Company portrait

With almost 20 years of experience Pharmbiocon GmbH in Bad Endbach is a reliable partner of the pharmaceutical and medical devices industry.

The company can draw from its resource pool of technical engineers (biotechnology, pharmatechnology, life science technology, process engineering and mechanical engineering) and natural scientists (biologists, chemists).

Main business areas are project leads, engineering, management and consulting services for international projects, planning and surveillance of technical transfer projectes in fill / finish facilities, GMP quality assurance as well as engineering of complex processes.
Furthermore, Pharmbiocon GmbH can be contracted as a general planer. The benefit for the customer will be the pooling of the ordering process with a single person of contact on site, combined with high fexibility and a reduced risk of down time.

In addition, we offer a fully equiped bio safety level II laboratory to our costumers. A pilot plant lyophilisation facility can be use here to develop or optimize your processes or performe failure mode analyses (production galenics).

Pharmbiocon
Life Science Engineering

Process engineering tools (sensor technology)

Theory 4:

- PT Sensors
- Pressure and Vacuum Sensors
- Vacuum Sensors
- Conductivity Sensors
- Massspectrometer
- Camera systems
- Alternatives Sensors

Process engineering tools (sensor technology)

PT – Sensors (platinum temperature sensor)

PT sensors use the effect of temperature dependence of the electric resistance of platinum. The resistance increases at higher temperatures (positive temperature coefficient) this sensors are named PTC Sensors (positive temperature coefficient). Another Type of a PT Sensor is an NTC Sensor, this kind of Sensor has an negative temperature coefficient, the resistance decreases at higher temperatures. NTC Sensors are normally not used in a Lyo.

Abbildung 6: Temperatursensorproduktion unter Reinraumbedingungen

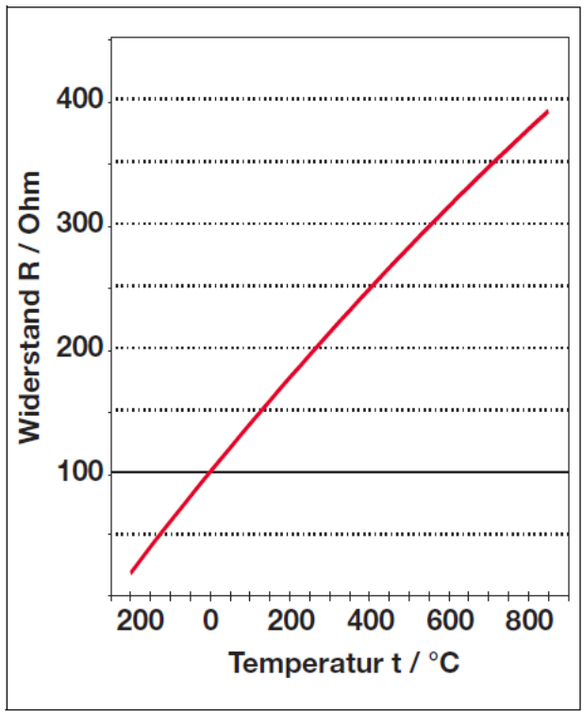


Abbildung 1: Pt100-Kennlinie

PT - Sensors (platinum temperature sensor)

The “standard” PT- Sensor is an PT100 (for Process control) and the PT1000 for example Safety issues.

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

Resistance changes

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

Abbildung 12: Laserabgleich der Platin-Chip-Temperatursensoren

Process engineering tools (sensor technology)

PT Sensors (platinum temperature sensor)

The long-time behavior is another important factor of PT Sensors. The accuracy of the PT Sensor is drifting depending on the age and on the Process use of the Sensor.

In order to determine the long-term stability all PT100 Sensors should have an regular calibration in their intended conditions of use i.e. for Sterilisationtemperatures 100°C, 120°C and 130°C

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

PT Sensors (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

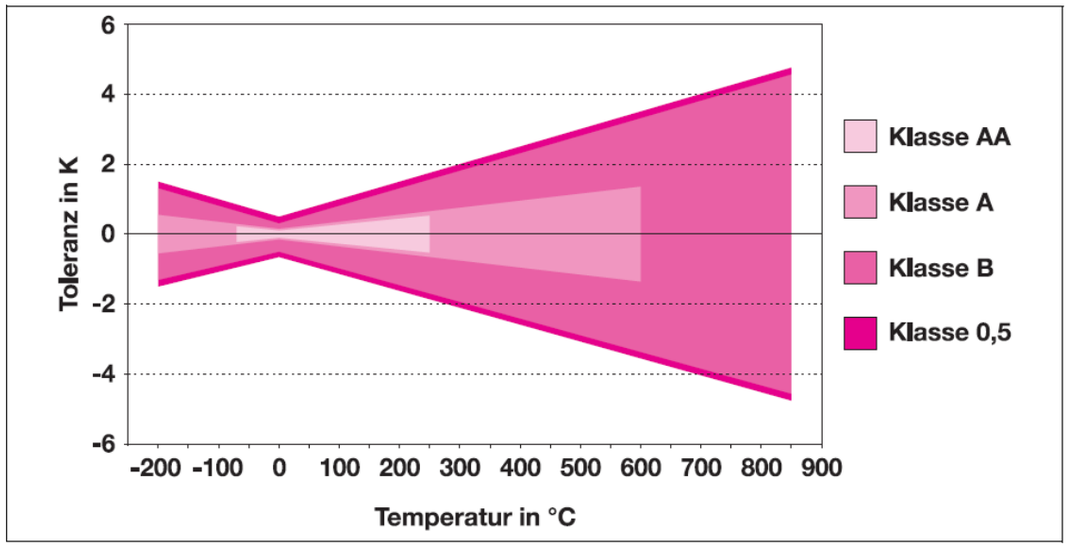


Abbildung 2: Toleranzverlauf in Abhängigkeit von der Temperatur

Process engineering tools (sensor technology)

