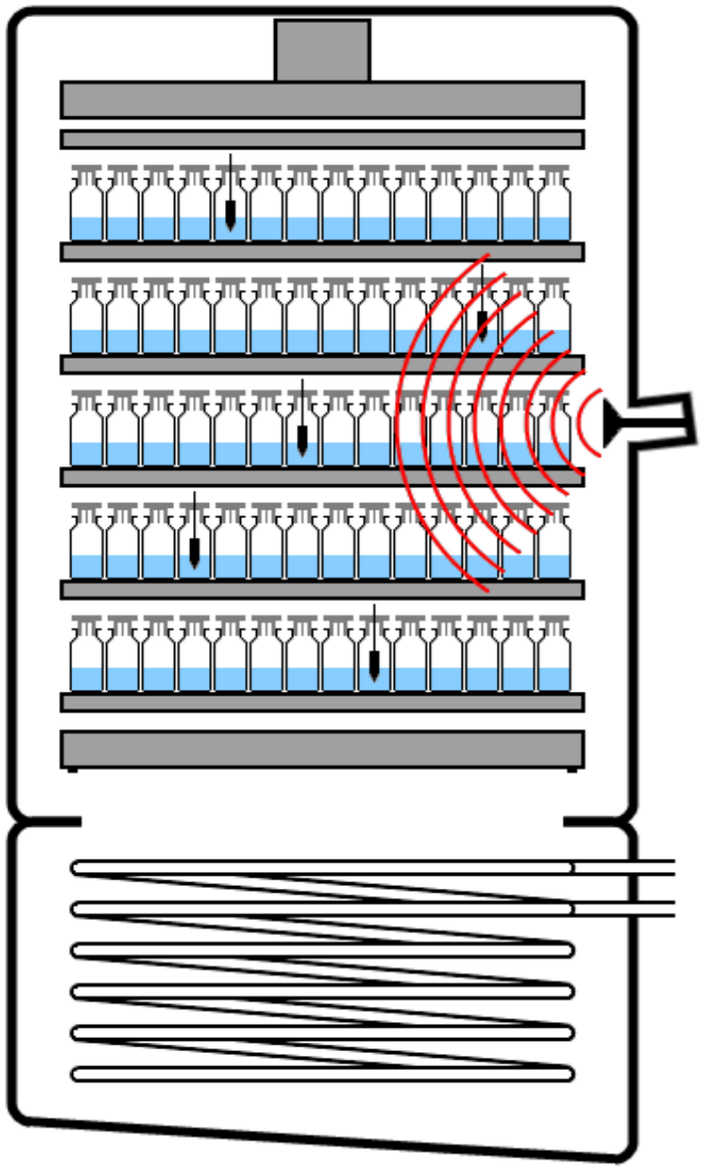

sensors
vial


shelf temperature
40,0
30,0
20,0
10,0
0,0
-10,0
-20,0
-30,0
-40,0
-50,0
temperature [°C]
0:00
5:00
10:00
15:00
20:00
25:00
30:00
35:00
40:00
45:00
time [hh:mm]

Process control tools (sensor technology)



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

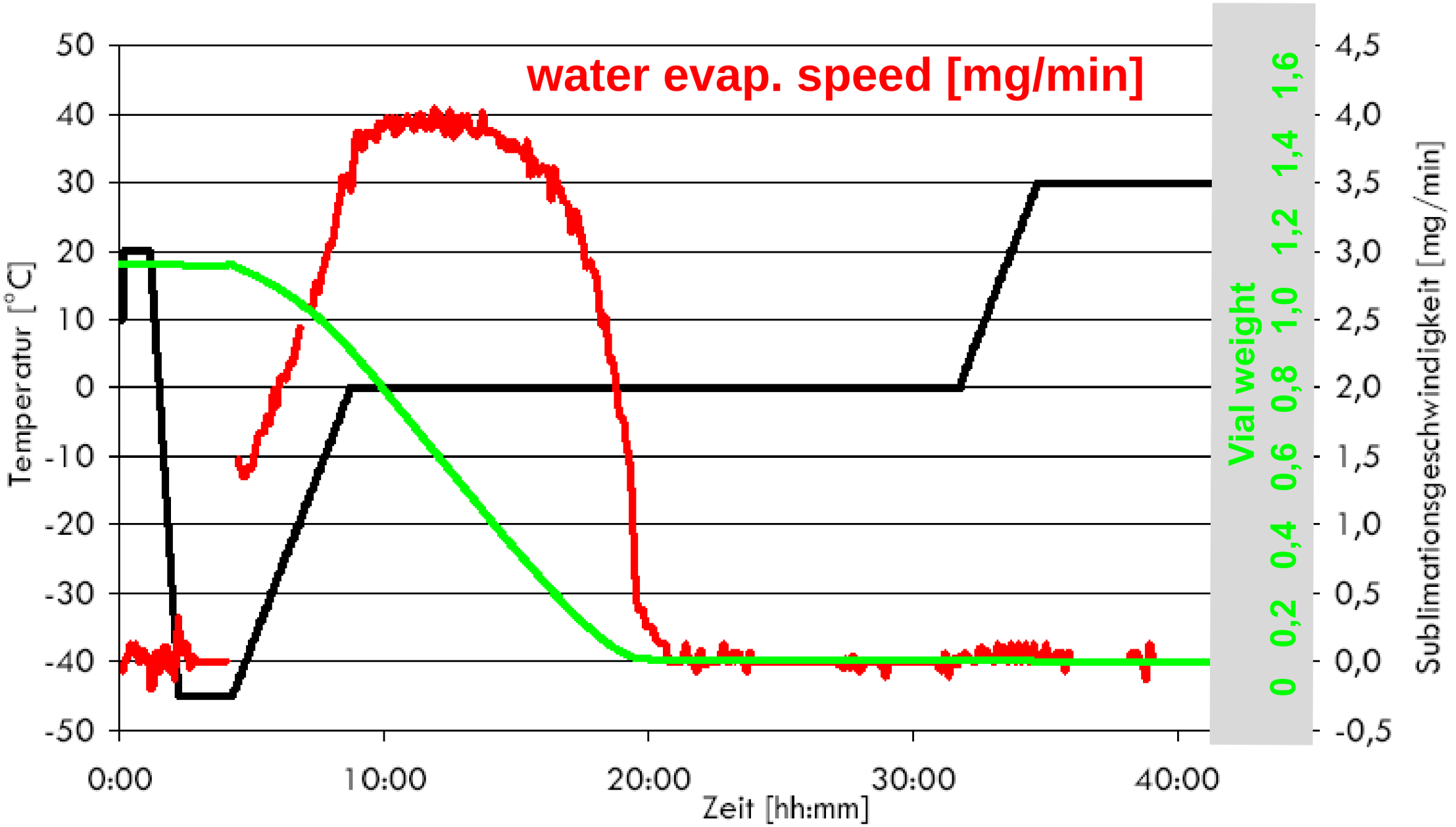
- small and robust, also for 2R vials and bulk
- no plugs and wires with cleaning and contact problems, GMP-design
- small and robust, also for 2R vials and bulk
- product temperature in the vial not influenced by energy input of conventional sensors
- high accuracy ± 0.5 K , resolution 0.1 K
- covers 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

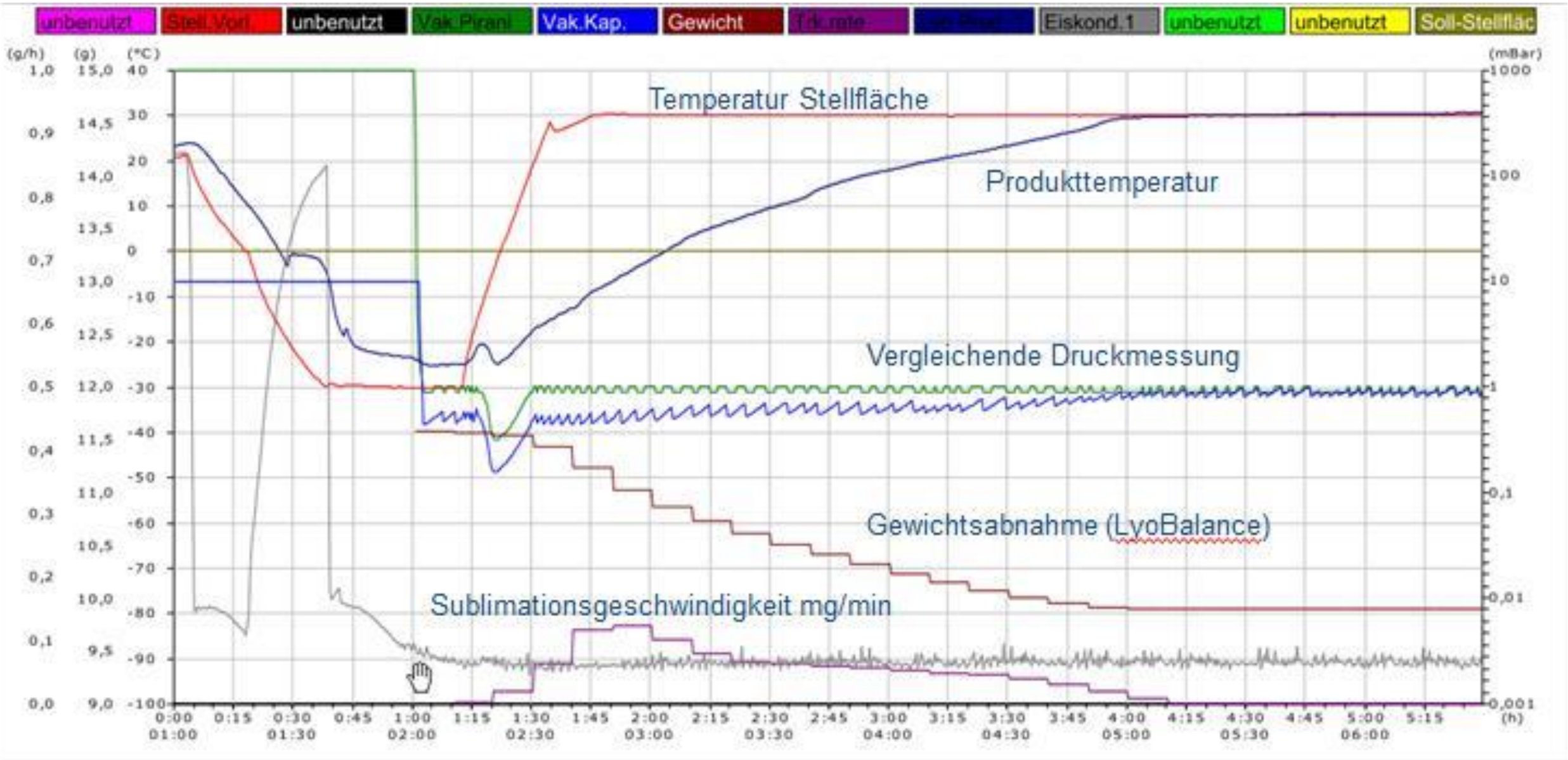
via LyoBalance (can be integrated in LSCplus units)

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

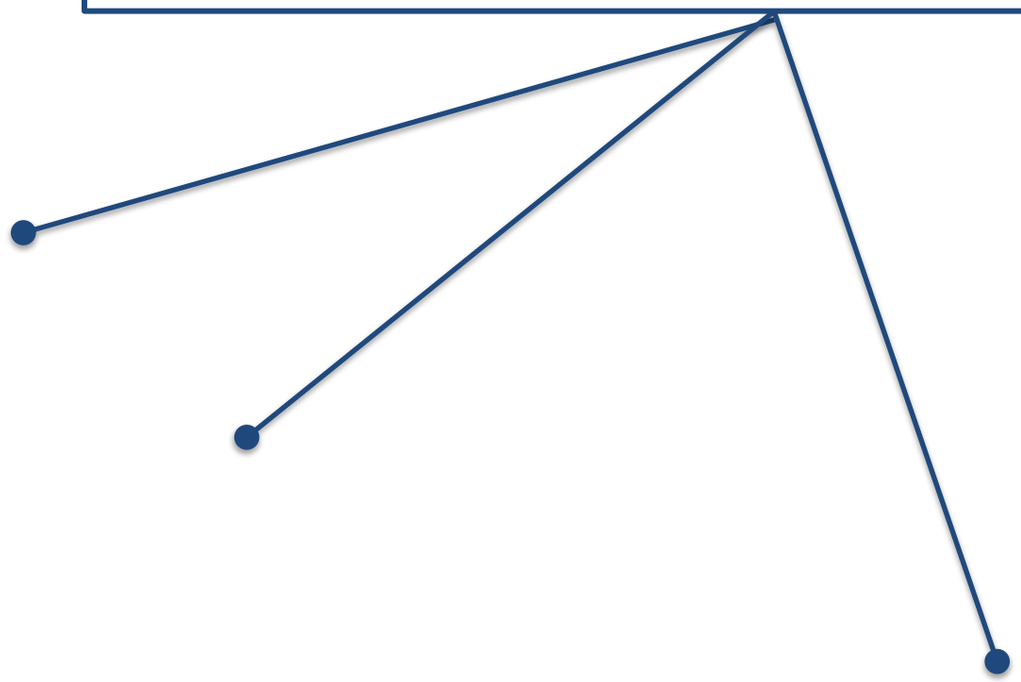


Inline camera LyoCam

- 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

synchronized presentation of process data, event list & video



Die Pharmbiocon LSE ist Ihr Partner in Pharmaindustrie und Medizintechnik, in den Bereichen Management / Qualitätssicherung / Forschung und Entwicklung / Engineering mit über 15 Jahren Erfahrung in der Pharmaindustrie.

Unser Leistungsspektrum umfasst die Durchführung von Qualitätsprüfungen von Pharmazeutischen Produkten in unserem zertifizierten Prüflabor, die Planung und Überwachung von technischen Transfer Projekten, die Sicherstellung der GMP Richtlinien, die Entwicklung nuer so wie die weiter Entwicklung bzw. die Optimierung von Prozessen wie z.B. Gefriertrocknungsprozessen.

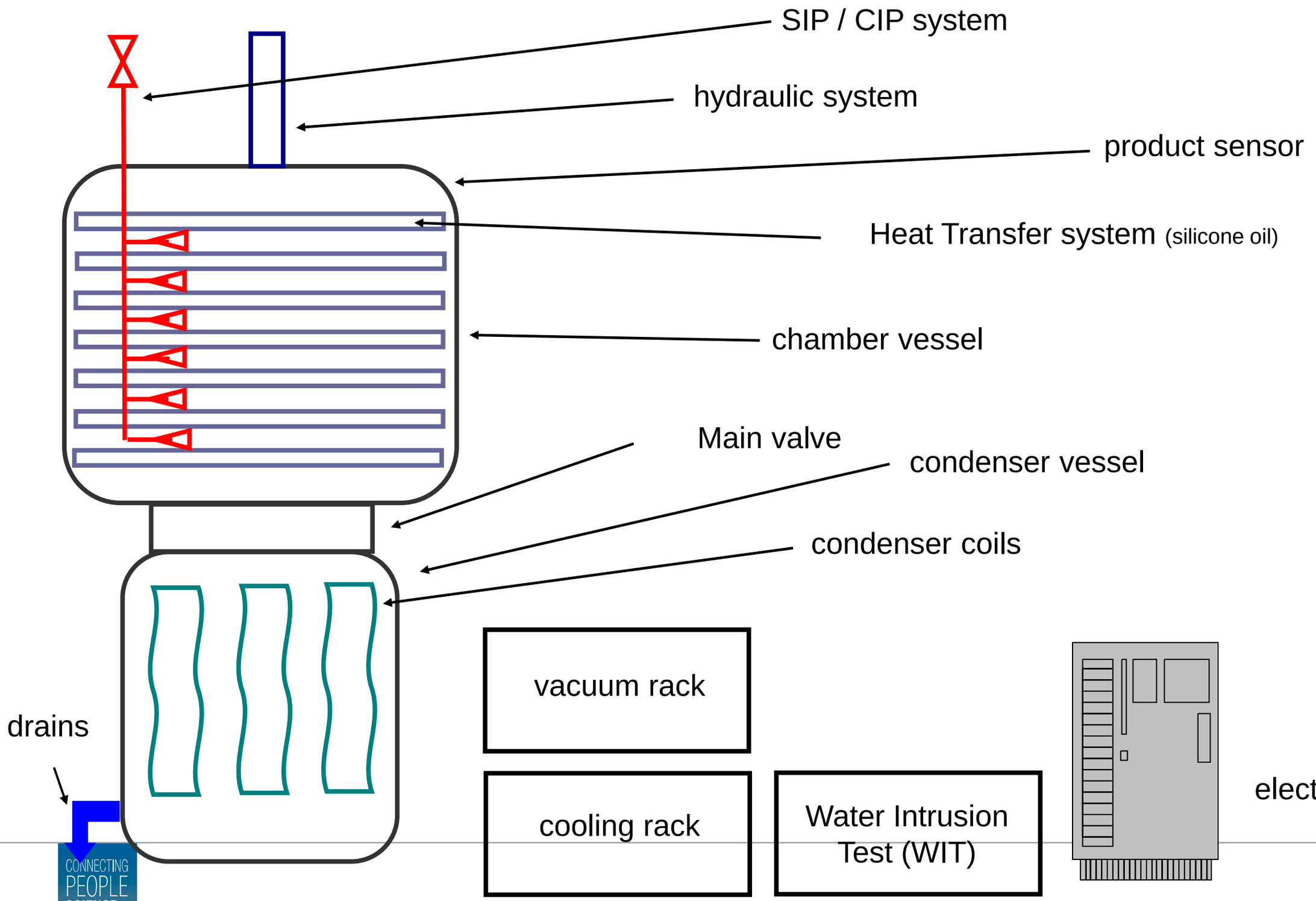
Sprechen Sie uns gerne an, unsere Erfahrenen Mitarbeiter aus den Bereichen der Herstellung und der Forschung und Entwicklung stehen Ihnen gerne zur Verfügung.

Pharmbiocon
Life Science Engineering

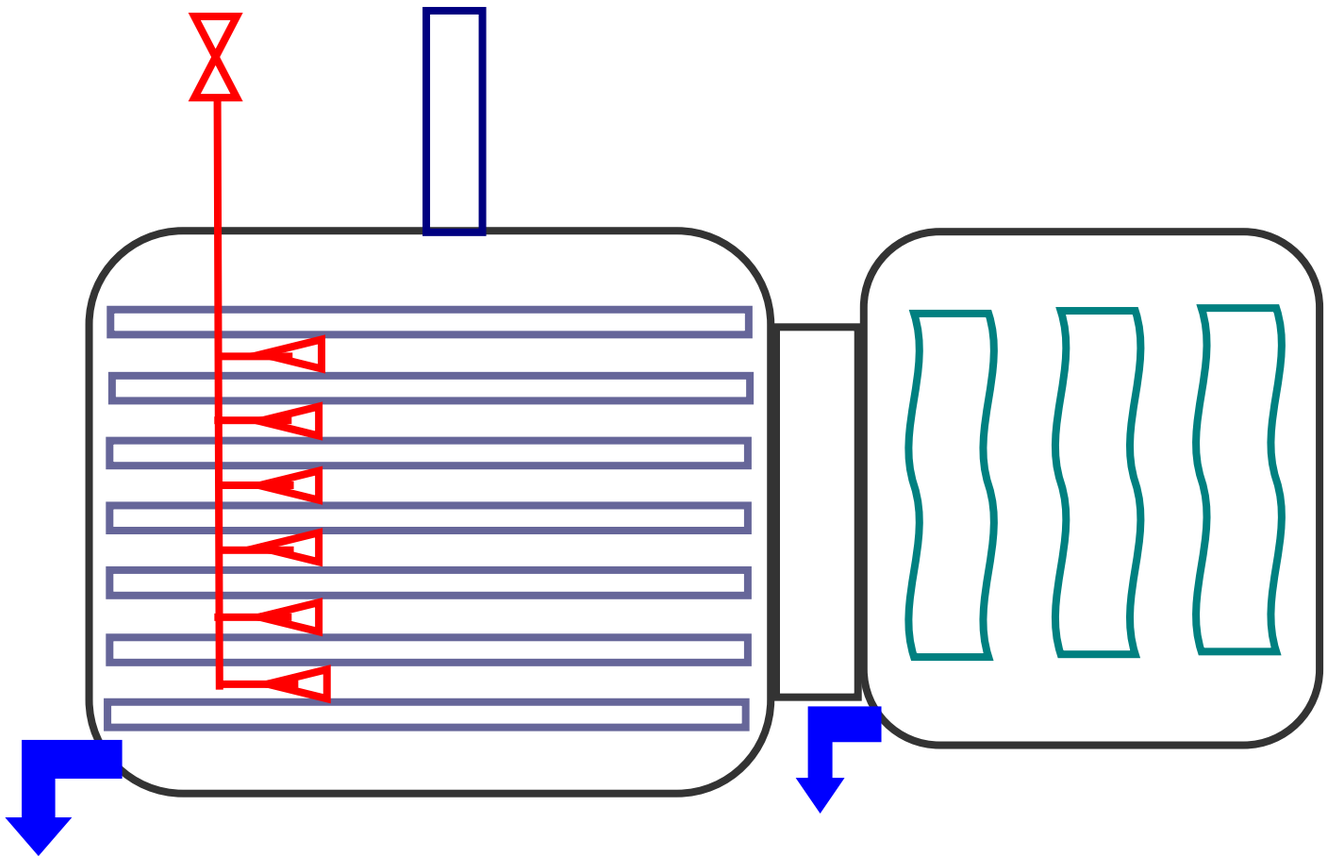
Theory 5:
Construction of freeze dryers

- construction of freeze dryers
- systems of freeze dryers
- different types of freeze dryers
- existing lines of freeze dryers
- parameters of freeze dryers

Lyophilisator



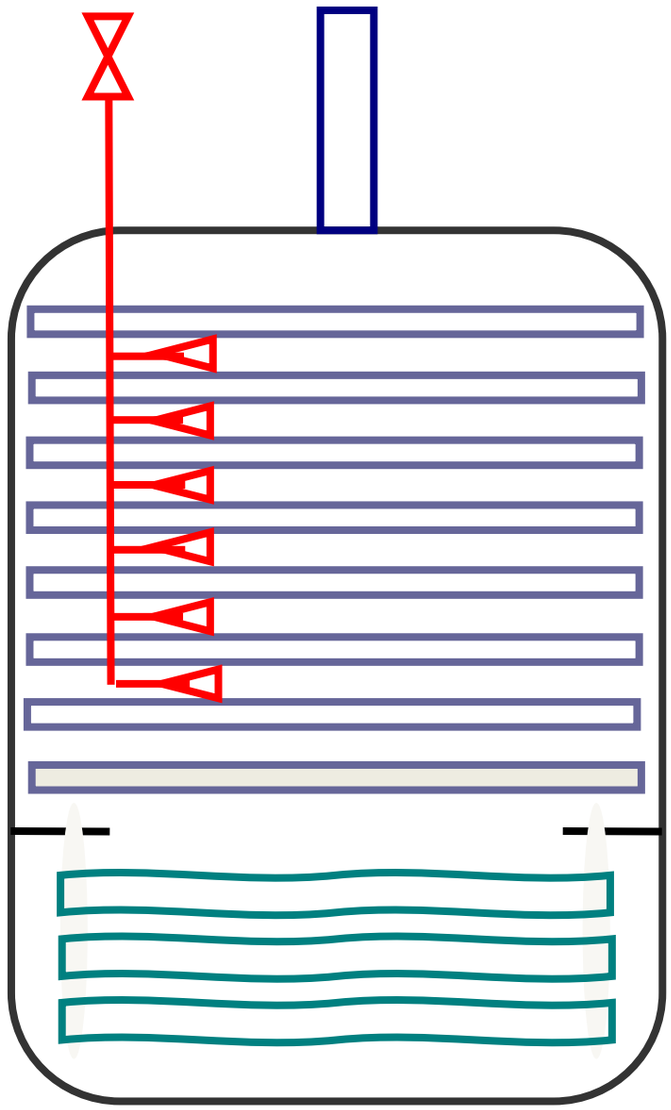
Lyophilisator



Side mounting of ice condenser:

- installation on one level
- potential risks for are the Radiation effects of the condenser to the vials which stand nearby the Main Valve

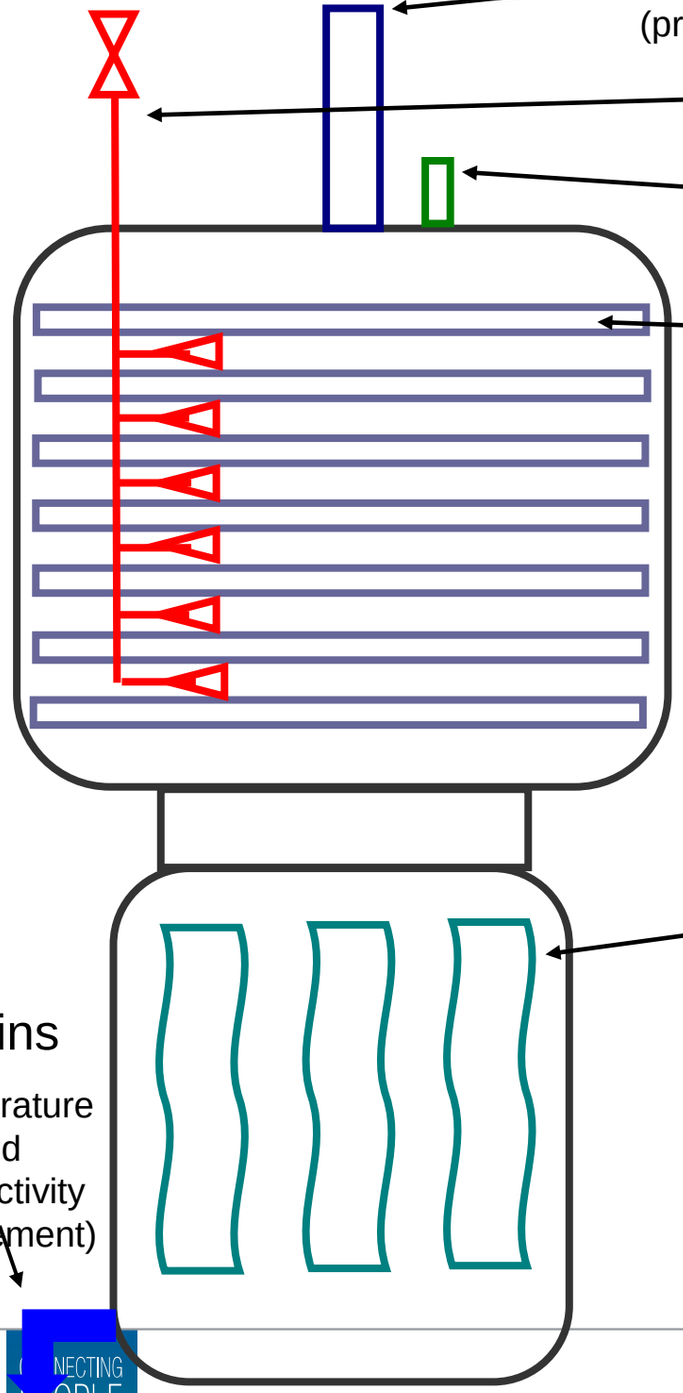
Lyophilisator



Compact design / one-chamber design:

- installation on one level
- compact design
- The Main Valve ist mounted on the Shelf Stack

Lyophilisator



hydraulic system
(pressure- and control sensors)

SIP / CIP system
(pressure- and temperature sensors)

vacuum- / pressure sensors

Heat Transfer system (temperature sensors)

product sensor (temperature and conductance)

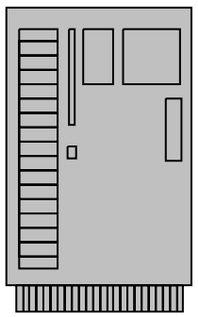
condenser coils (temperature sensors)

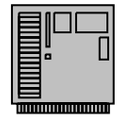
drains
(temperature and conductivity Mesurement)

vacuum rack
(vacuum sensors)

cooling rack
(temperature sensors)

Water Intrusion Test (WIT)
(pressure- and temperature sensors)





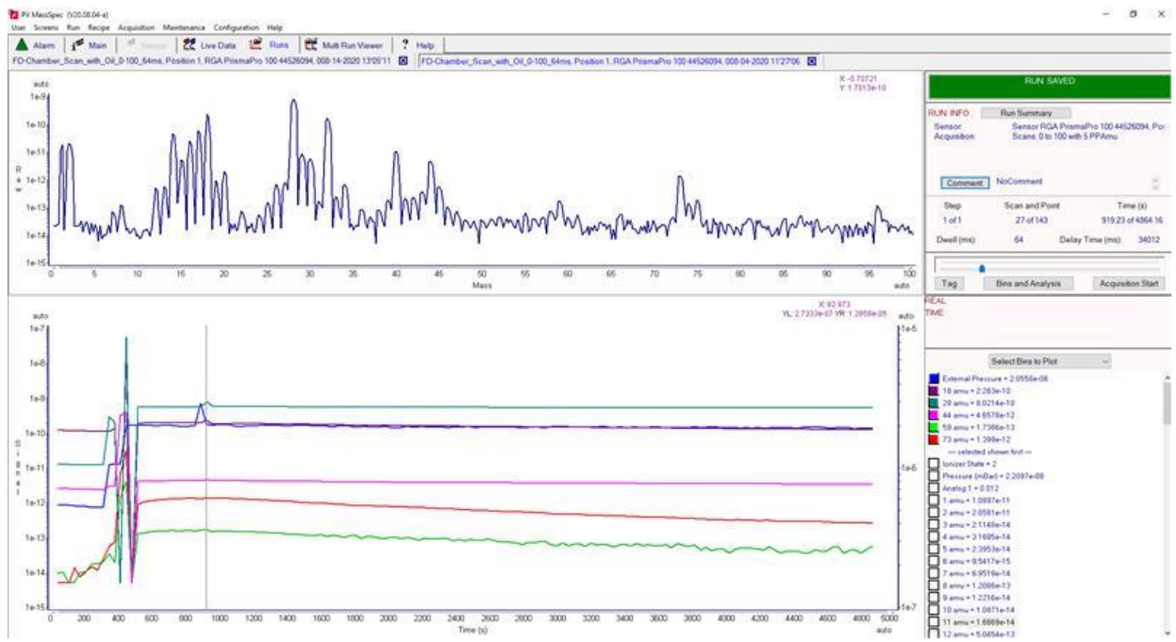
PC systems
(SCADA / operator panel)

power and communication systems
(PLT / PLS systems)