Construction PT-sensor

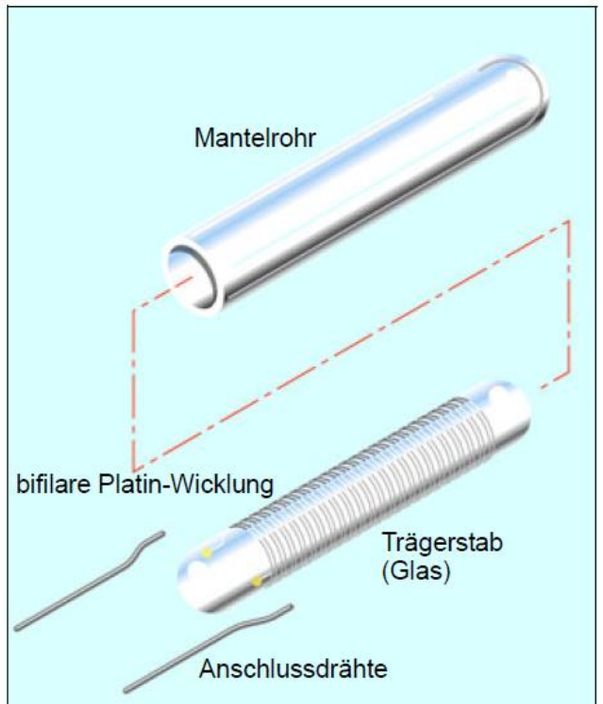


Abbildung 7: Prinzipieller Aufbau von Platin-Glas-Temperatursensoren

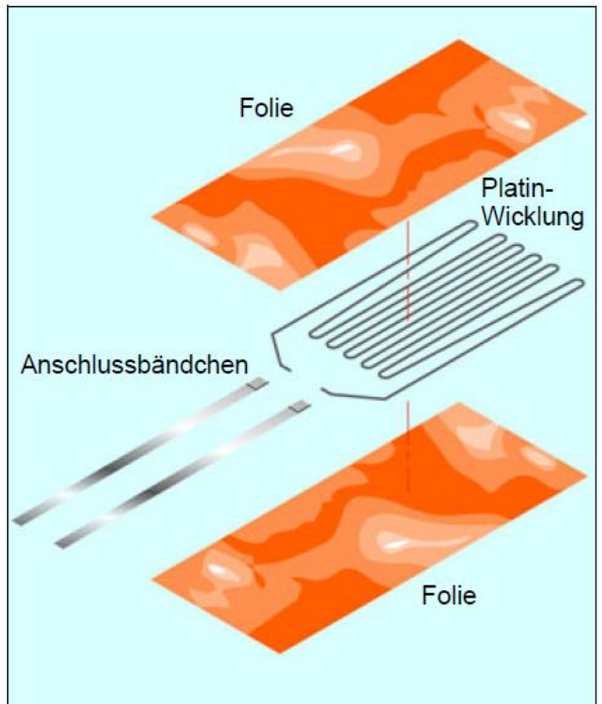


Abbildung 11: Prinzipieller Aufbau von Platin-Folien-Temperatursensoren

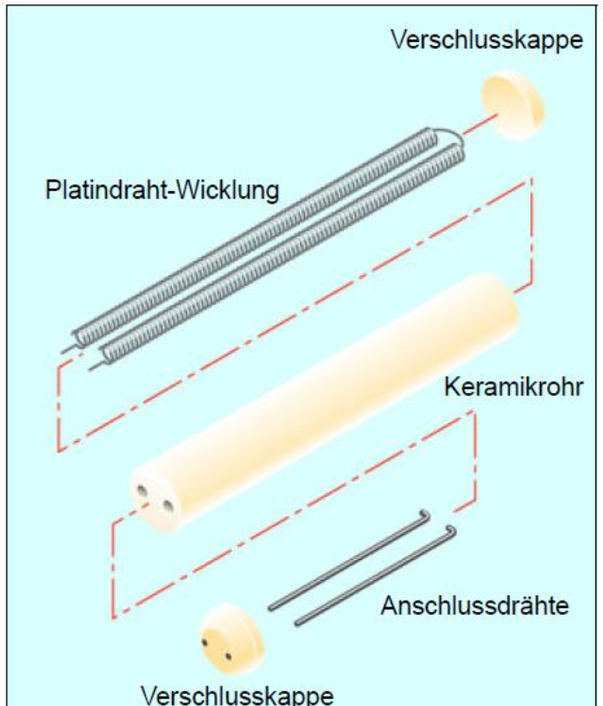


Abbildung 10: Prinzipieller Aufbau von Platin-Keramik-Temperatursensoren

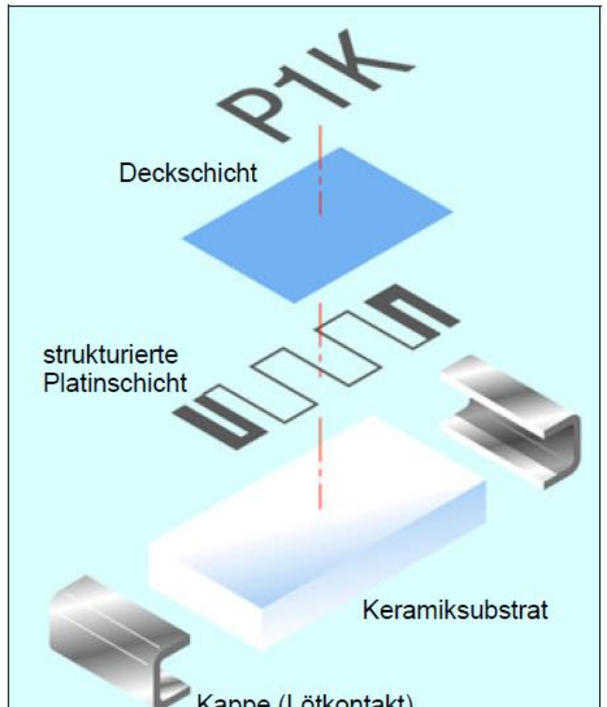


Abbildung 16: Prinzipieller Aufbau von Platin-Chip-Temperatursensoren in SMD-Bauform

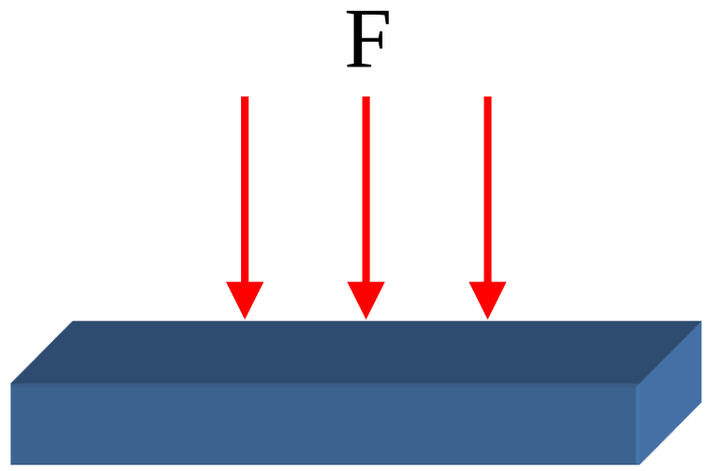
Pressure Sensors

Definition

How is pressure defined?

Pressure (p) is defined as the **force (F)** divided by **area (A)**

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



Separate technical units of pressure:

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.**

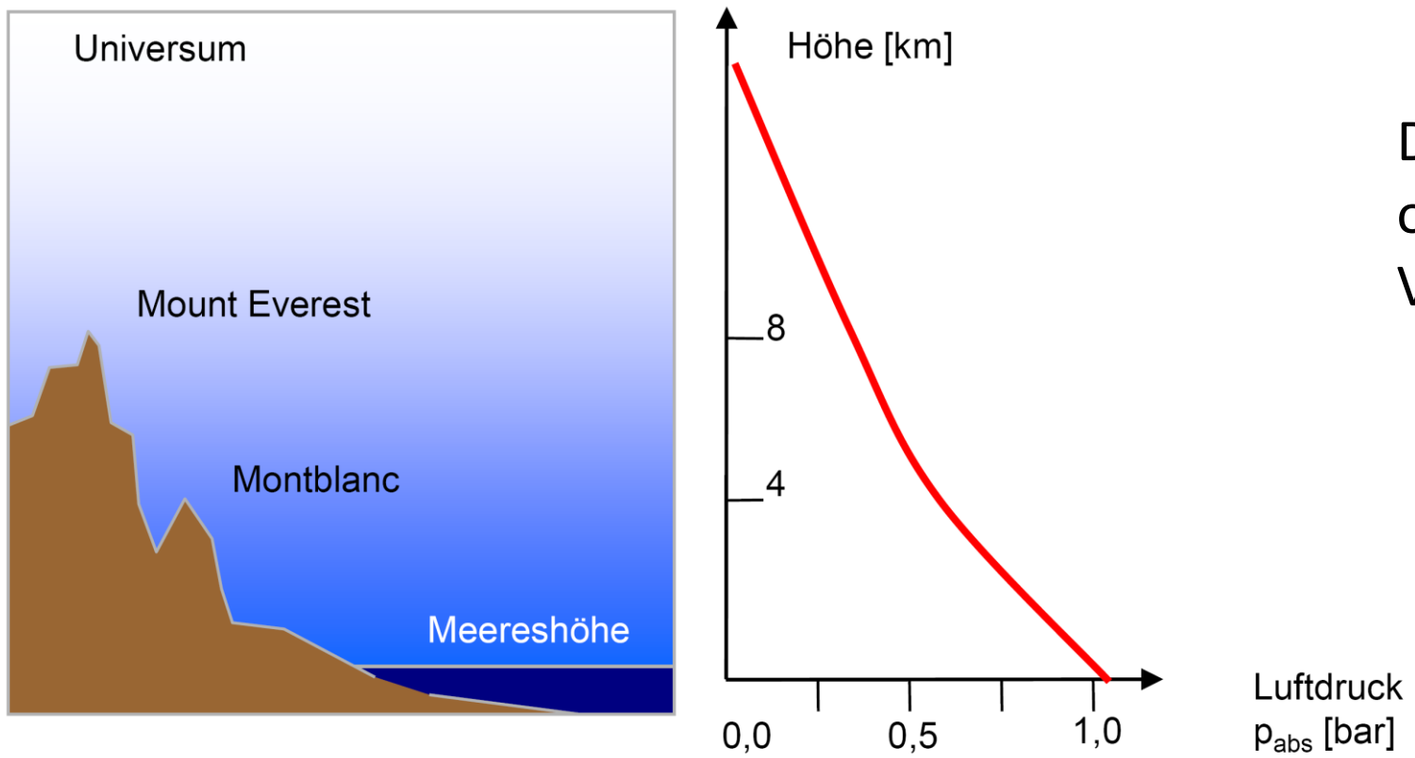
Each unit can be transferred to another:

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

Absoulute Pressure

P_{abs}

Referenz Pressure (Universe)