Lyophilisator

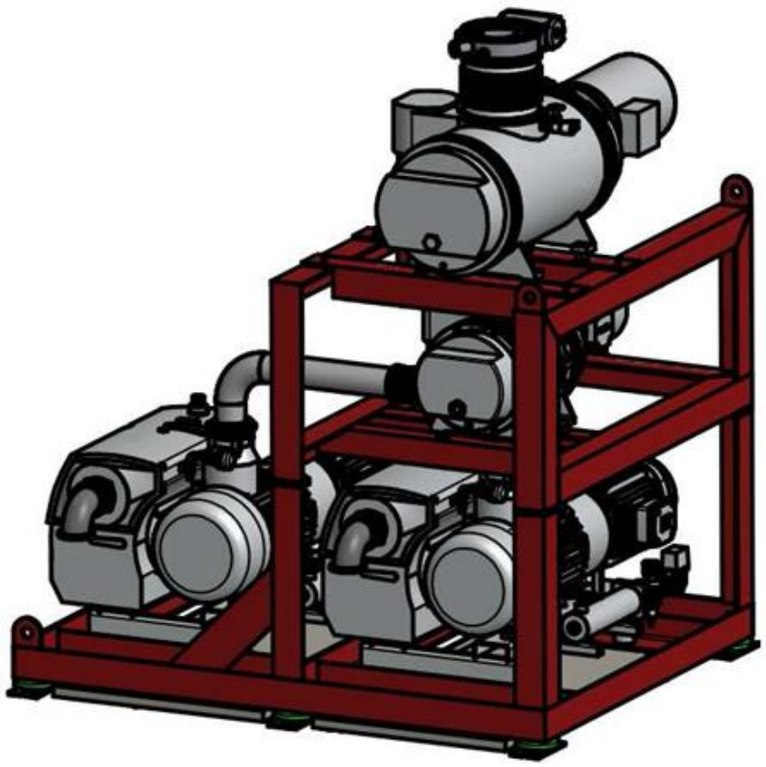
Special Sensor

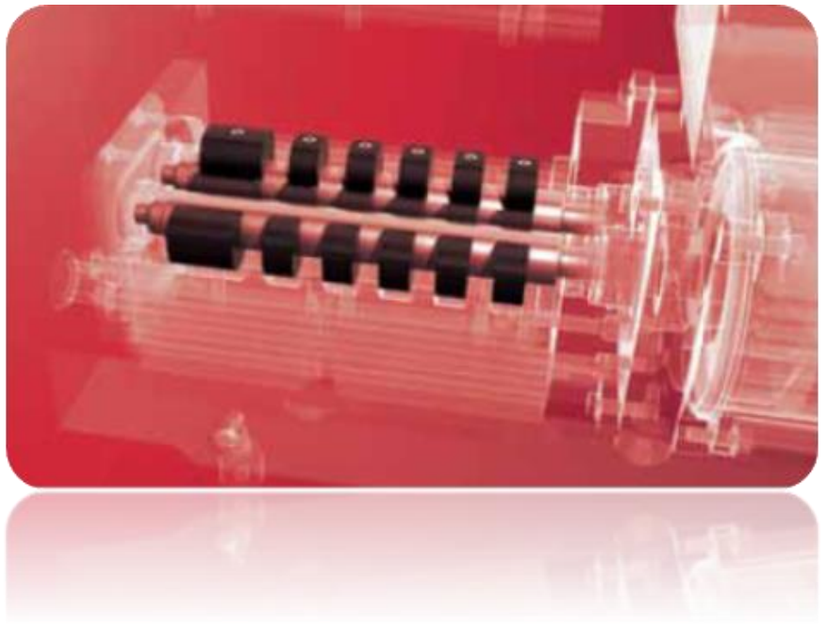
Mass spectrometer Sensors for silicone oil detection mounted in the Main Valve



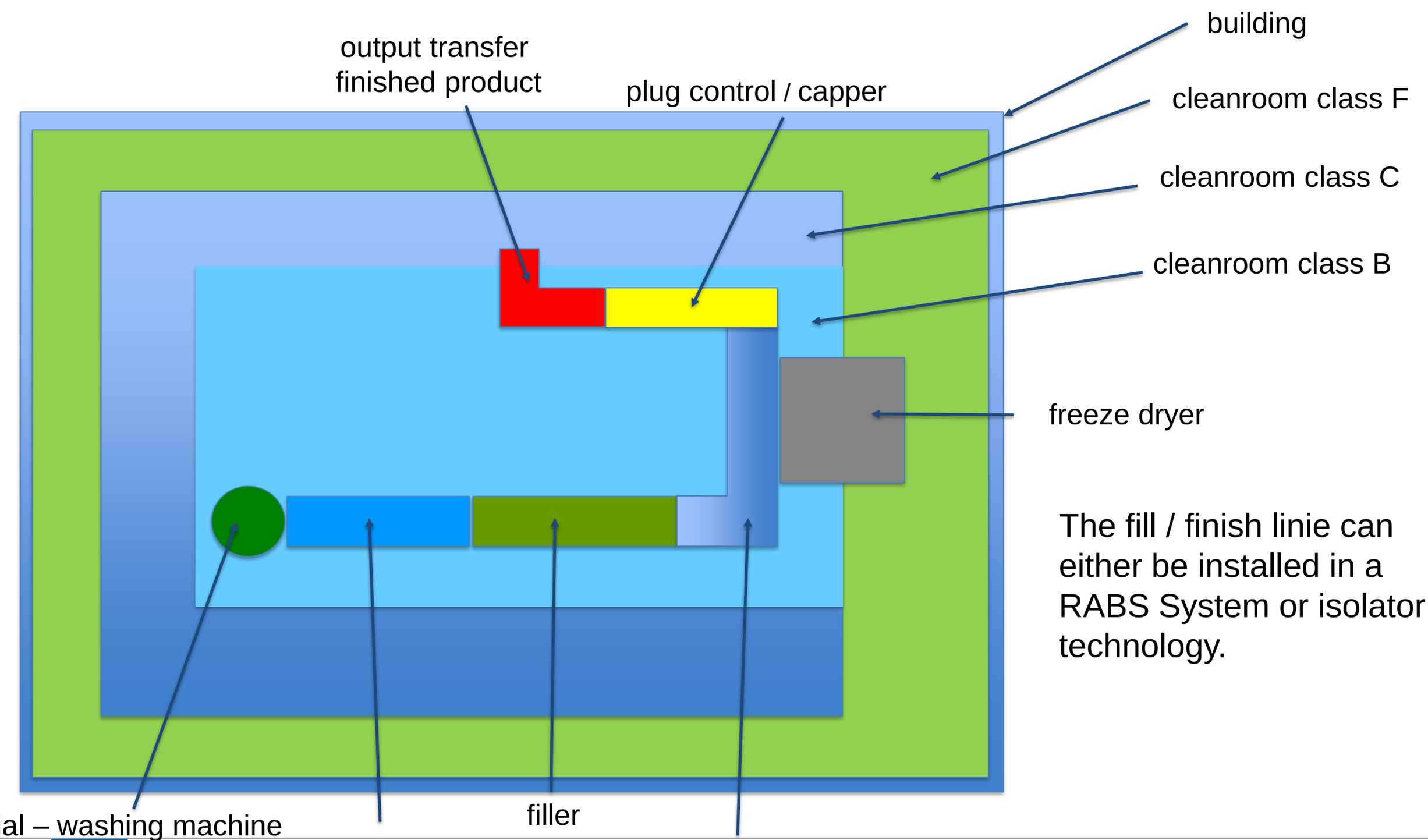
Lyophilisator

vacuum pump units



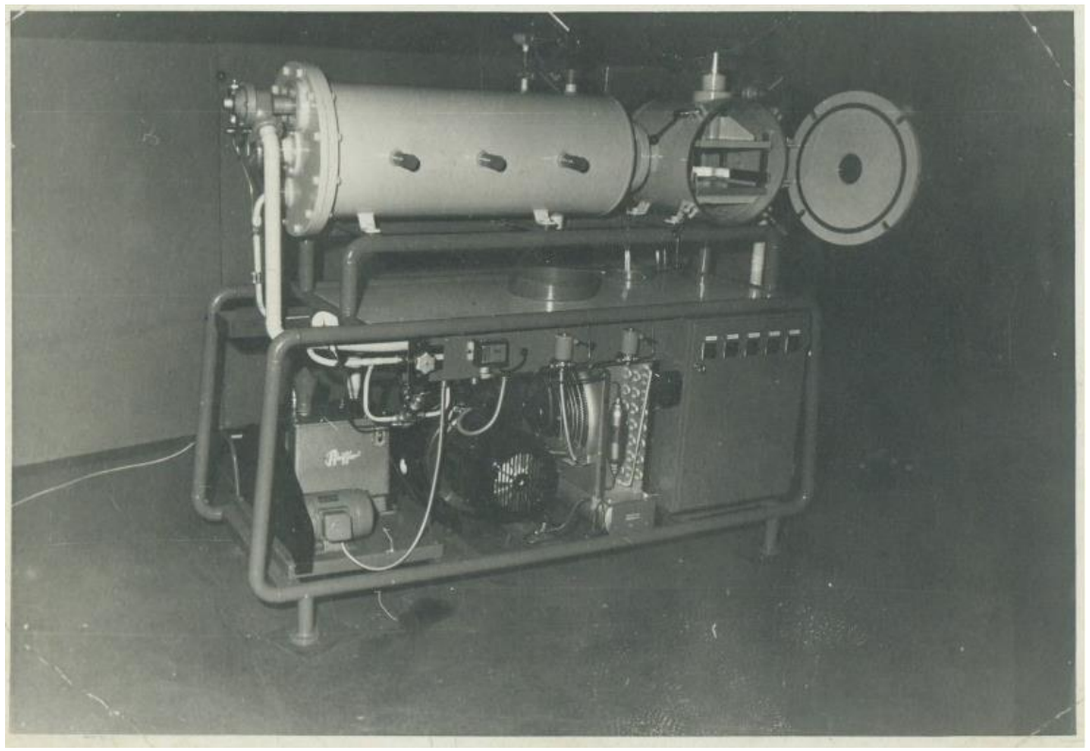


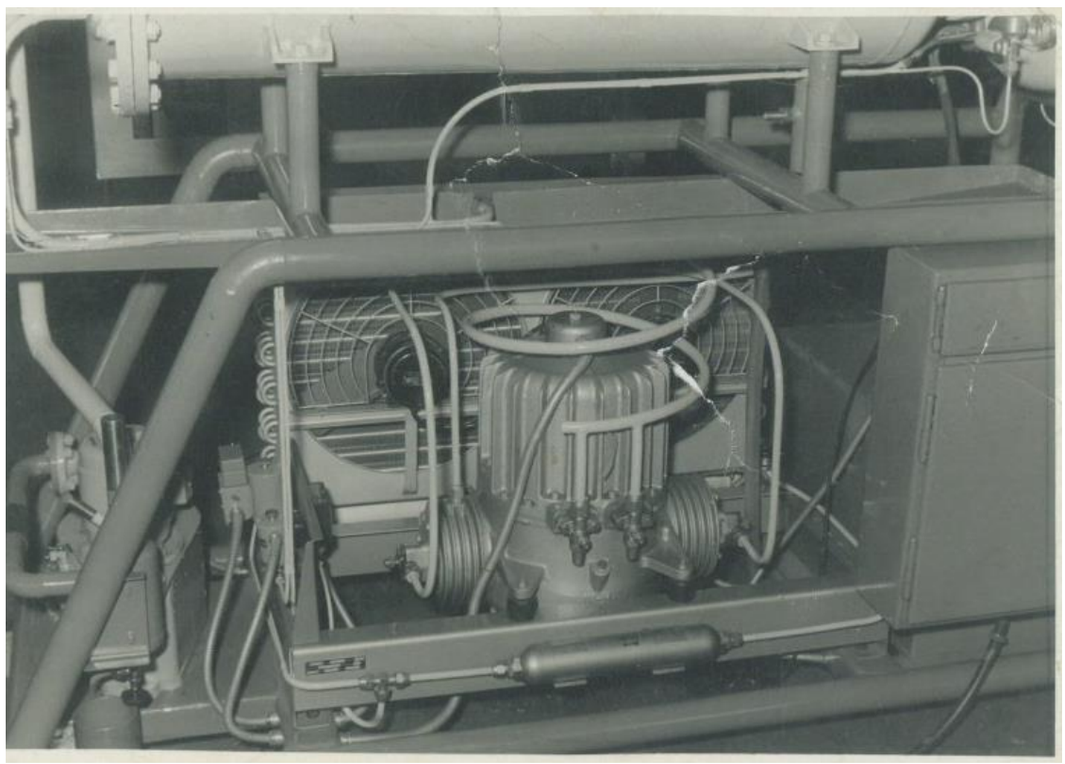
Exemplary construction of GT range



The fill / finish linie can either be installed in a RABS System or isolator technology.

Old treasures





RESEARCH & DEVELOPMENT | DESIGN | INSTALLATION | COMMISSIONING | FUNCTIONALITY | PERFORMANCE

Die Pharmbiocon LSE ist Ihr Partner in Pharmaindustrie und Medizintechnik, in den Bereichen Management / Qualitätssicherung / Forschung und Entwicklung / Engineering mit über 15 Jahren Erfahrung in der Pharmaindustrie.

Unser Leistungsspektrum umfasst die Durchführung von Qualitätsprüfungen von Pharmazeutischen Produkten in unserem zertifizierten Prüflabor, die Planung und Überwachung von technischen Transfer Projekten, die Sicherstellung der GMP Richtlinien, die Entwicklung nuer so wie die weiter Entwicklung bzw. die Optimierung von Prozessen wie z.B. Gefriertrocknungsprozessen.

Sprechen Sie uns gerne an, unsere Erfahrenen Mitarbeiter aus den Bereichen der Herstellung und der Forschung und Entwicklung stehen Ihnen gerne zur Verfügung.

Pharmbiocon
Life Science Engineering

Theory 6:
Qualification/ requalification /maintenance

- GMP principles
- risk-based approach of qualification
- stage of qualification process (DQ-PV)
- change in the new annex 15
- basis of calibration

GMP principles

What means GMP?

G → Good

M → Manufacturing

P → Practice

What is included in GMP?

Regulations of production of medicinal products.

What is the aim of GMP?

The aim of GMP is to protect the People of dubious products.

For whom the regulations applies?

The GMP regulations aims to manufacturers of pharmaceutical products and the manufacturers of food- and feed industry.

GMP principles

Regulatory aspects:

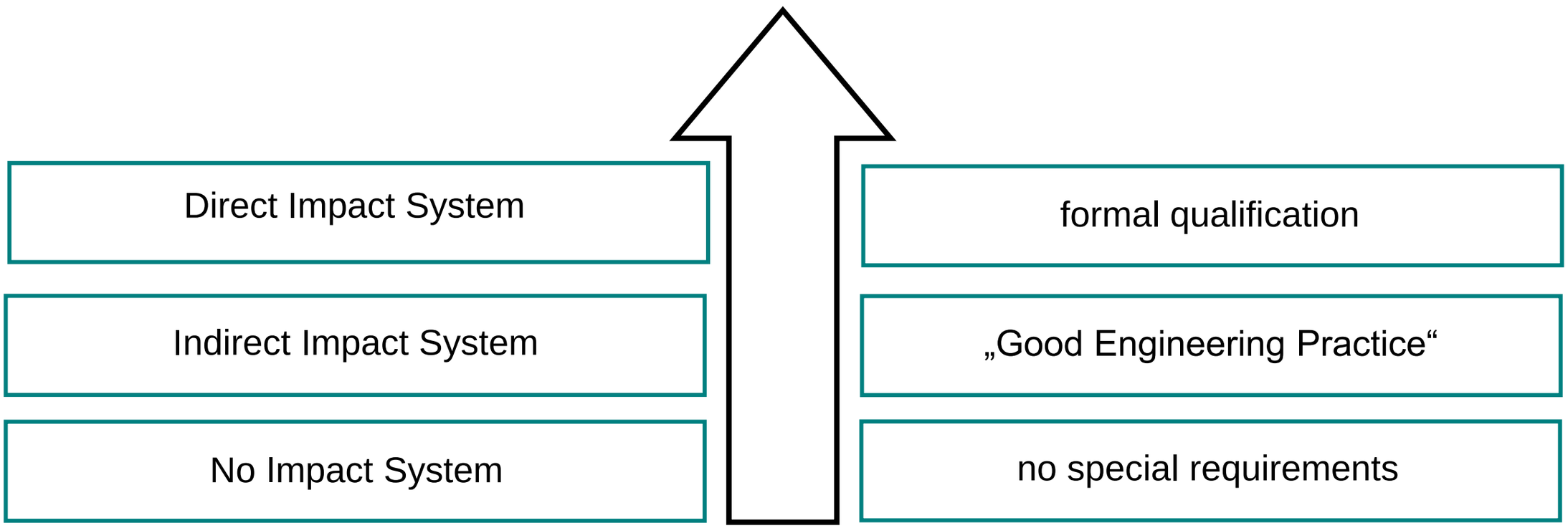
Policy of a GMP inspectors:

Everything that is not recorded, is considered as an finding and has never taken place!!!

GMP principles

Basic Quality Risk Management

Classification of systems



GMP principles

Basic Quality Risk Management

Definitions

Direct Impact System

A “Direct Impact System“ is expected to have direct impact on product Quality

Indirect Impact System

A“Indirect Impact System“ is not expected to have direct impact on product Quality,
but typically will support a „Direct Impact System“

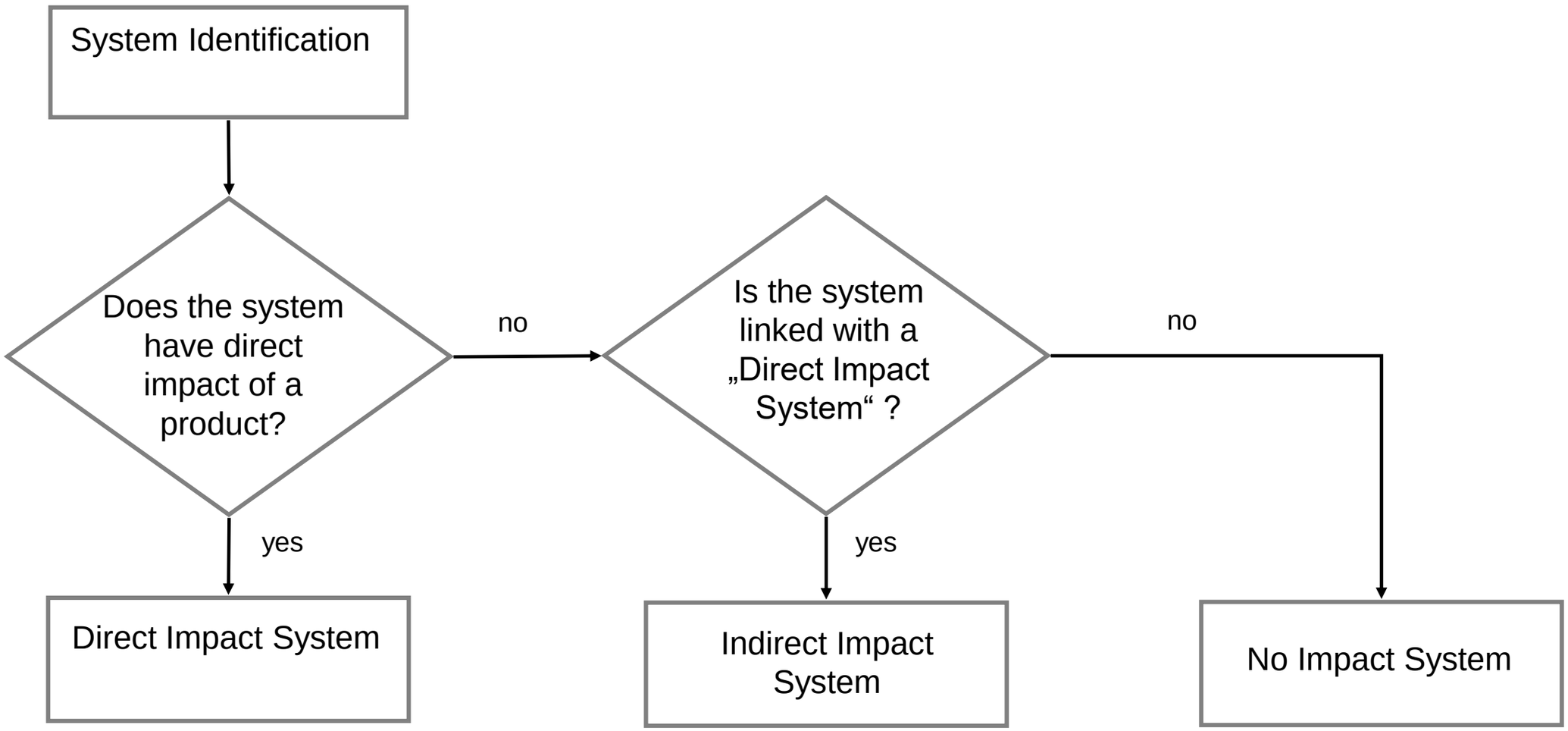
No Impact System

A “No Impact System“ will not have any impact, either directly or indirectly on product Quality

GMP principles

Basic Quality Risk Management

Impact Assessment Process



Lyo qualification

The different Qualification phases according GMP annex 15:

- DQ → Design Qualification (design phase / engineering phase)
- IQ → Installation Qualification (facility is constructed such as specified)
- OQ → Operation Qualification (function control)
- PQ → Performance Qualification (tests under production conditions)

After completion of one of theses phases, a Change Control is needed.

Lyo qualification

Qualification is the documented evidence, that the machine is built as specified.

What does it mean for…

DQ – It must be demonstrated and documented, that the design meets the GMP requirements.

IQ – It is verified that the machine meets the drawing schemes e.g. layout, PID, etc.

OQ – all processes runs as described in the design documents e. g. flowcharts, FS, etc.

PQ – The performance of the Equipment is in compliance with the specification.

Lyo qualification

Machines are completely validated if,…

… all qualification steps and validation steps have been completed.

This means that:

DQ – Design Qualification

IQ – Installation Qualification

OQ – Operating Qualification

PQ – Performance Qualification

CV – Cleaning Validation

PV – Prozess Validation

ATTENTION: validation includes all phases of qualification

Lyo qualification

Conclusion:

<u>What is qualification:</u>

Qualification is the documented evidence, that the Equipment is installed and perform as described in the specifications.

<u>What is validation:</u>

Validation is the documented evidence that the procedure or the process of the Equipment comes to the expected result.

Lyo qualification

Change Control process keep the machine in a validate condition.

It means:

- changes must be described
- changes must be justified
- implementation of measures must be evaluated
- changes must be checked for efficiency
- changes need the approval from the responsible person

Lyo qualification

A not well run change management System may have an influence of the production approval.

If a Production runs without a validate Status and bring a product to the market, in the worst case scenario, a human live can be destroyed by a not validate Process.

For us it means:

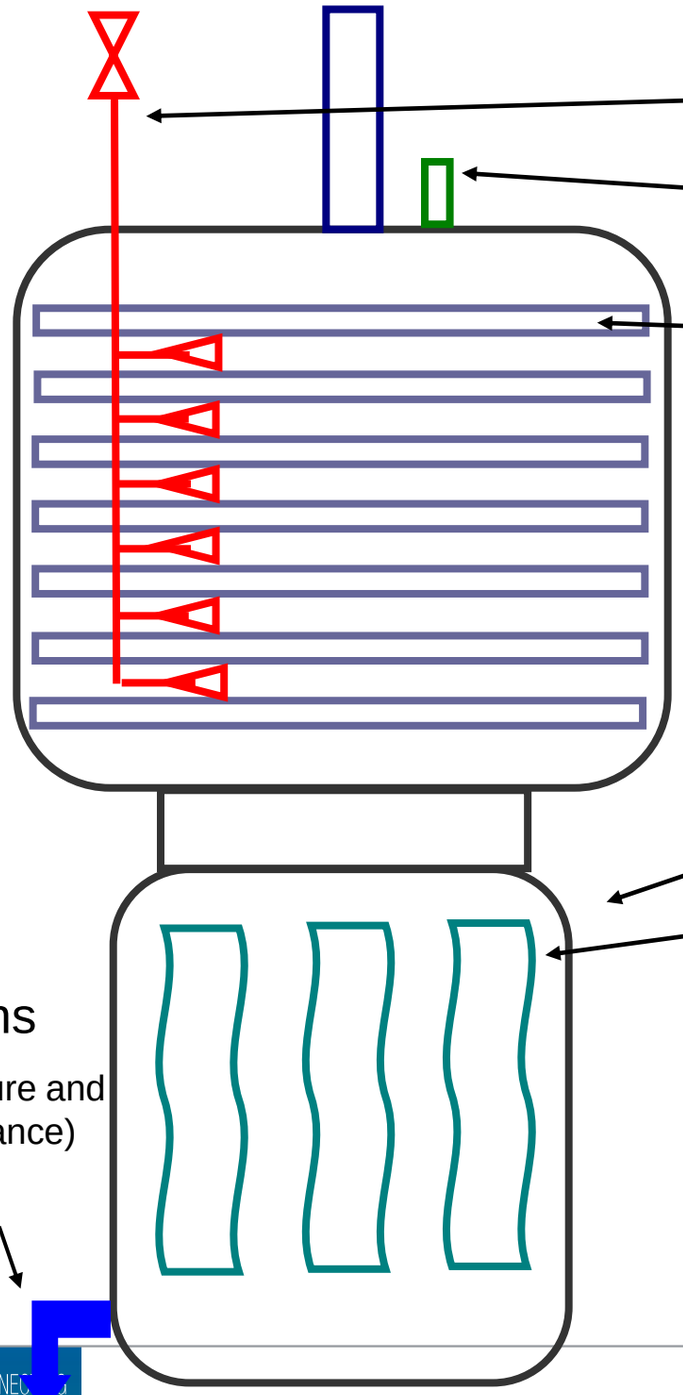
Do no modifications at validated machines, if the responsible persons (Head of Production, QA, etc.) have not release the Change.

In an emergency (product in chamber) a written confirmation is sufficient including signature of the responsible persons , in which they take responsibility for the modification.

ATTENTION: After this intervention the machine is not anymore in a valid condition!!!

In order to restore the valid condition, a Change Control must be filled out.

Calibration / Official Verification / Adjustment



SIP / CIP system
(pressure- and temperature sensors)

vacuum- / pressure sensor technology

brine system (temperature sensors)

product sensor (temperature and conductance)

condenser container

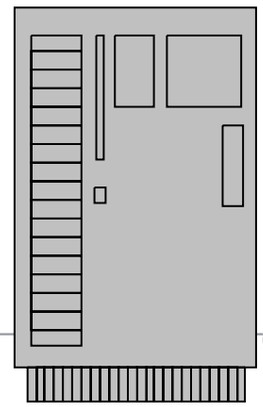
condenser coils (temperature sensors)

drains
(temperature and conductance)

vacuum rack
(vacuum sensors)

cooling rack
(temperature sensors)

Water Intrusion Test (WIT)
(pressure- and temperature sensors)



electrical cabinet

Calibration / Official Verification / Adjustment

Calibration

Definition of calibration by DIN 31051 is the evaluation and recording of the difference between the displayed value (Device) and the true value (Reference), without any technical intervention.

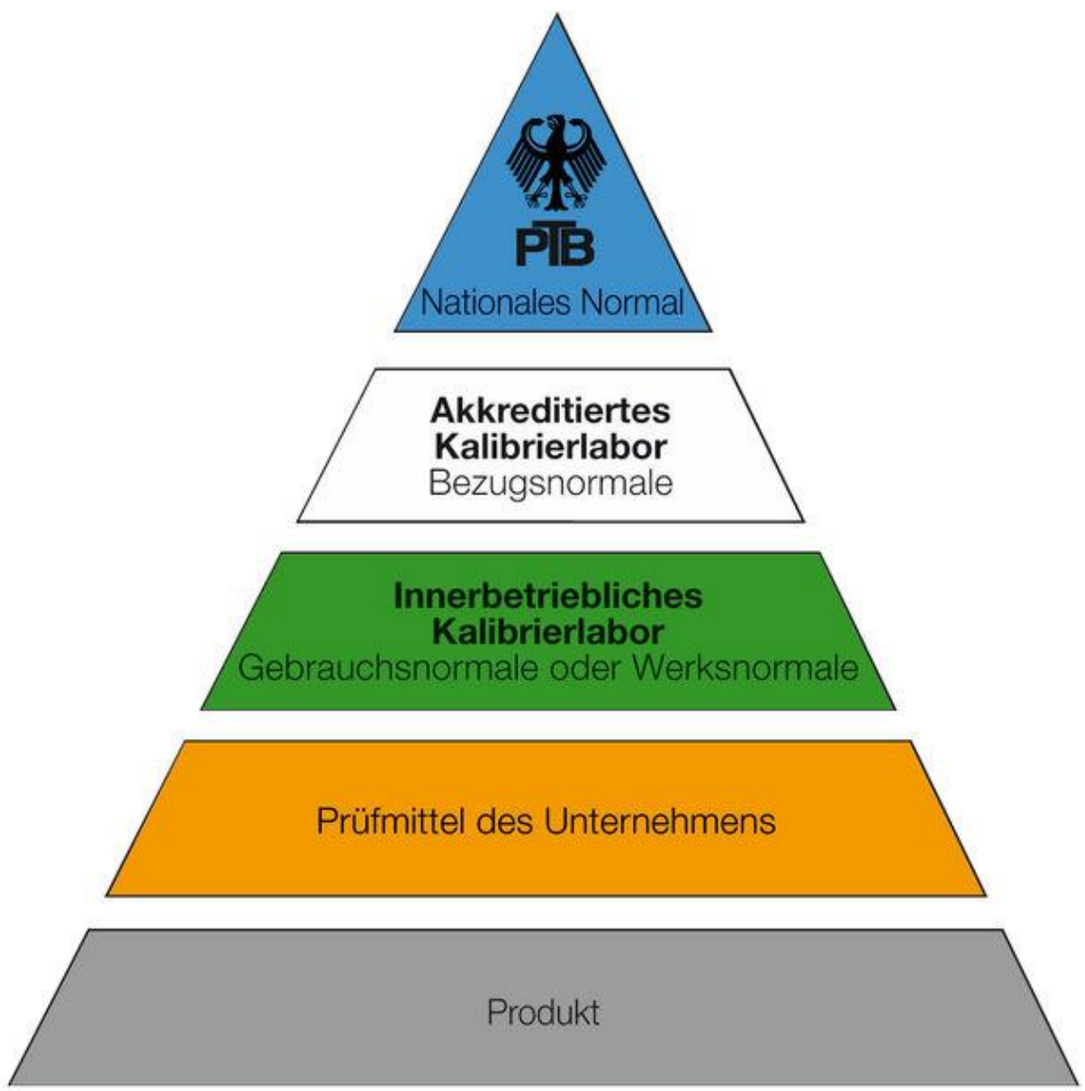
Official verification (NIST)

A official verification is also a calibration, however official verification may only be carried out by government Institues (NIST).