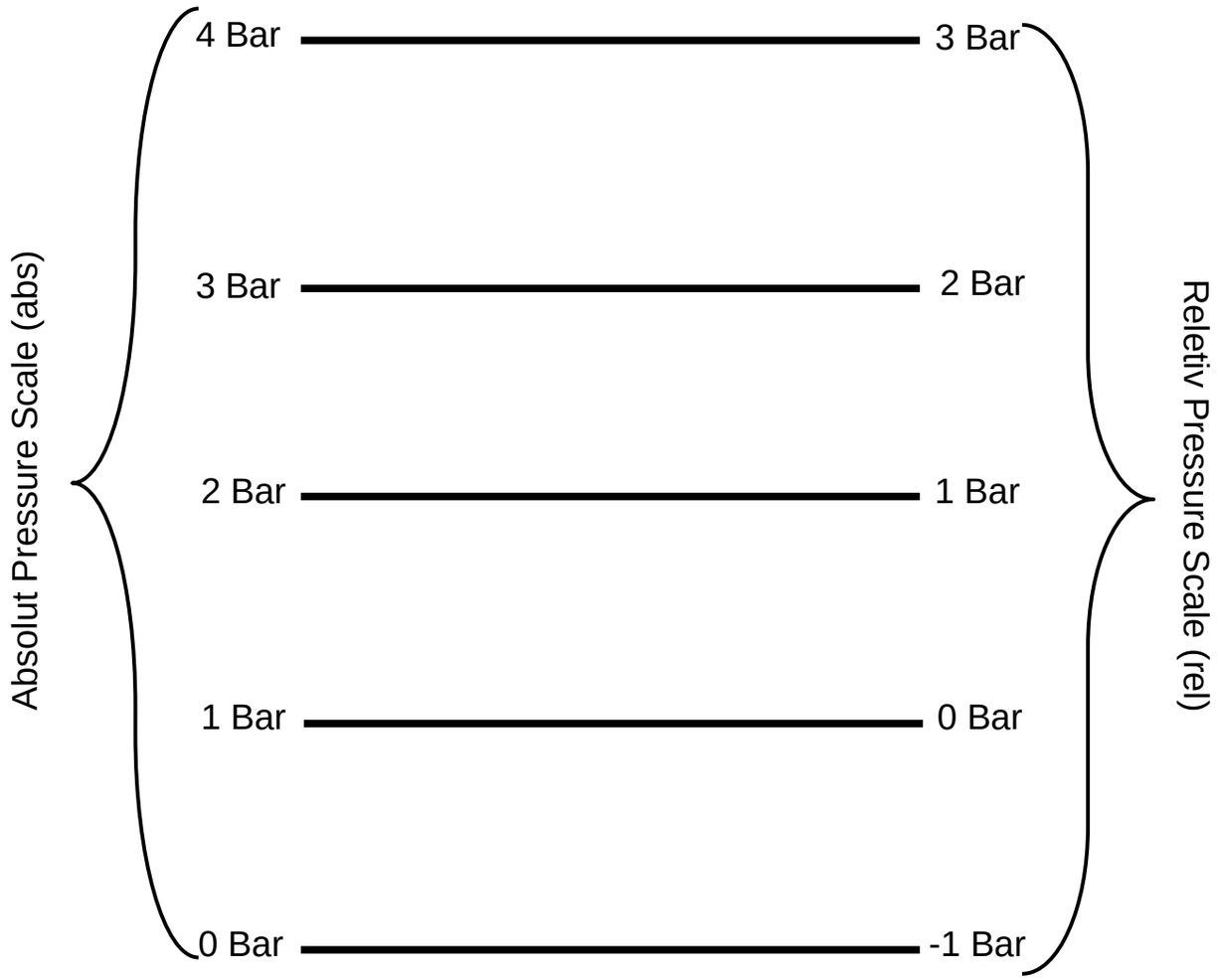


During the Manufactoring Process of a Pressure Sensore a Reference Vacuum is needed.

The Referenz Pressure will be generaded by Vacuumpumps

Process engineering tools (sensor technology)

Pressure scale



Process engineering tools (sensor technology)

Pressure examples

Druck in hPa (mbar)	Moleküle pro cm^3	mittlere freie Weglänge
1013,25	$2,7 \times 10^{19}$	68 nm
300…1	$10^{19}…10^{16}$	0,01…100 µm
1…10^{-3}	$10^{16}…10^{13}$	0,1…100 mm
$10^{-3}…10^{-7}$	$10^{13}…10^{9}$	100 mm…1 km
$10^{-7}…10^{-12}$	$10^{9}…10^{4}$	1…10^{5} km
$<10^{-12}$	$<10^{4}$	$>10^{5}$ 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

Pressure measurement (vacuum and overpressure)

One of the most important parameter of Lyophilisation is the pressure measurement, it is important

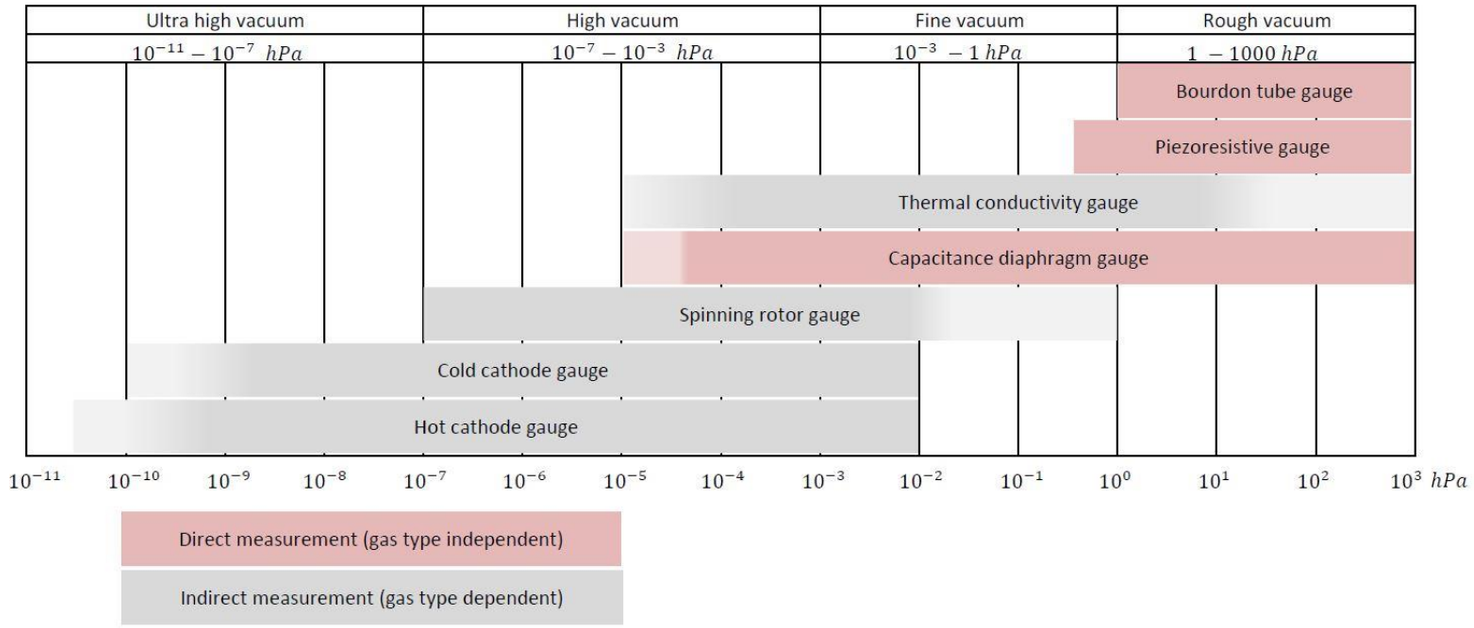
- during a Lyo process the pressure measuring device must have a high accuracy (freeze-drying and sterilisation)
- during a freeze-drying the pressure measurement may be used for comparative pressure measurement (capacitive sensor / Pirani)
- during a sterilisation process the pressure measurement is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

Process engineering tools (sensor technology)

Pressure measurement (vacuum)

The most common vacuum sensors for Lyo Process are:

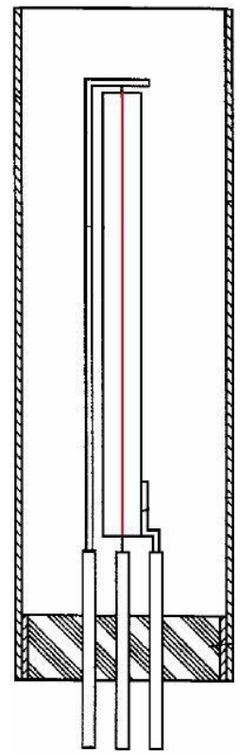
- conductive Sensor (Pirani)
- capacitive Sensor (absolute Sensor)



Pressure measurement (Pirani)

Design of an Pirani Sensor

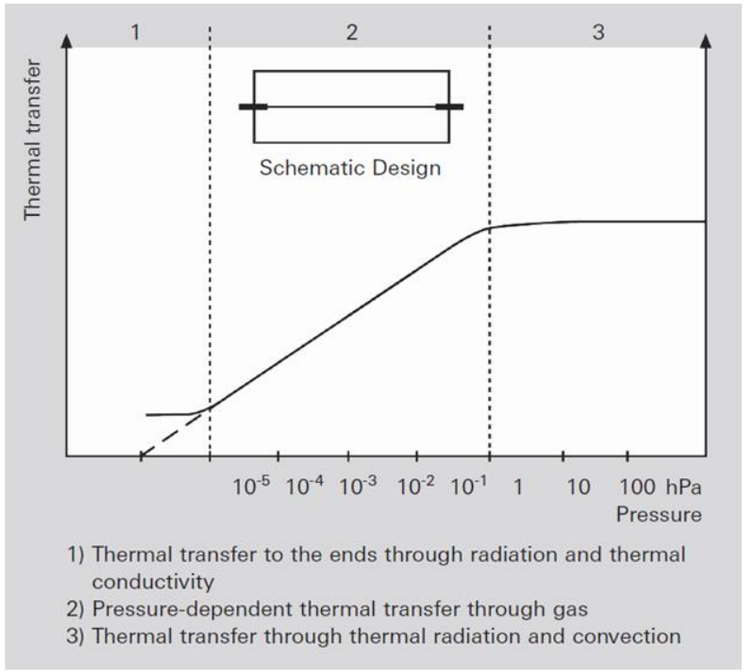
Heat up the wire approximately at a temperature of 110°C to 130°C. The heated wire forms a part of a Wheatstone bridge.