Adjustment

A Adjustment is a technical Change in measurement chain. A measuring instrument is adjusted in such a way, that it does not exceed the tolerances. After adjustment a new calibration must be carried out.

The hierarchy of calibration is regulated from the national standard to the product.



e.g. German NIST Organisation

Calibration / Official Verification / Adjustment

Three general rules for correct measurement

1. Acceptance Criteria must be clearly defined.

2. Reference value (unit) must be agreed or defined through convention (traceability).

3. Measurement method must be specified with all boundary conditions, which have an effect on the measured value.

e. g.

Value → temperature

unit → °C

measurement method → reference Sensor and Device in a liquid bath

Calibration / Official Verification / Adjustment

Chapter 3.41 of EG-GMP Guideline:

“Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.”

Product critical instruments:

Product critical instruments are instruments which failures have an influence of product quality.

Process- and system critical instruments:

Process and system critical instruments are instruments which failures have an influence of machine- and process functions without influence the product quality.

Calibration / Official Verification / Adjustment

Good calibration practice

A master SOP describes the basic procedures of a calibration.

The calibration method reflects the state of the art, is qualified and documented in calibration instructions.

Devices under Testing are adapted to the Reference Sensor and mounted as describe from the Supplier. The Reference Sensor must have the right measuring range and accuracy.

Calibration / Official Verification / Adjustment

GAMP:

In accordance with GAMP a classification of measuring points can be made.

Machine Safety Sensors:

Machine Safety Sensors are Sensors which have an influence of Equipment readiness.

Uncritical Sensors:

Uncritical Sensors are Sensors have no influence on product quality, machine- and process functions or system security.

Calibration / Official Verification / Adjustment

Specifications:

The accuracy of test equipment must not be less than the accuracy of measurement equipment and must be more accurate by a factor of 3 than the measurements needed (where possible).

The Calibration of temperature measurement systems, used for validation, must be performed in a range that is in the range of e.g. sterilization temperature.

Condenser Stresstest

The Condenser Stresstest is one of the main Tests during Qualification, this Test confirms:

- that the specified Condenser Capacity can be Reached from the System
- that the System has enough cooling Power (LN2 or Compressor) to handel the Process
- that the System has enough vacuum Power to handel the Process
- that the System can absorb the Water Vapor in a difined Time e.g. 400kg in 24h

To ensure that the Condenser can handel the specified Water the following calculation can be used:

URS Specification – 400kg of Water

400kg (Water) + 10% = 440kg (Batch Size)

Lyo qualification – typical Test

Condenser Stresstest – In Vials

Chamber

Main Valve

Sublimation

Condenser

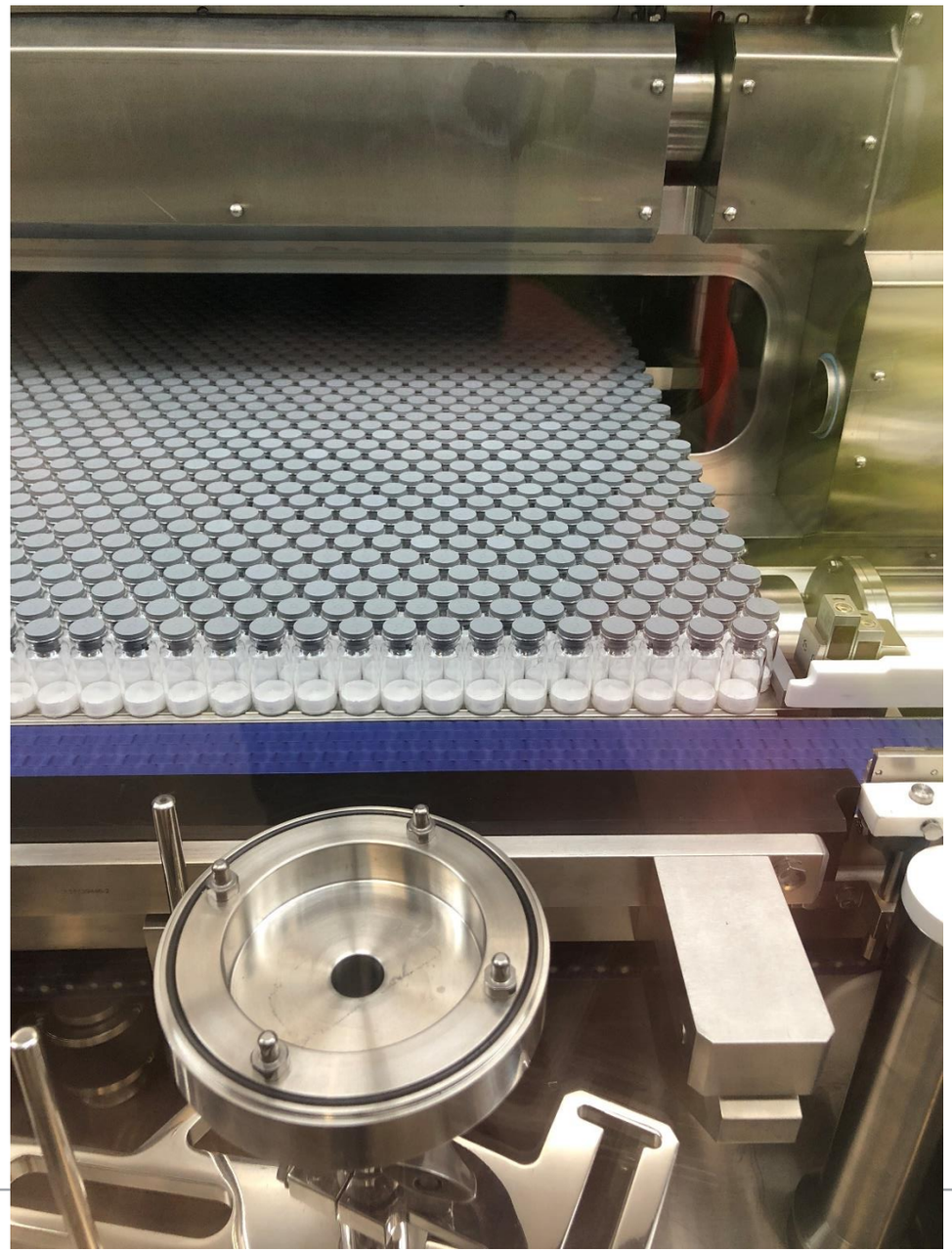
Condenser Stresstest - Vial

View from the Top of the Ice Condenser.

Lyo qualification – typical Test

Condenser Stresstest - Vial

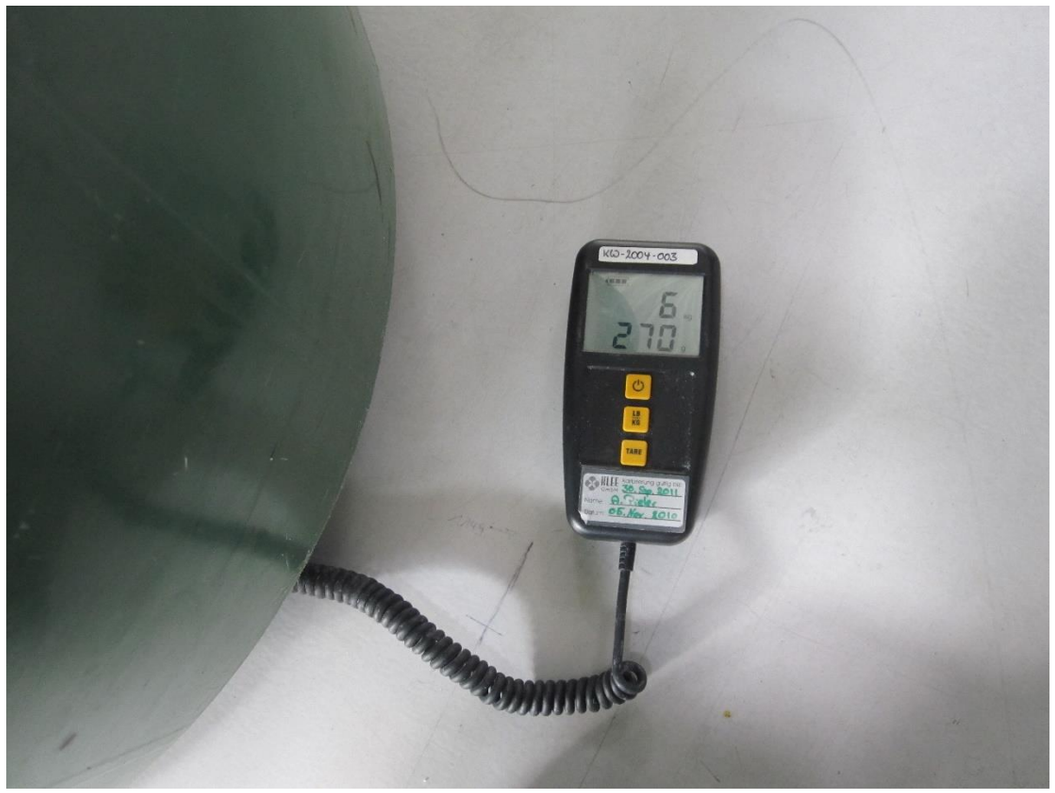
Row by Row Unloading of
Freeze dried Vials



Lyo qualification – typical Test

Condenser Stresstest - Frames

Weight of Solution

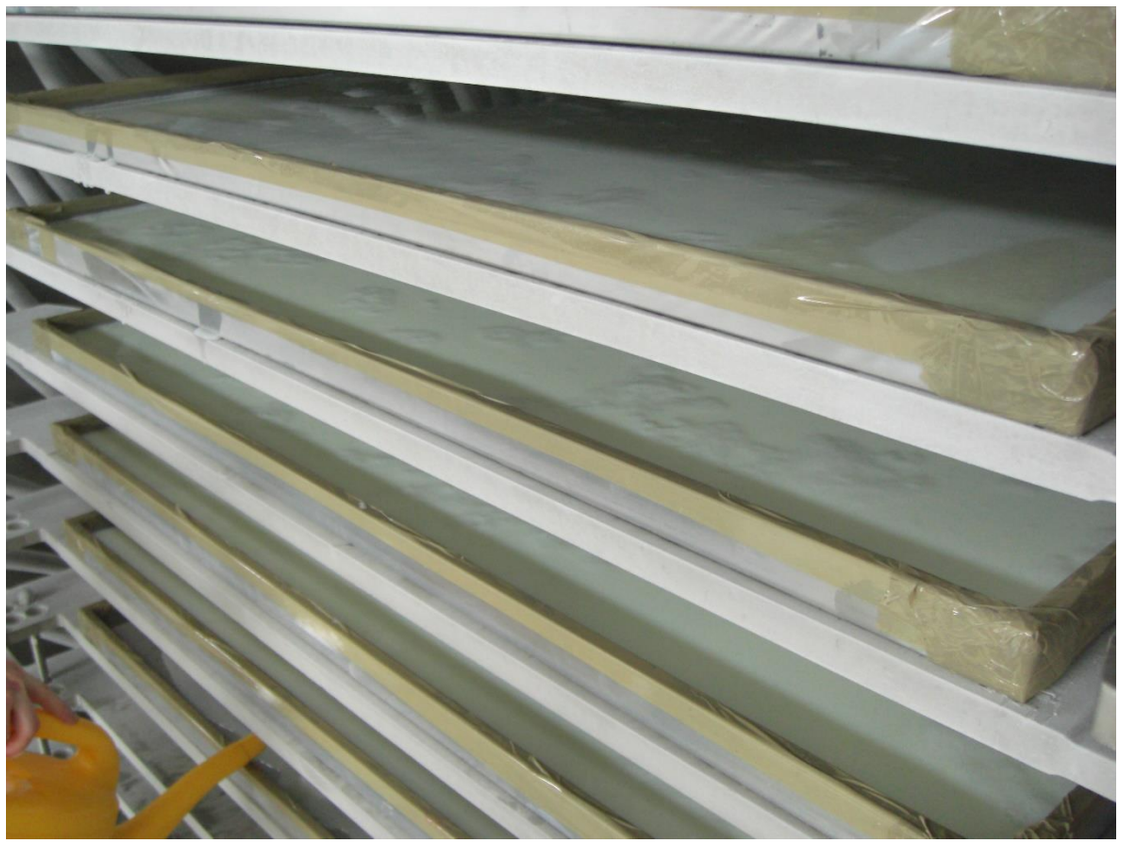


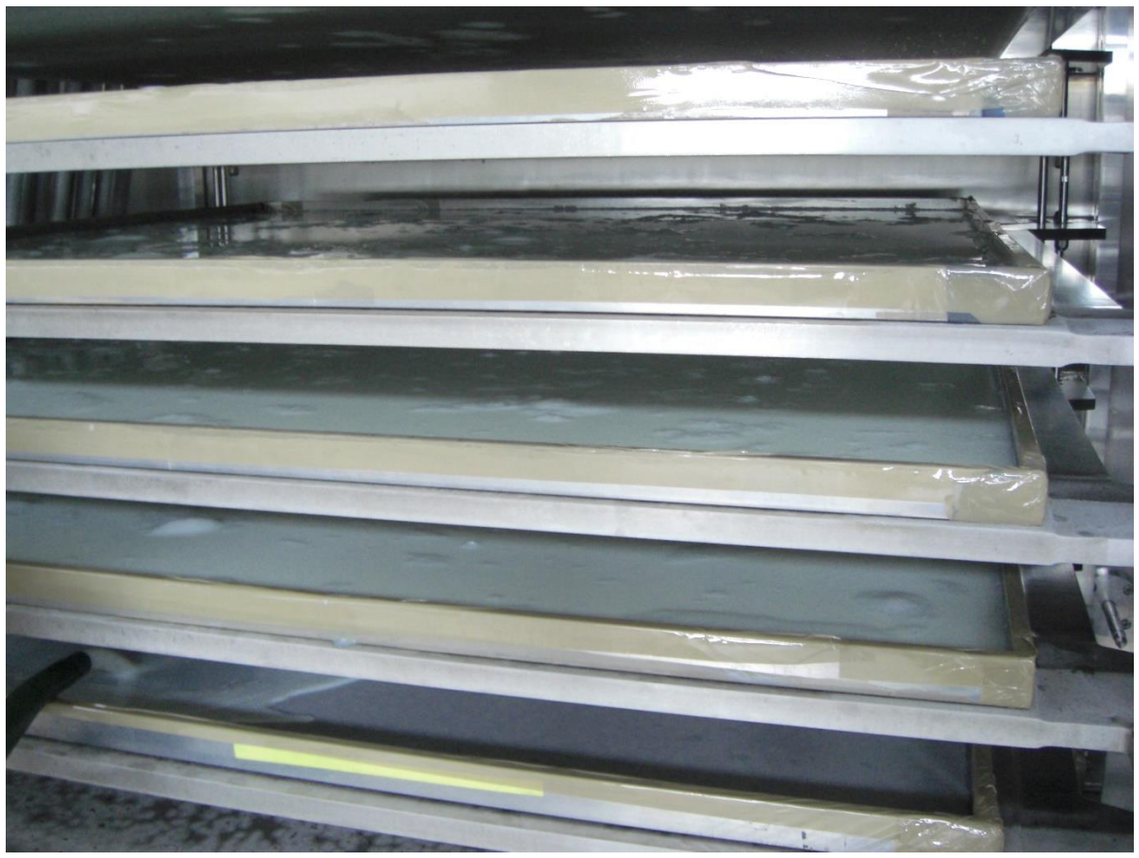
Filling the Frames

with a High Performance watering Can

Condenser Stresstest

All Frames should be filled similar to avoid different Sublimation on the shelf stack

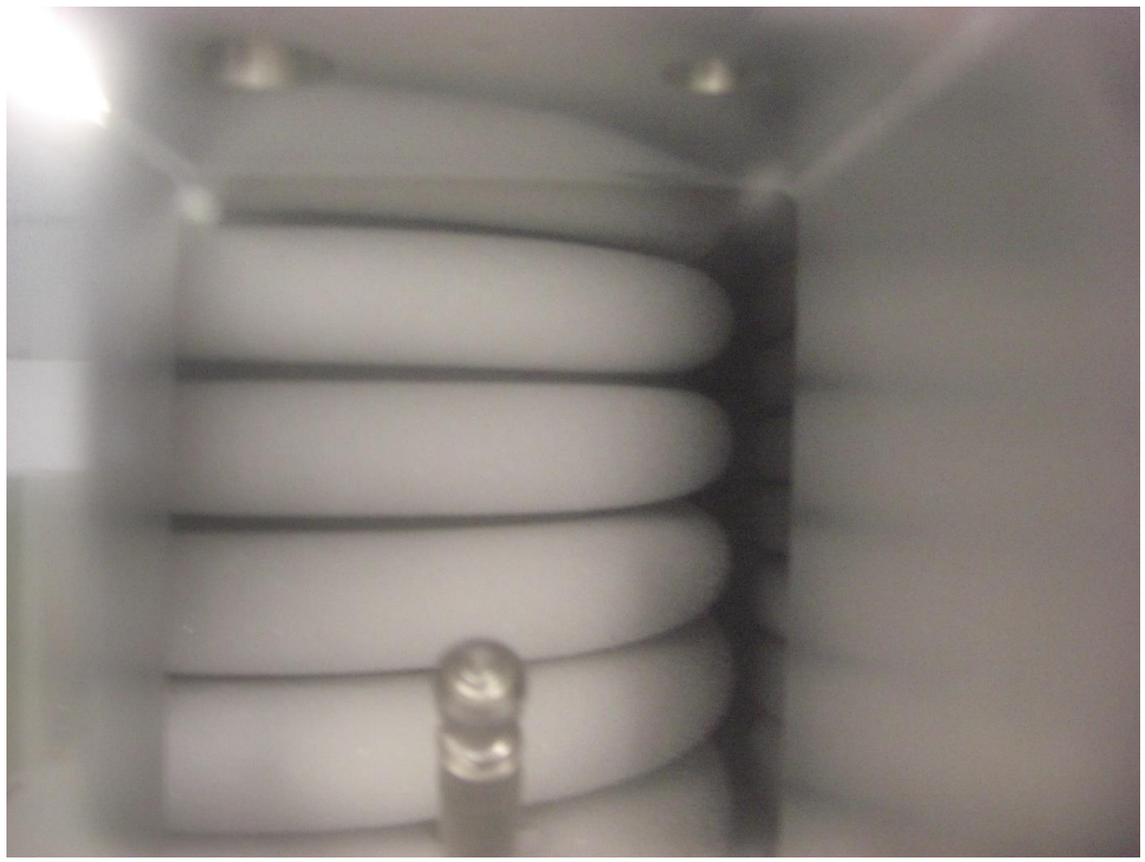




Lyo qualification – typical Test

Condenser Stresstest

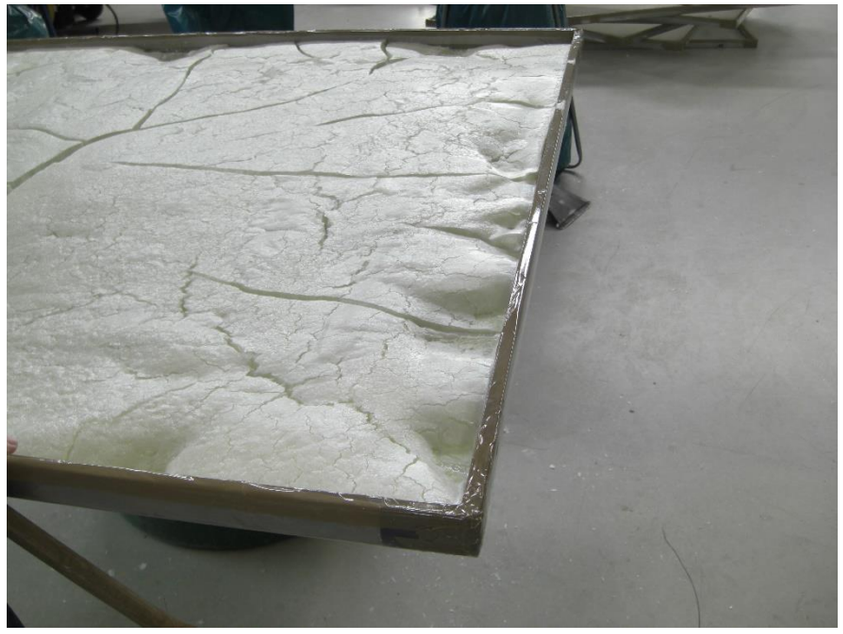
View into the Condenser during Process

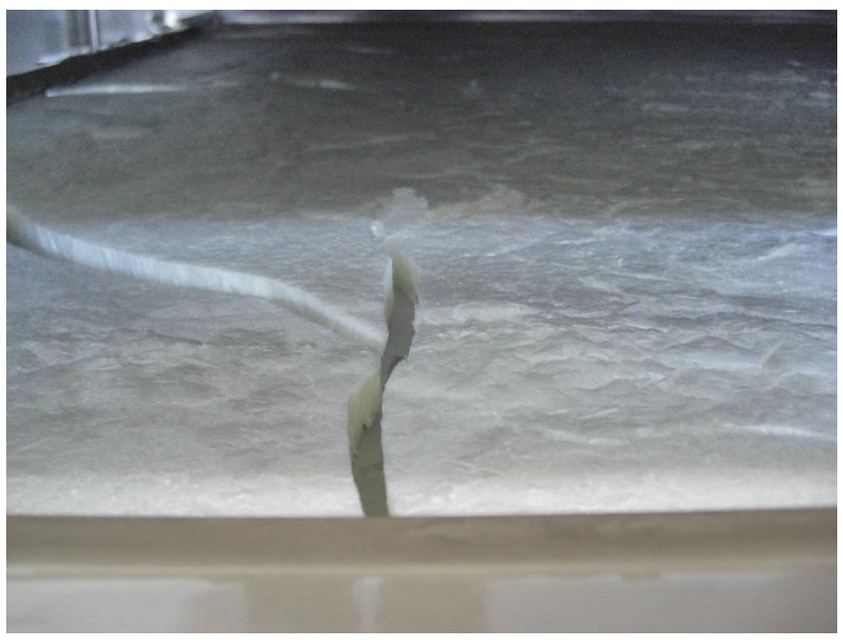


Lyo qualification – typical Test

Condenser Stresstest

Fully dried Frames





Shelfmapping

The Shelf Mapping is the main Test to demonstrate that the System can regulate the Shelf temperature as specified in URS.

This Test confirms:

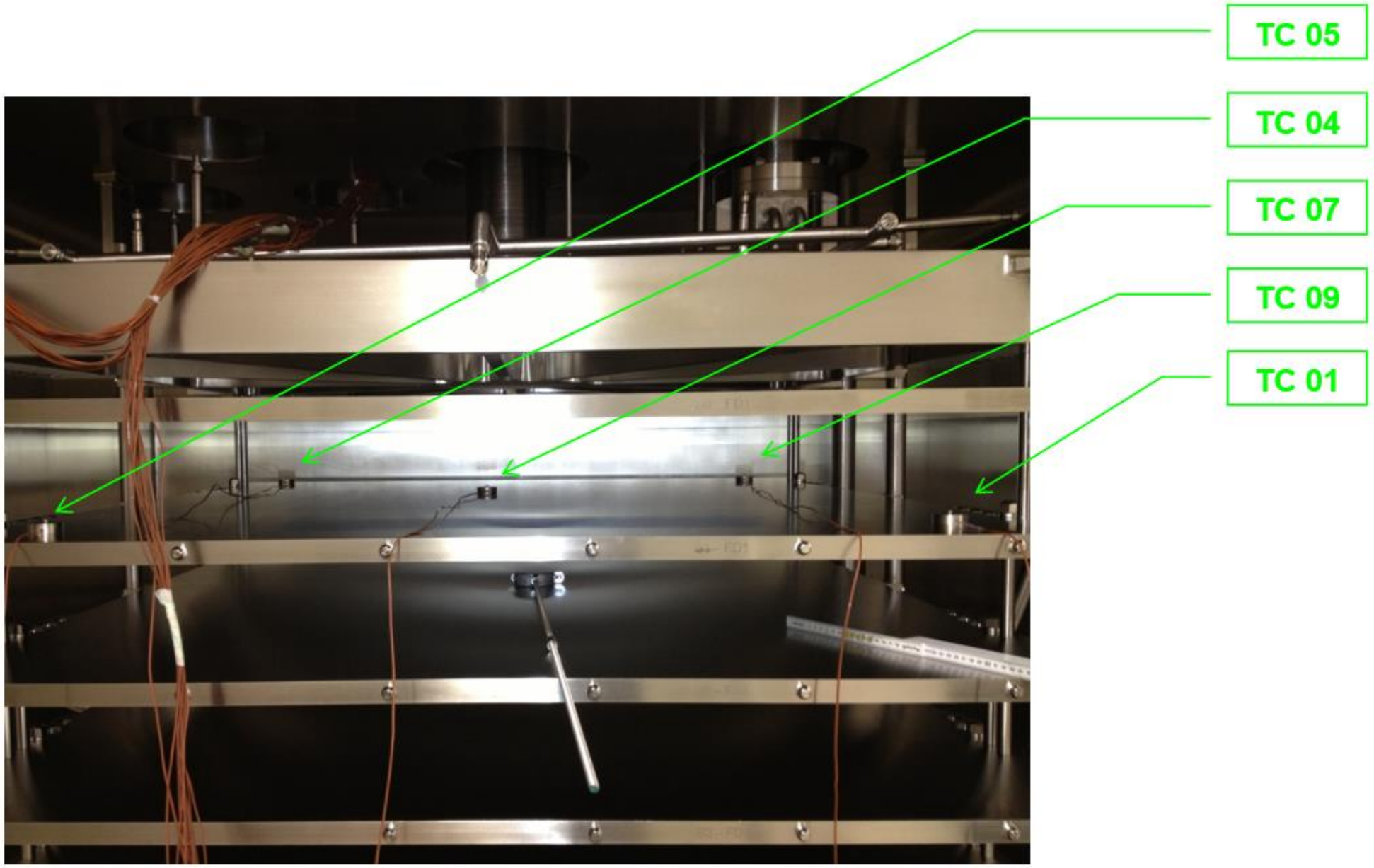
- that each shelf is inside the Spec e.g. +/- 0,5°C
- that the hole shelf stack is inside the Spec e.g. +/- 1,0°C
- that the controller System for Silicon oil works correct (Calibration is done)
- that the Heat Transfer System is filled correct (no air inclusions)

Shelfmapping

Positioning of Shelfmapping Sensors

Lyo qualification – typical Test

Shelfmapping



Lyo qualification – typical Test

Shelfmapping

Preconditions for Shelfmapping:

- the Lyo should be fully installed
- the commissioning of the Lyo should be done
- the Calibration of the Lyo is done
- all Medias should be available and qualified

Die Pharmbiocon LSE ist Ihr Partner in Pharmaindustrie und Medizintechnik, in den Bereichen Management / Qualitätssicherung / Forschung und Entwicklung / Engineering mit über 15 Jahren Erfahrung in der Pharmaindustrie.

Unser Leistungsspektrum umfasst die Durchführung von Qualitätsprüfungen von Pharmazeutischen Produkten in unserem zertifizierten Prüflabor, die Planung und Überwachung von technischen Transfer Projekten, die Sicherstellung der GMP Richtlinien, die Entwicklung nuer so wie die weiter Entwicklung bzw. die Optimierung von Prozessen wie z.B. Gefriertrocknungsprozessen.

Sprechen Sie uns gerne an, unsere Erfahrenen Mitarbeiter aus den Bereichen der Herstellung und der Forschung und Entwicklung stehen Ihnen gerne zur Verfügung.