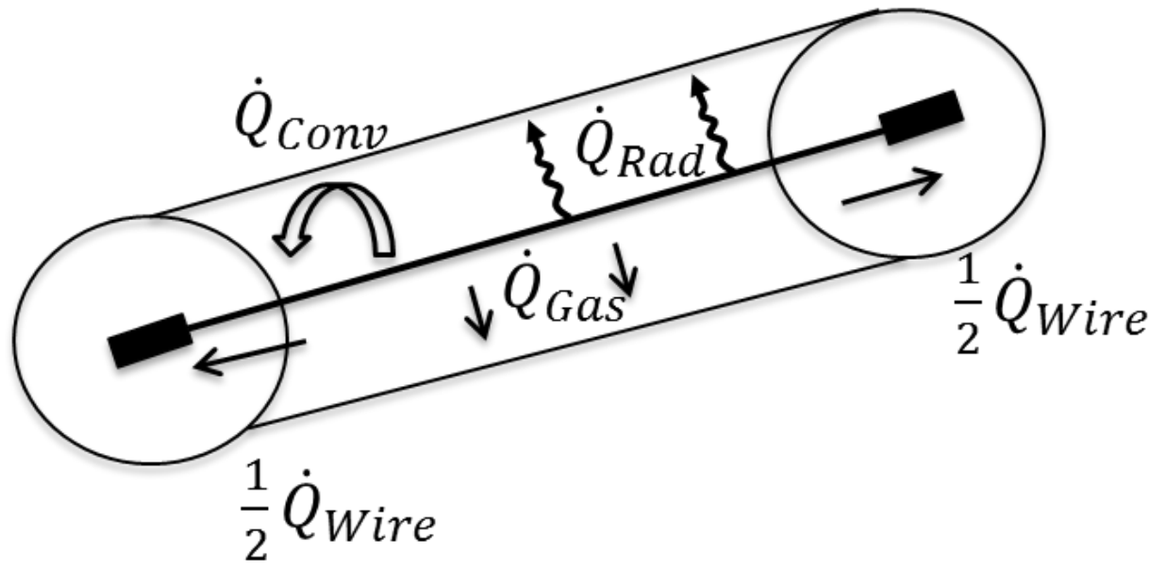
Process engineering tools (sensor technology)

Pressure measurement (Pirani)

The Pirani sensor works with radiation which changes depending on process 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 (Pirani)

Adjustment of Pirani:

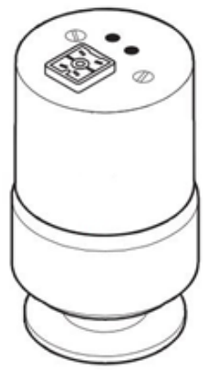
- adjustment of Pirani takes place under real installation conditions
- depending on the age and usage of the Pirani sensor it is necessary to do a zero point calibration (offset)

Process engineering tools (sensor technology)

Pressure measurement (Pirani)

When using a Pirani you must think about the following:

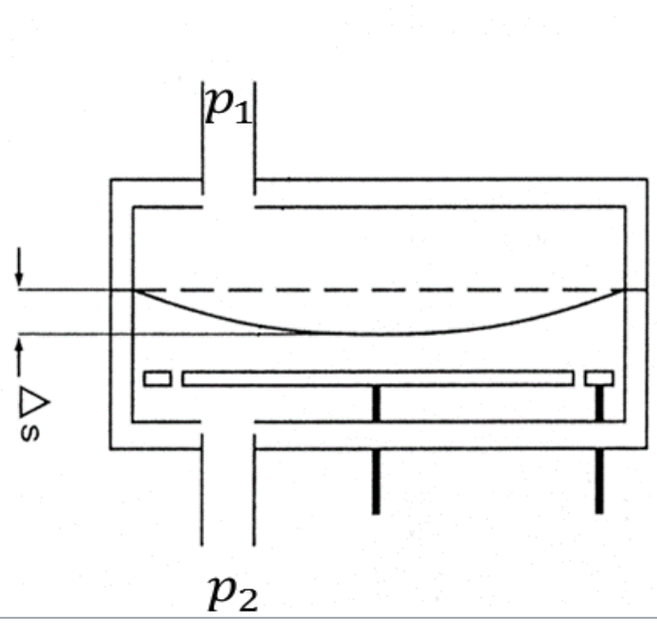
- vertical installation of the Pirani
- Regular Changing of the Pirani depending on Life Time and Process Turnaround
- depending on the age and usage of the Pirani it is necessary to do a zero point adjustment (offset)
- the accuracy of the Pirani sensor depends on the measured gas



Pressure measurement (absolute Sensor)

Construction of a capacitive pressure measurement system:

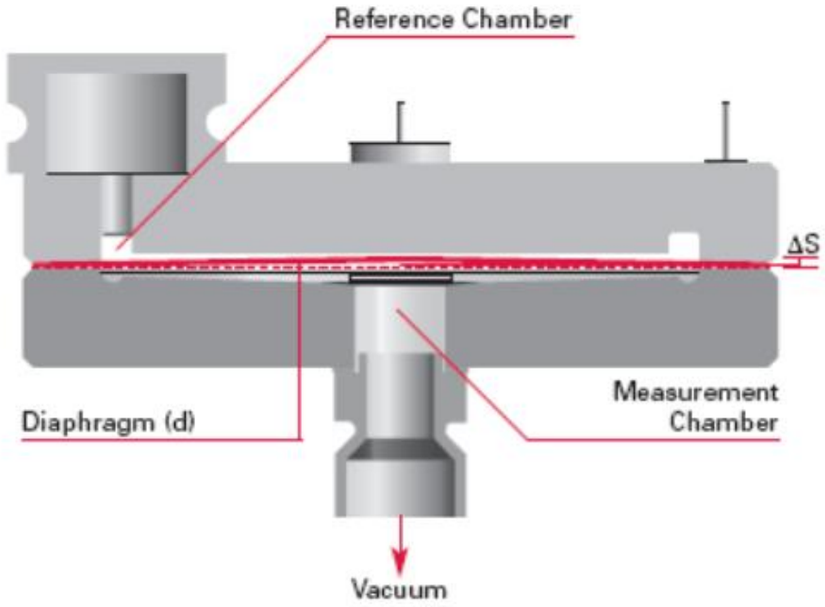
- a capacitive pressure measurement system is independent of the measured gas
- a flexible membrane is mounted inside the Sensor



Process engineering tools (sensor technology)

Pressure measurement (absolute Sensor)

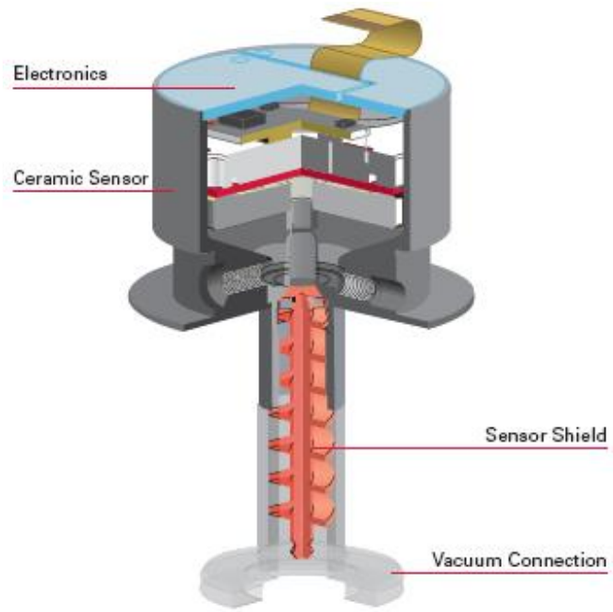
Construction of a capacitive pressure measurement system:



Pressure measurement (absolute Sensor)

Construction of a capacitive pressure measurement system:

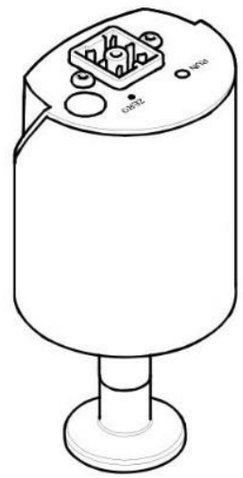
- To avoid a risk of an influence from Temperatures, the capacitive measurement sensors is heated. The temperature of the Sensor is between 45 °C and 200 °C depends on the type of the sensor.
- a freeze dryer which can be sterilized, the capacitive sensors should be heated higher than 150 °C because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