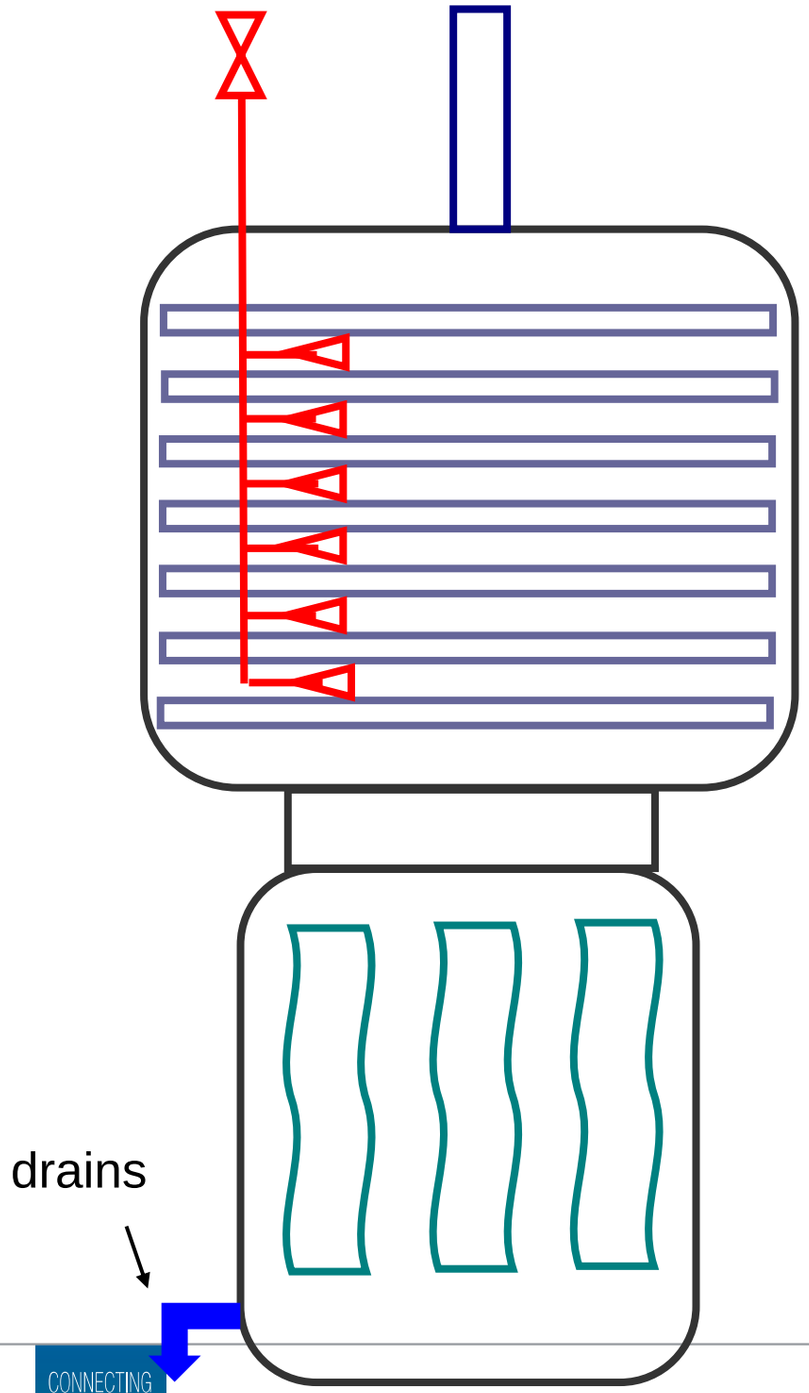
Pharmbiocon
Life Science Engineering

Cleaning and sterilisation

Theory 8:
Cleaning and sterilisation

- CIP / SIP systems
- acceptance of CIP / SIP systems
- cleaning validation
- sterilisation qualification
- turnaround process

CIP / SIP system

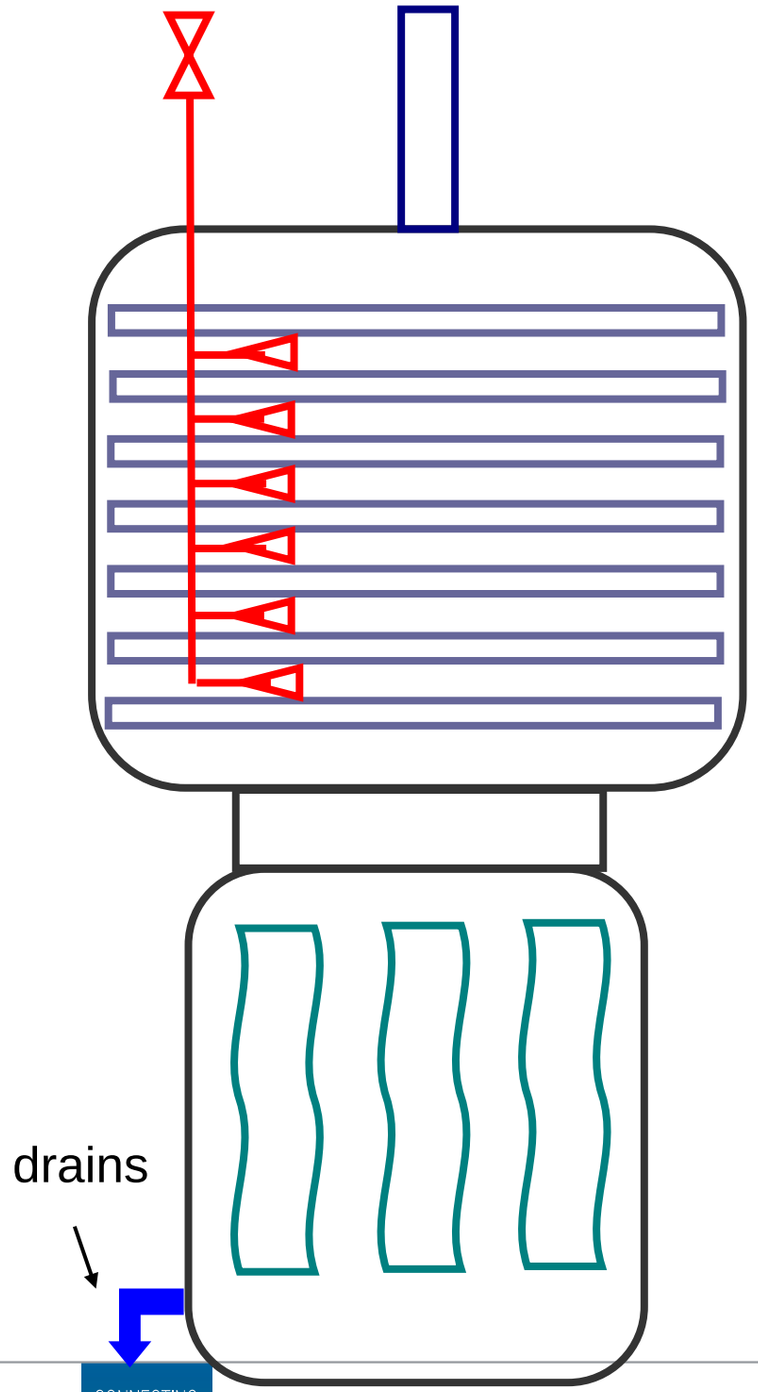


The aim of a CIP / SIP system is to clean the system and to sterilize the Freeze Dryer according to Specification.

GMP guidelines:

- assignment of responsibility of cleaning
- creation of cleaning time schedule
- description of cleaning
- define the acceptance criteria of cleaning
- proof of successful system cleaning (validation)

CIP / SIP systems



Prozess of CIP / SIP:

The system must be easy to clean in accordance to the applicable GMP rules (e. g. no dead spaces, corners should be rounded, etc.).

CIP / SIP systems can be integrated in a freeze dryer or as stand-alone System.

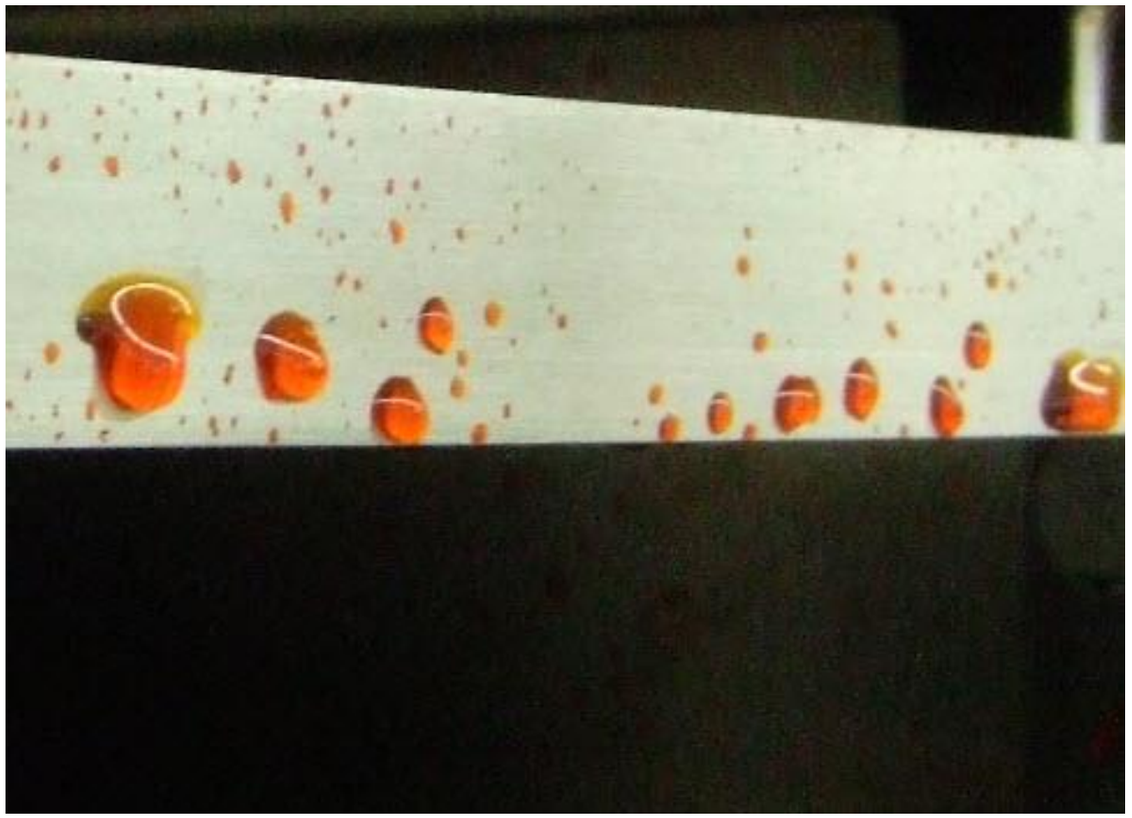
CIP / SIP systems ensure sufficient and qualitative supply of media for machines.

The Media supply for a CIP / SIP system, depends on other Equipments e.g. clean steam generators, WFI generators and distribution Loops.

CIP / SIP systems

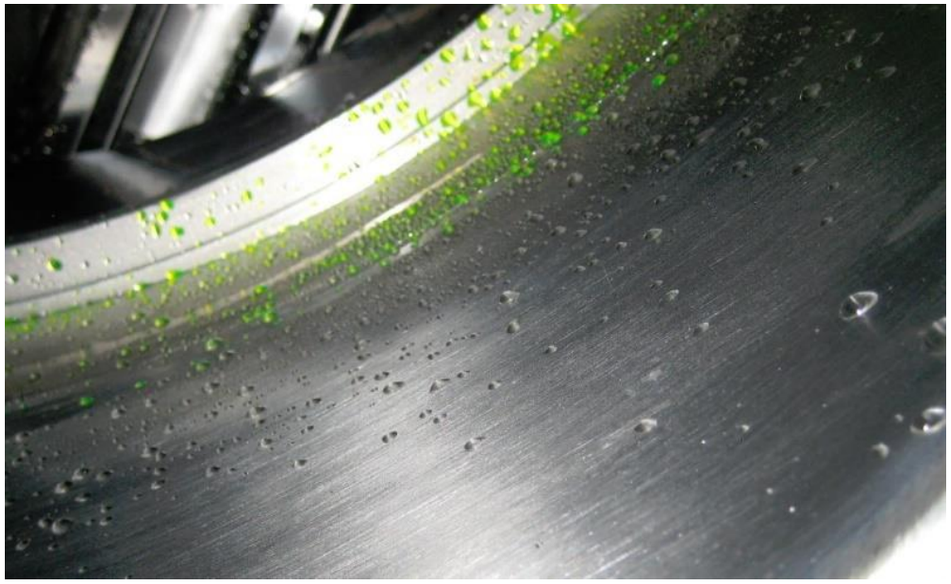
The riboflavin test can used as proof of solid design of a the CIP system.

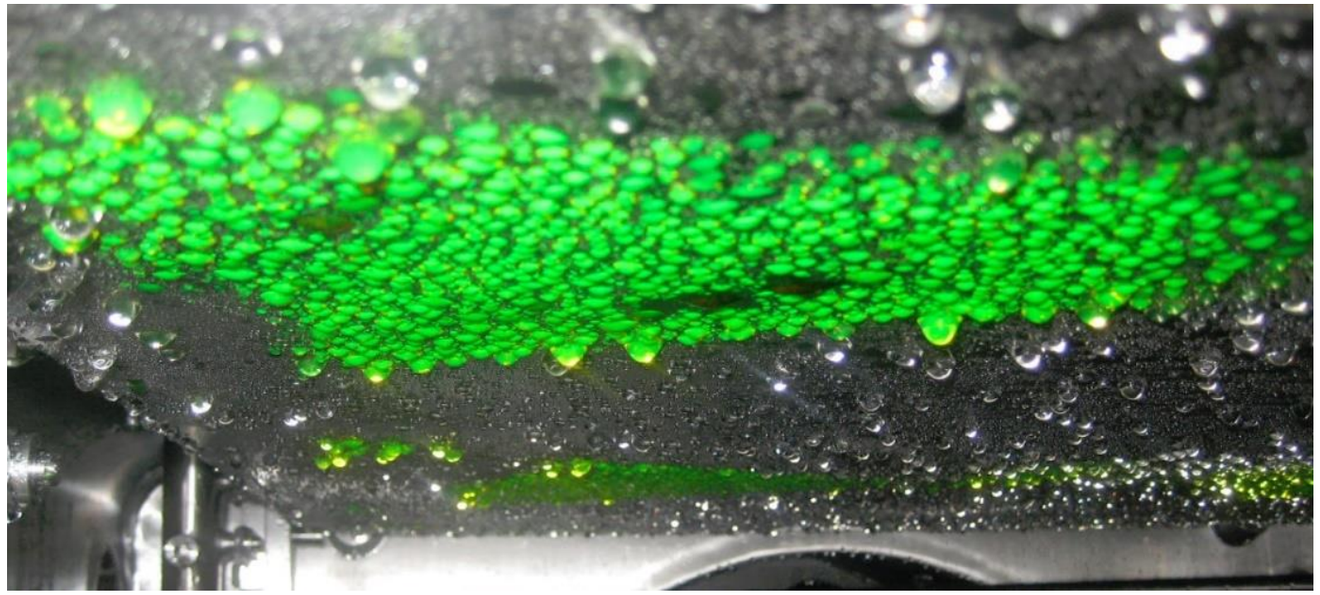
- the riboflavin test shows potential weakness of the CIP system (spray shadows)
- demonstrate cleaning success
- spray shadows can help to setup the CIP System

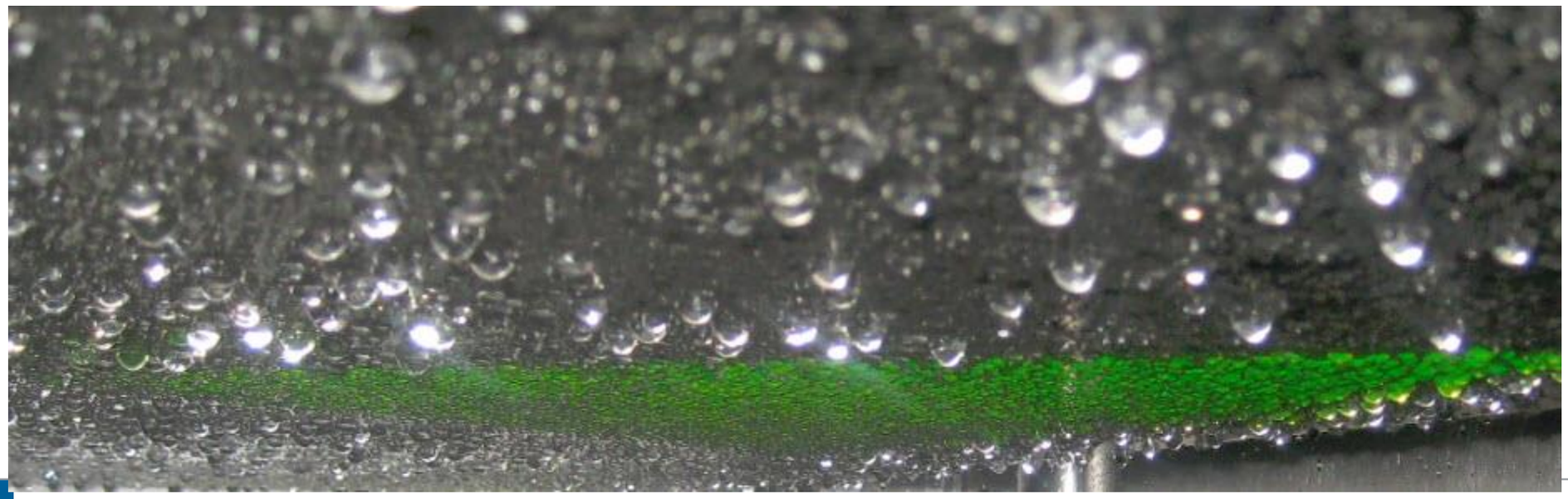


CIP / SIP systems

Examples of spray shadows:







CIP / SIP systems

Cleaning validation:

After verification of good design of CIP system, the cleaning validation (CV) can be stared. The CV of the cleaning process demonstrate the Process is valid to do the same each Run and also that the Process have the expacted cleaning success.