Pressure measurement (absolute Sensor)

When using a capacitive measurement sensor it should be remembered:

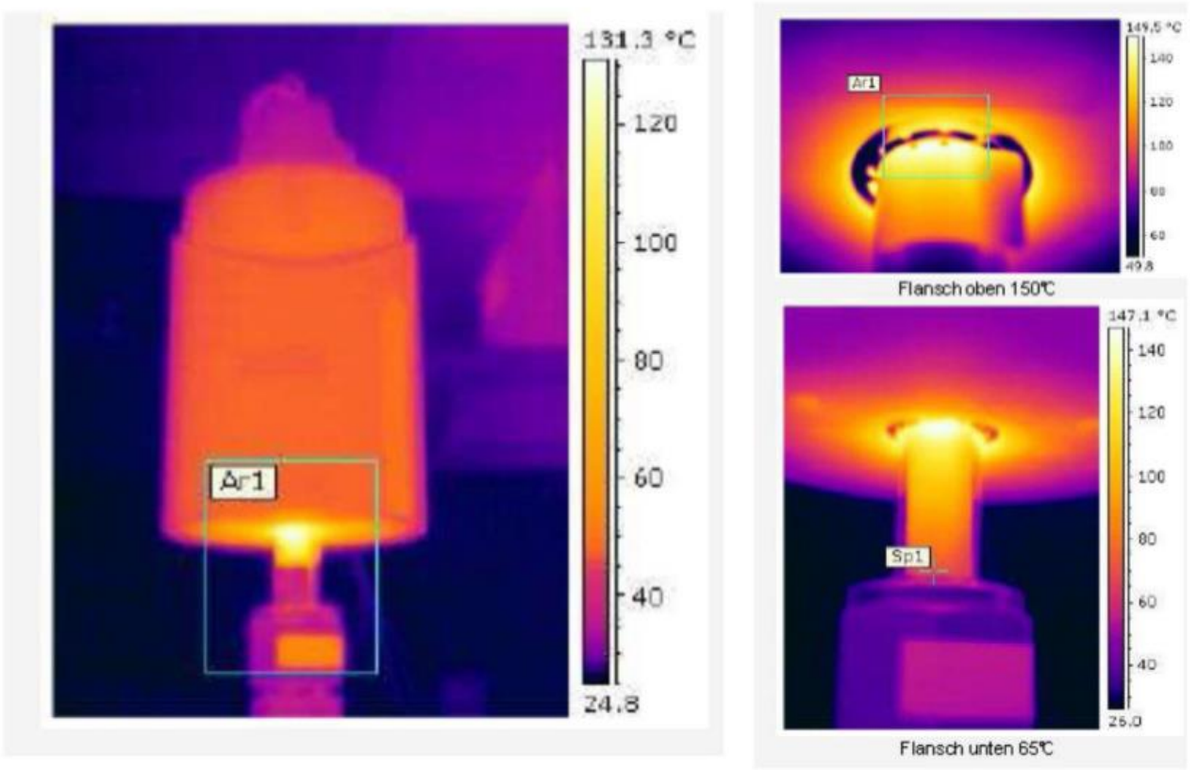
- measurement sensor have a heating up Time (some Sensors up to 9h)
- a contaminated membrane have an influence to the accuracy of the Sensor
- Because of the mounted flexible Membrane the installation position is important



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

Process engineering tools (sensor technology)

Comparative pressure measurement (Pirani / capacitive pressure measurement)

Pressure measurement

Principle:

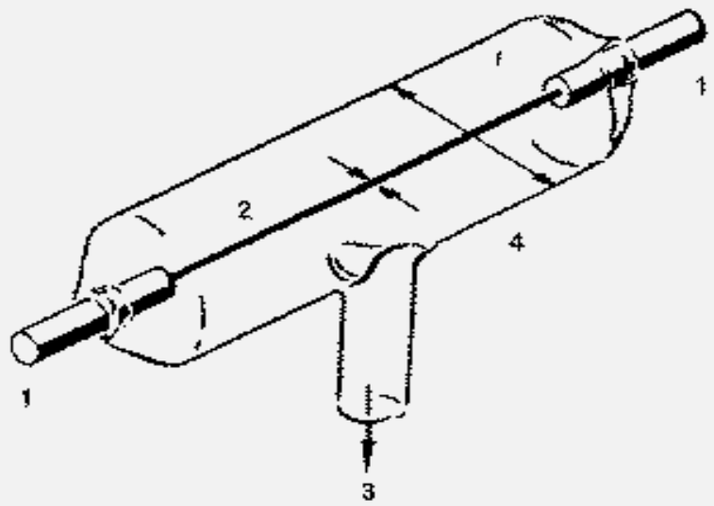
pressure measurement for determining the end of main drying

Measurement of camber pressure with Pirani sensor

based on radiation of heatwire;

depends on the gas inside the Freeze Dryer

Pirani sonde



Process engineering tools (sensor technology)

Comparative pressure measurement (Pirani / capacitive pressure measurement)

Pressure measurement

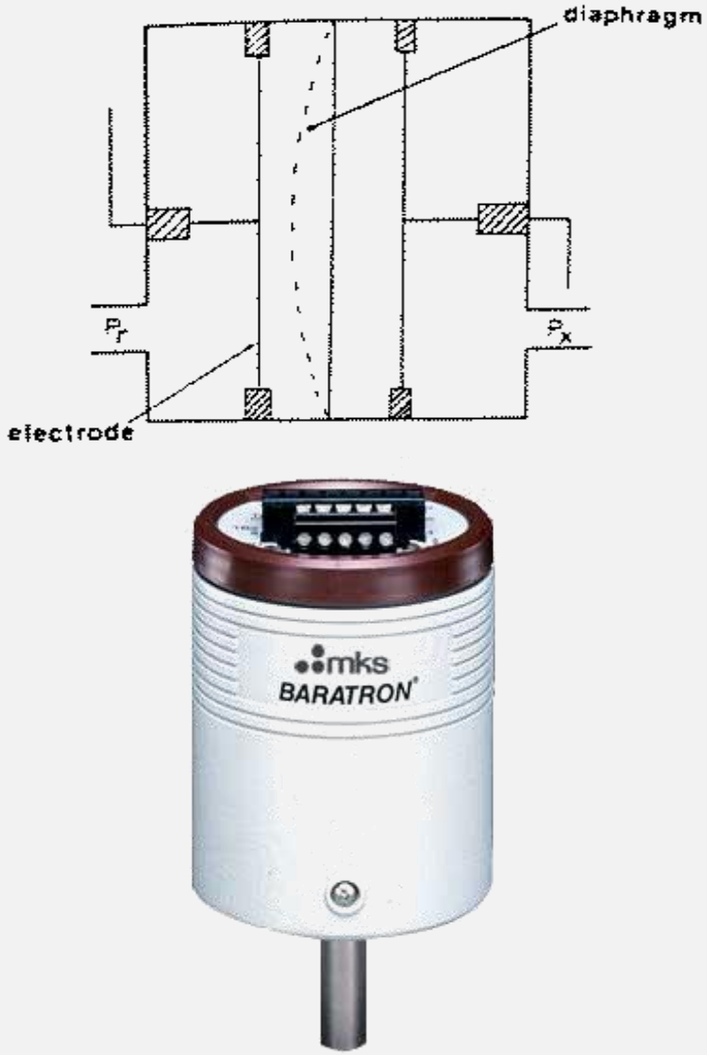
Measurement of camber pressure with

capacitive sensor

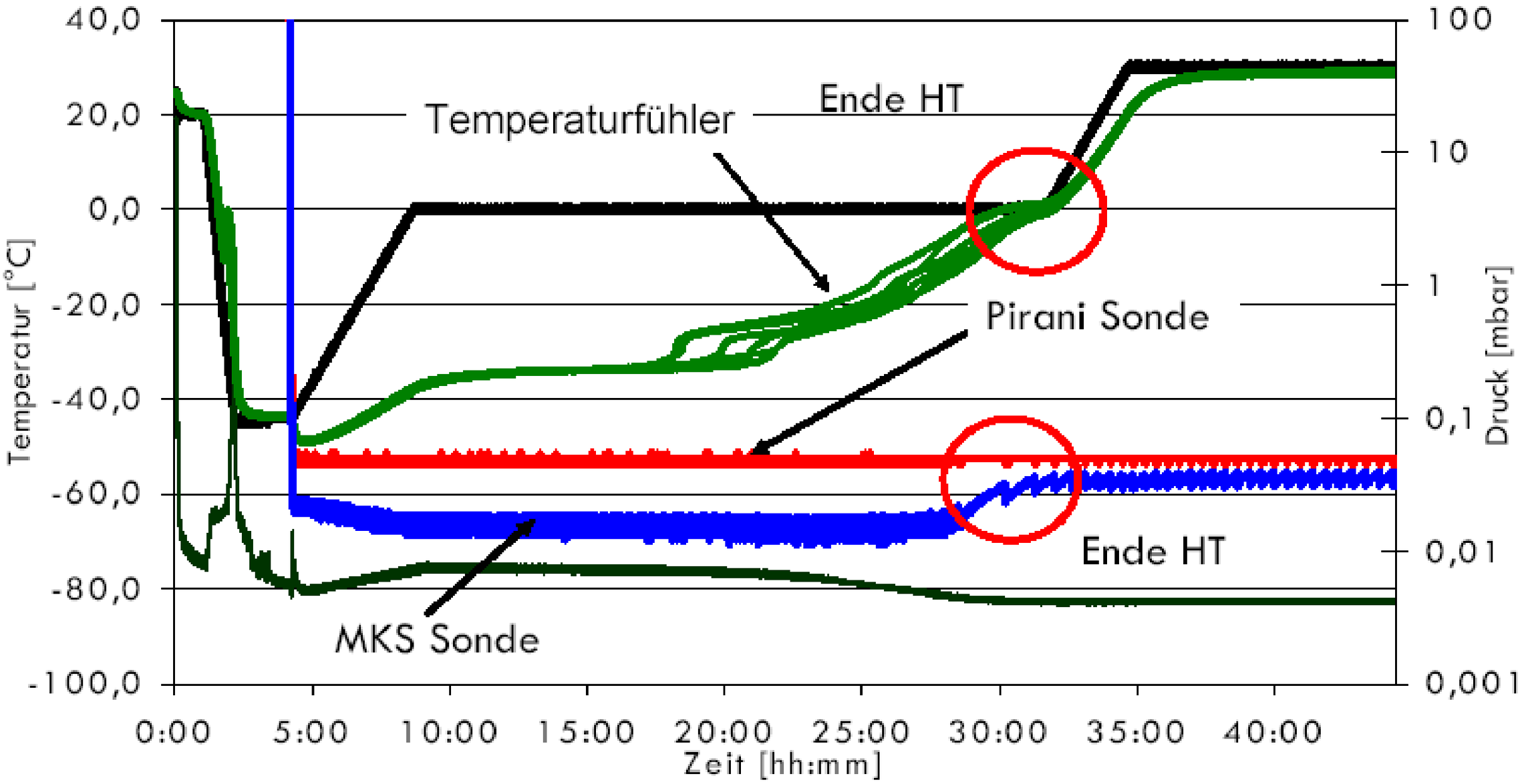
Based on a electrical measurement (Piezo),

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

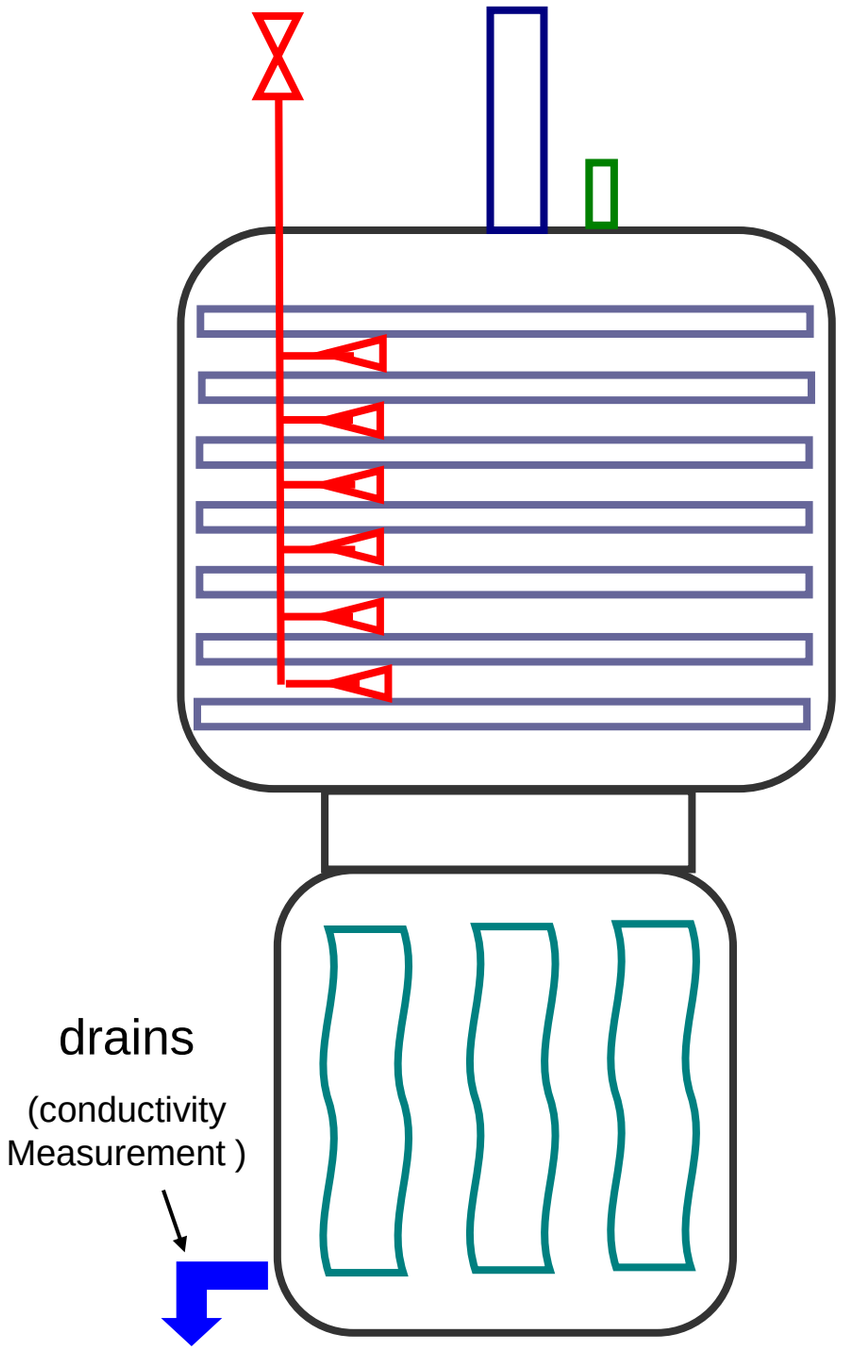
(high content of water vapor inside the Freeze Dryer)

- 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)

Example is for a leading capacitive Sensor!

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).

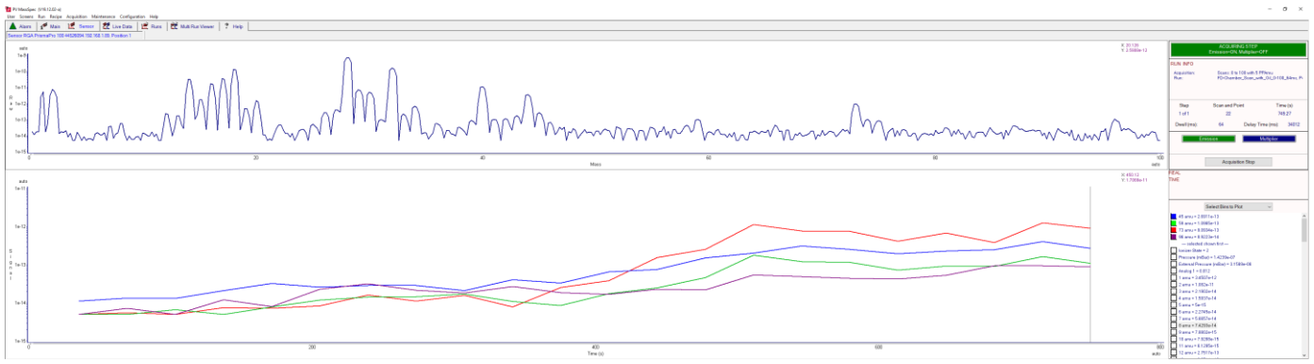
Process control tools (sensor technology)

- the cleaning Media e.g. Concentrate Base or acid are injected with dosing valves into the CIP System. A conductivity sensor is mounted in circulation loops or in the vesele to monitor the dosing of the cleaning Medias.