Testmethods are e. g.:

- do the cleaning cycle three times, all three cycles should have the same result and be reproducible
- proof of cleaning success with bioindicators
- test samples from surfaces (Swap)

In cases of validation the automation Part should also checked, If an automated process is used the process should be validated (Software Validation).

If a manual cleaning takes place, it must also be validated and revalidated at defined time intervals. The employees for this purpose must be trained.

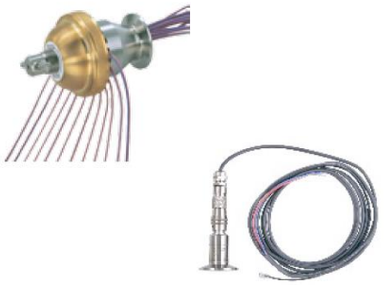
Sterilisation qualification

The qualification of sterilisation generally takes place with external equipment (recorder). The recorder e. g. can be a wired system with thermocouples (online measuring system) or a wireless system (logger).

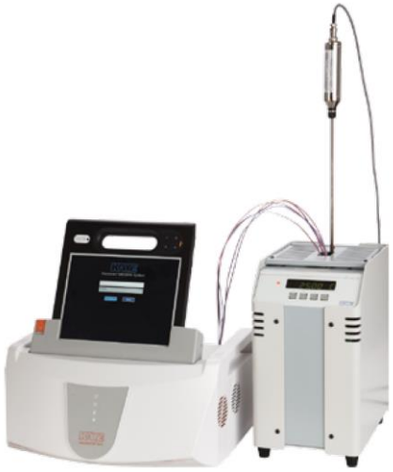
Before each run the Equipment should be calibrated, as well as after each run a system check should be carried out.

Calibration system with oil

Calibration system dry block



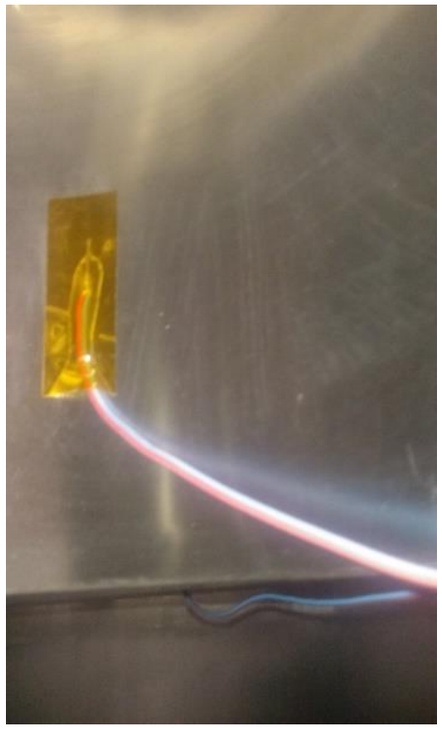
Qualification pout / absolute pressure tube

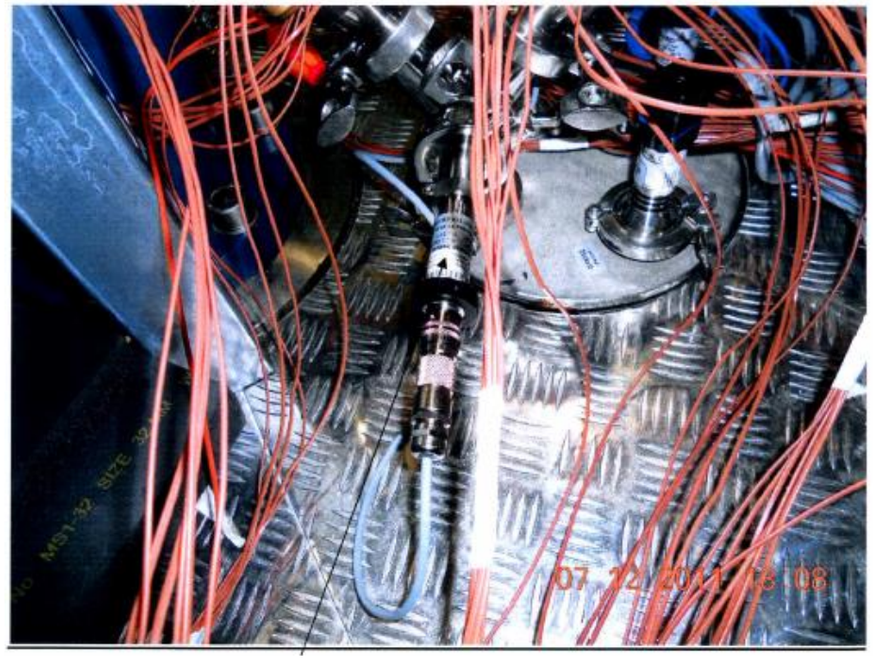


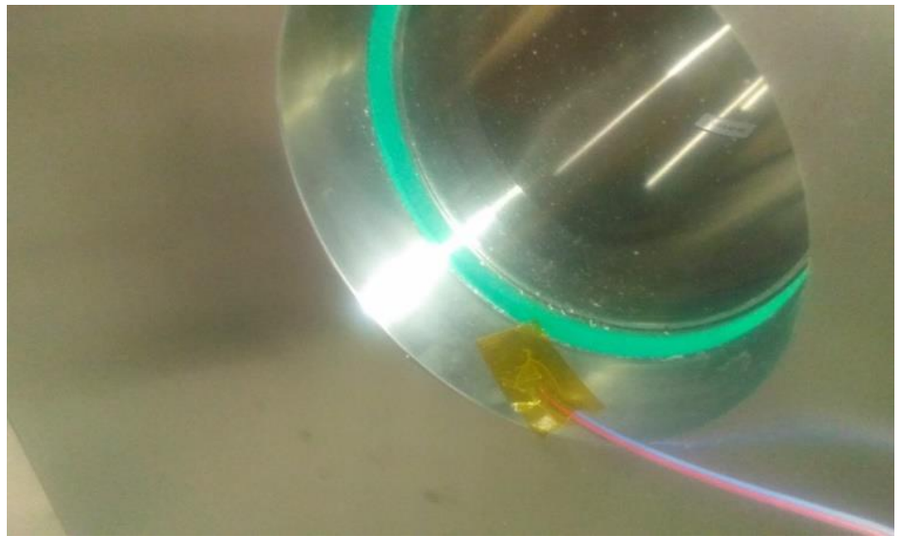
Construction of a recorder system including a temperature standard

CIP / SIP systems

Examples:



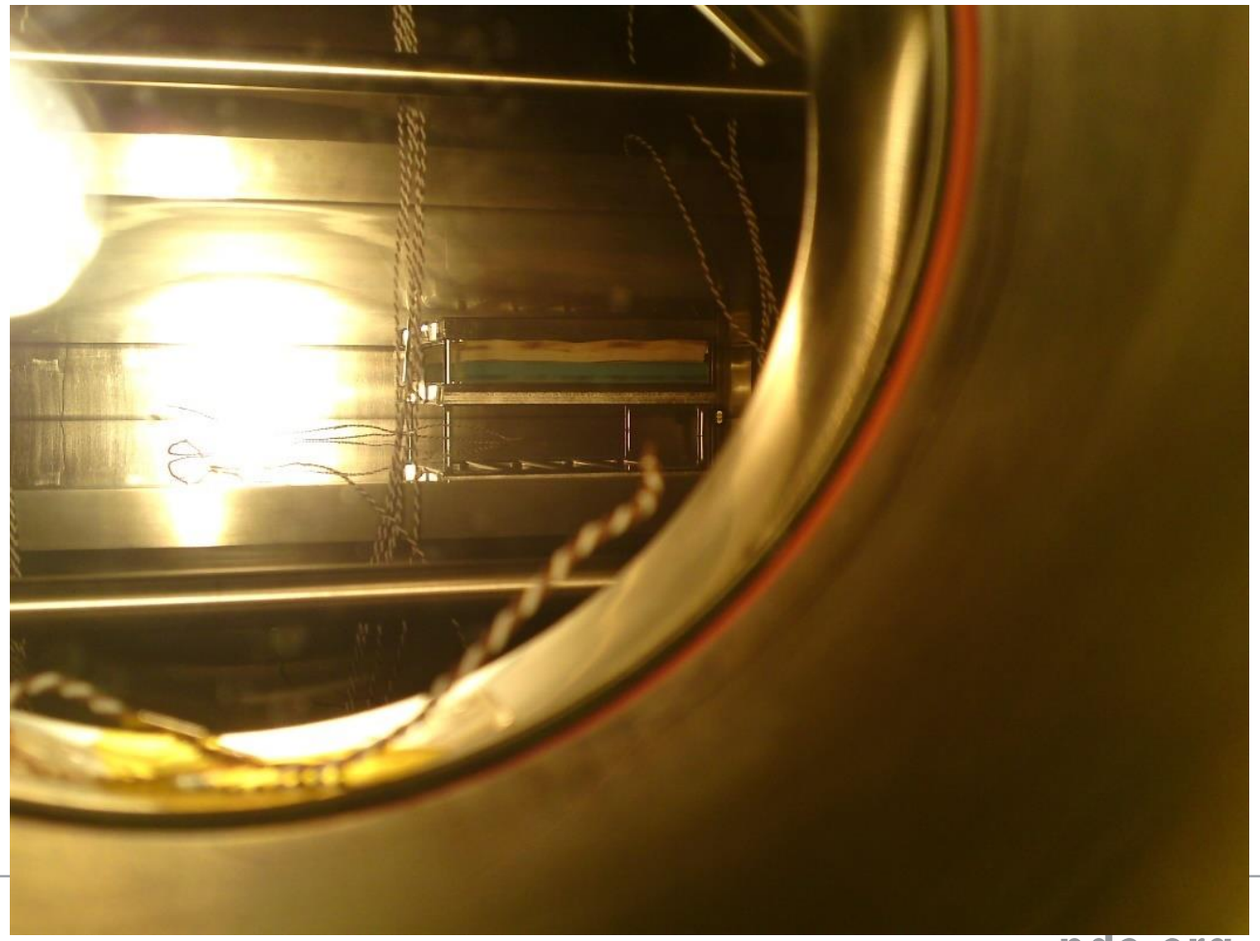




CIP / SIP systems

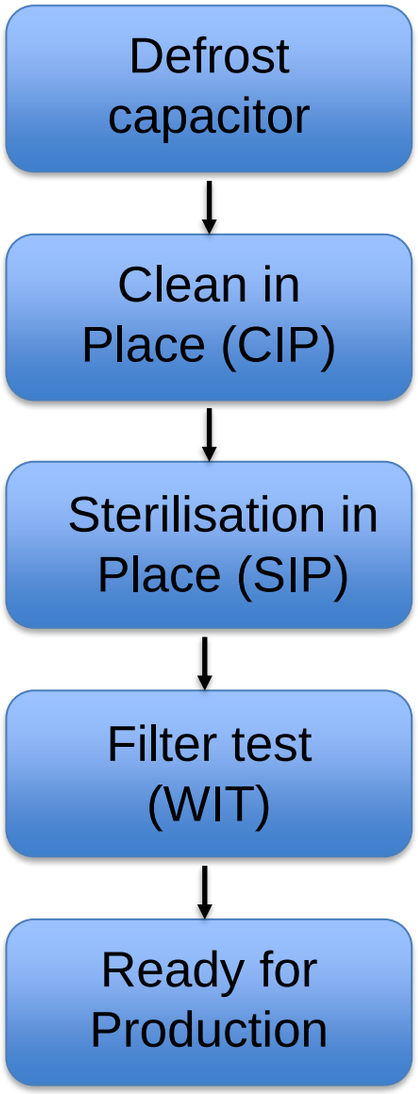
Special Tests for sterilization process are:

- use of bioindicators
- use of Bowie-Dick-Test



CIP / SIP systems

Turnaround - process:



The turnaround process includes different processes like defrost / CIP / SIP / WIT.

The turnaround time is the time from the end of production (unloading GT) till the start of a new production.

Attention:

After the turnaround process the system is not endlessly sterile. A validation of a sterile hold time has to be determined. This time should be fixed at relevant machines (e. g. as sterile bit).

Die Pharmbiocon LSE ist Ihr Partner in Pharmaindustrie und Medizintechnik, in den Bereichen Management / Qualitätssicherung / Forschung und Entwicklung / Engineering mit über 15 Jahren Erfahrung in der Pharmaindustrie.

Unser Leistungsspektrum umfasst die Durchführung von Qualitätsprüfungen von Pharmazeutischen Produkten in unserem zertifizierten Prüflabor, die Planung und Überwachung von technischen Transfer Projekten, die Sicherstellung der GMP Richtlinien, die Entwicklung nuer so wie die weiter Entwicklung bzw. die Optimierung von Prozessen wie z.B. Gefriertrocknungsprozessen.

Sprechen Sie uns gerne an, unsere Erfahrenen Mitarbeiter aus den Bereichen der Herstellung und der Forschung und Entwicklung stehen Ihnen gerne zur Verfügung.

Pharmbiocon
Life Science Engineering

Loading / unloading

loading and unloading systems

- type of loading (RR, Frame, Batch)
- design loading and unloading systems in existing lines
- examples for loading and unloading systems

Loading / unloading

Row by Row loading

- installation in clean rooms class B in a RABS system
- installation in rooms class C with isolator
- Vial Transfer over a loading table into the FD

Loading / unloading

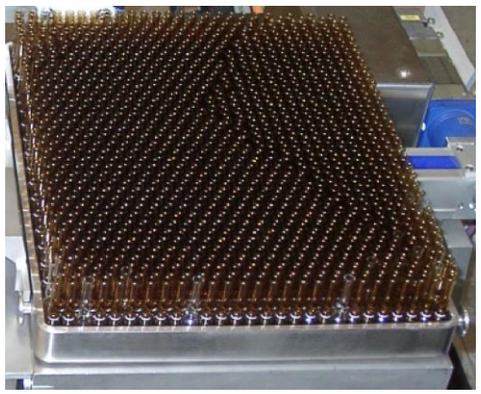
Batch loading

- Loading of a hole shelf at once
- Assembly of the Vials in HEX
- Cooling Table for filled Vials
- Loading with e. g. loading car or loading handlings
- Complete loading in clean room class A including LF
- No operator activities in loading rooms

Frame loading

Frames are stored in a magazine

Assembly of Ampules in HEX



loading frames into the Freeze Dryer