- after a CIP Cycle with cleaning Medias the cleaning Medias must be completely removed from the Freeze Dryer. These include that the complete system must be rinsed with WFI. The rinsing process is monitored a conductivity sensor at drain

Mass Spectrometer

- Basics mass spectrometer
- Background
- Interpretation of the measurement result



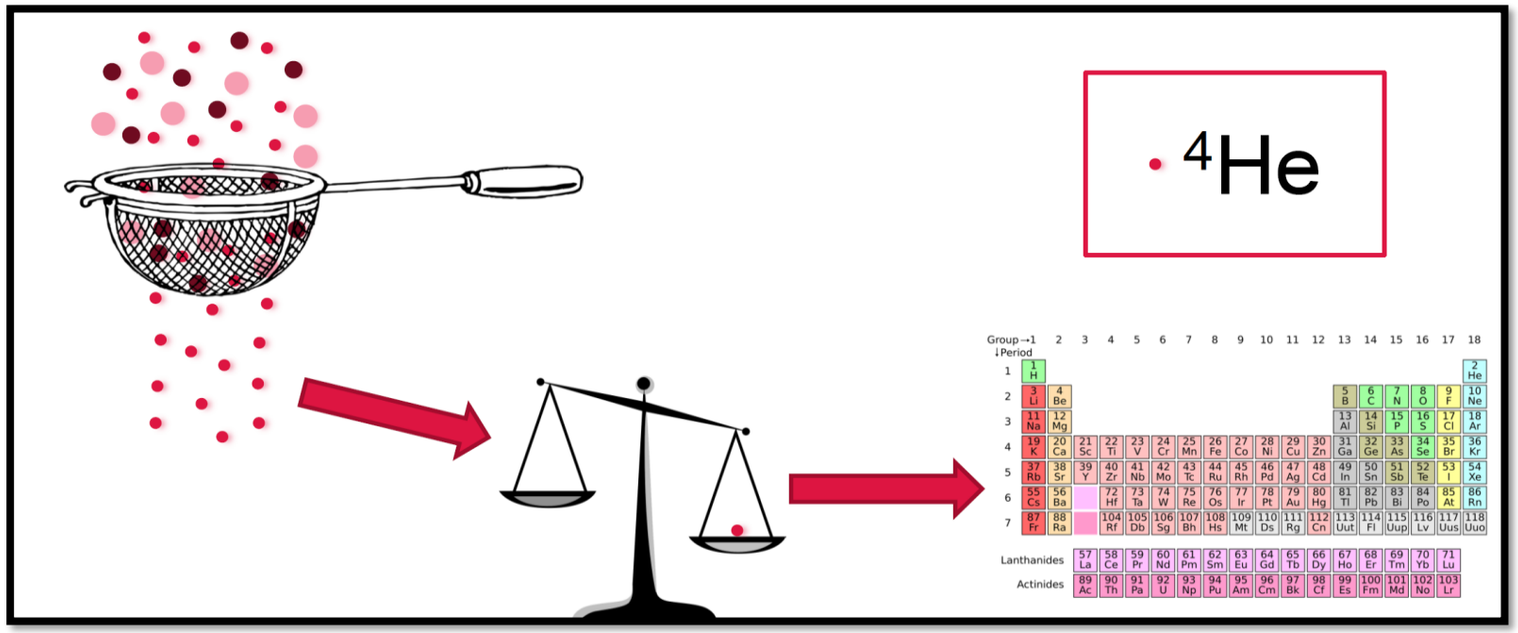
Mass Spectrometer

Applications of mass spectrometry:

- Process analysis in freeze drying processes, exhaust gas analysis
- Quality control / Vacuumsystems (outgassing, **leak detection**)
- Silicon oil detection

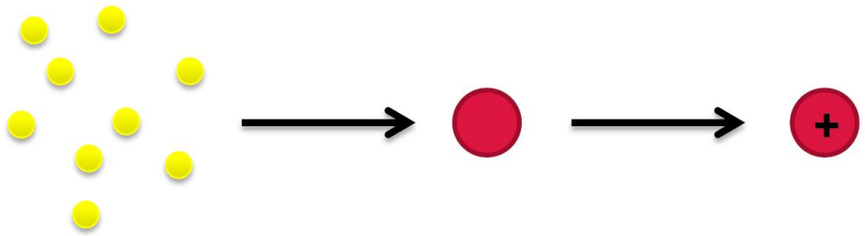
Mass Spectrometer

Basic principle of mass spectrometry:

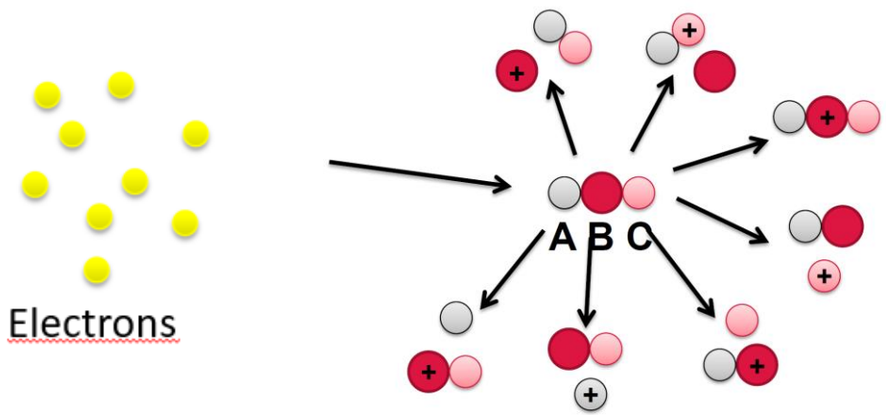


The individual atoms or molecules are separated, the mass / charge ratio is determined and the chemical product is assigned to a specific mass spectrum (fingerprint).

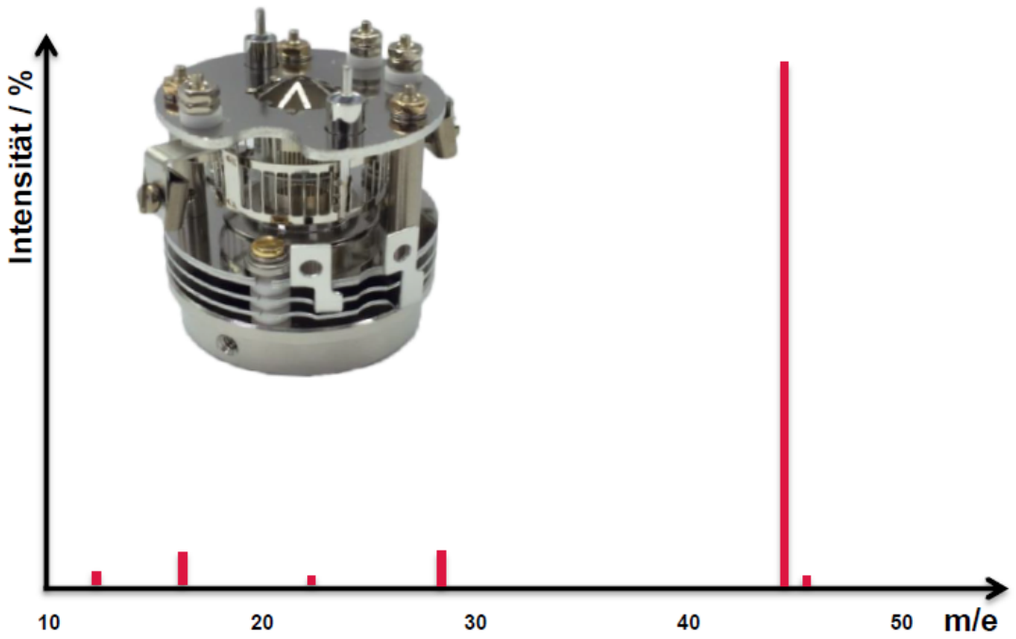
Ionization of the gases:



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



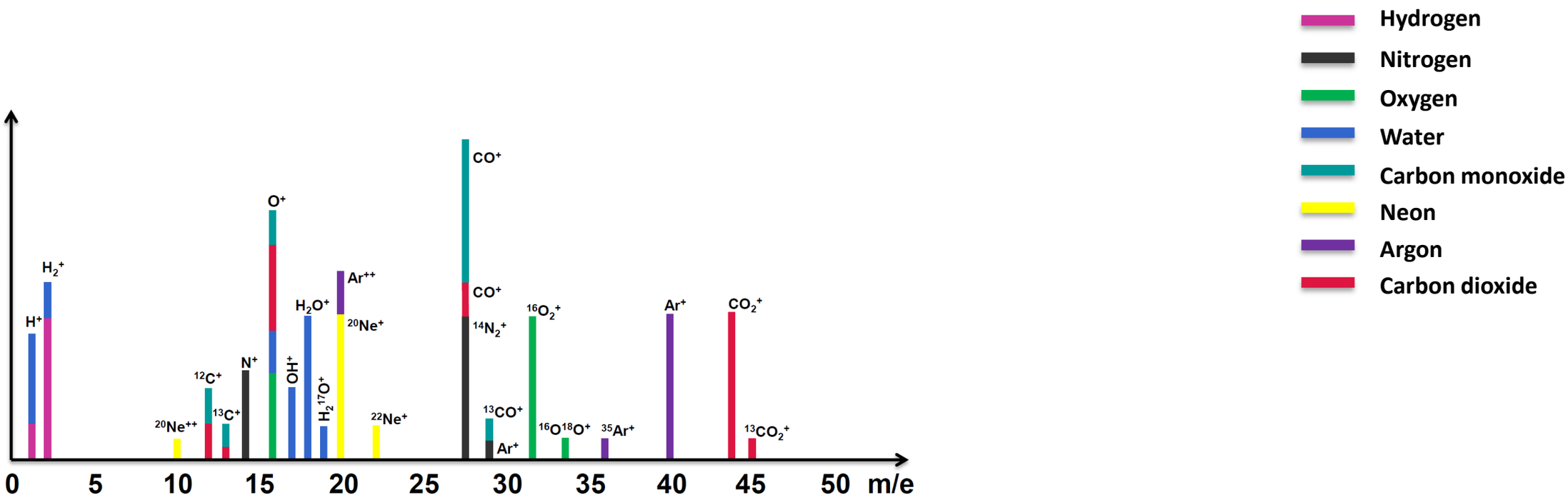
CO2 fragmentation



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:

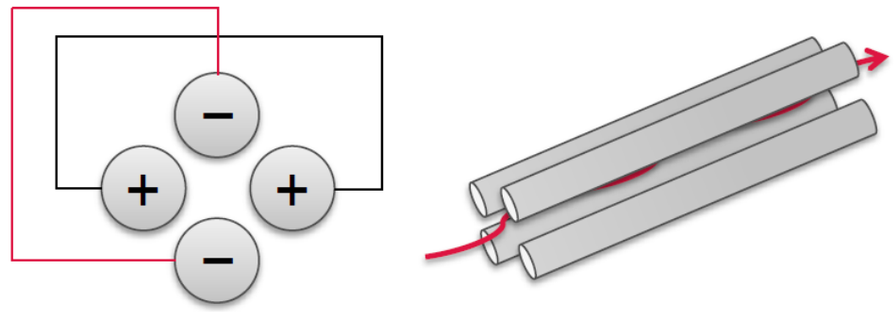


Due to the Gaussian normal distribution, a unique mass spectrum is created for each molecule

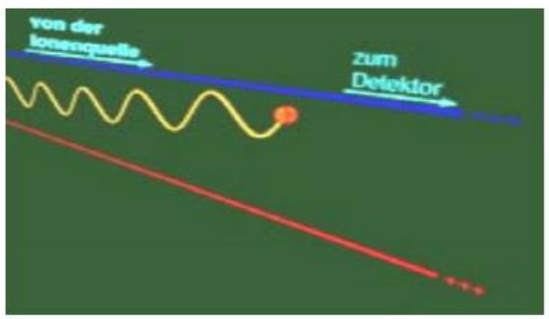
Mass Spectrometer

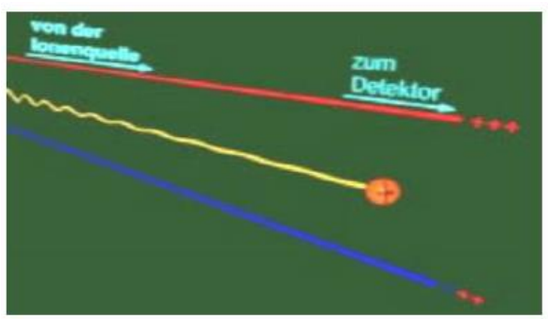
Separation of masses:

- 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



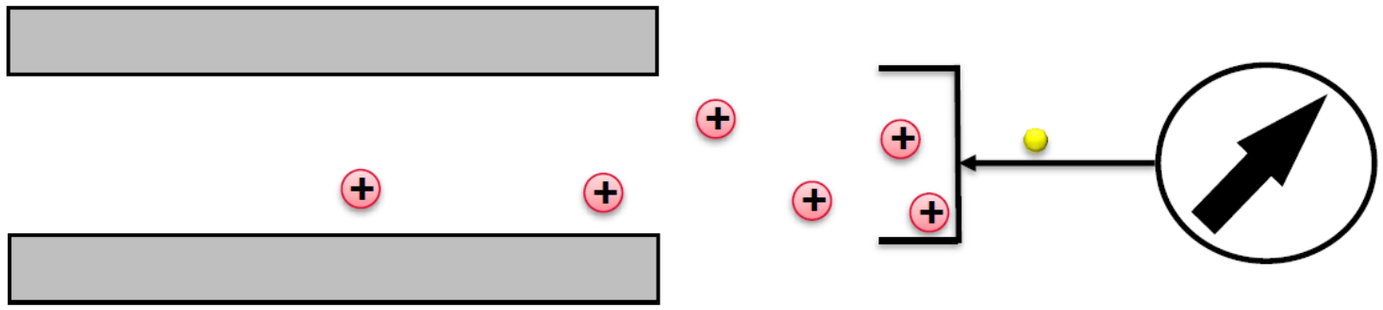
- if the relation does not fit, the ion is deflected before it hits the detector





Mass Spectrometer

Detector:

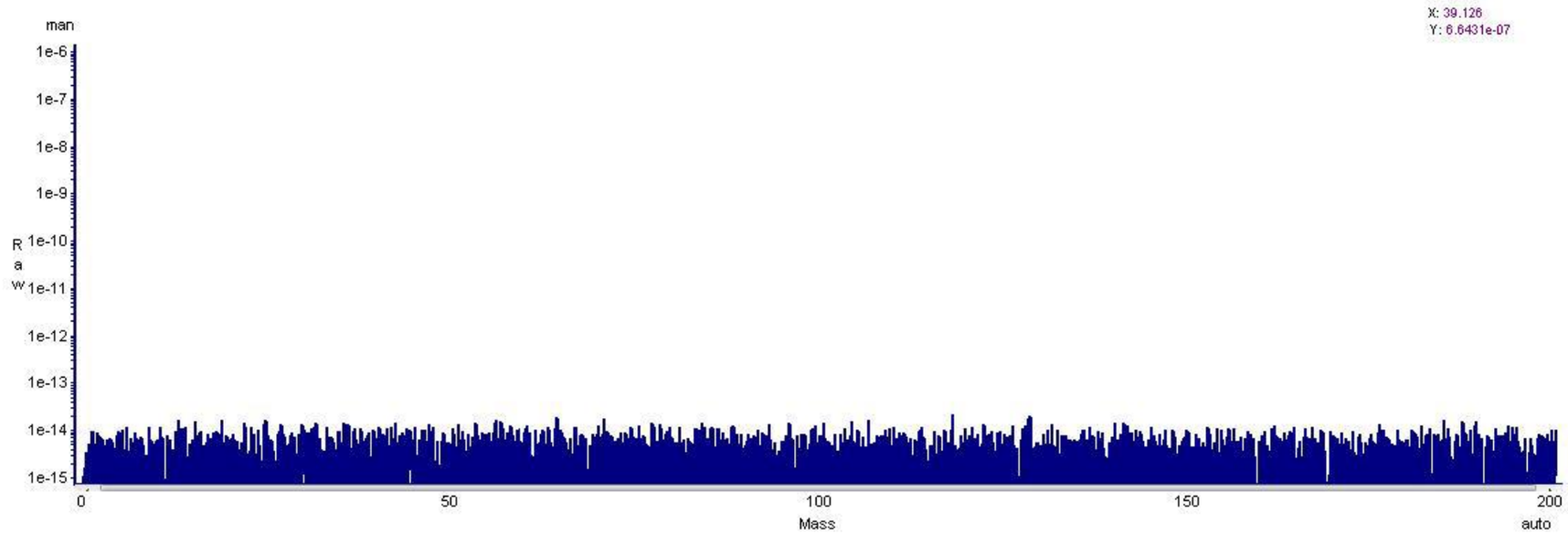


- If the m/e- relation is correct, the corresponding ion flies through the magnetic field and hits the detector.
- The relation m/e- is adjusted for each mass, so that only the corresponding mass crosses the path.

Mass Spectrometer

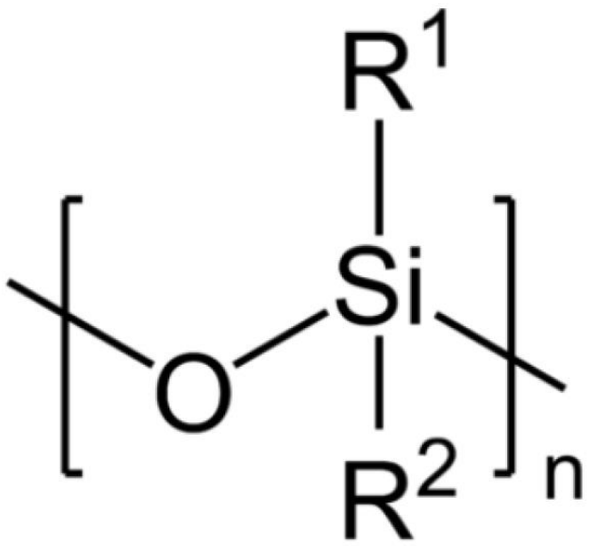
Detector:

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

Silicone oils



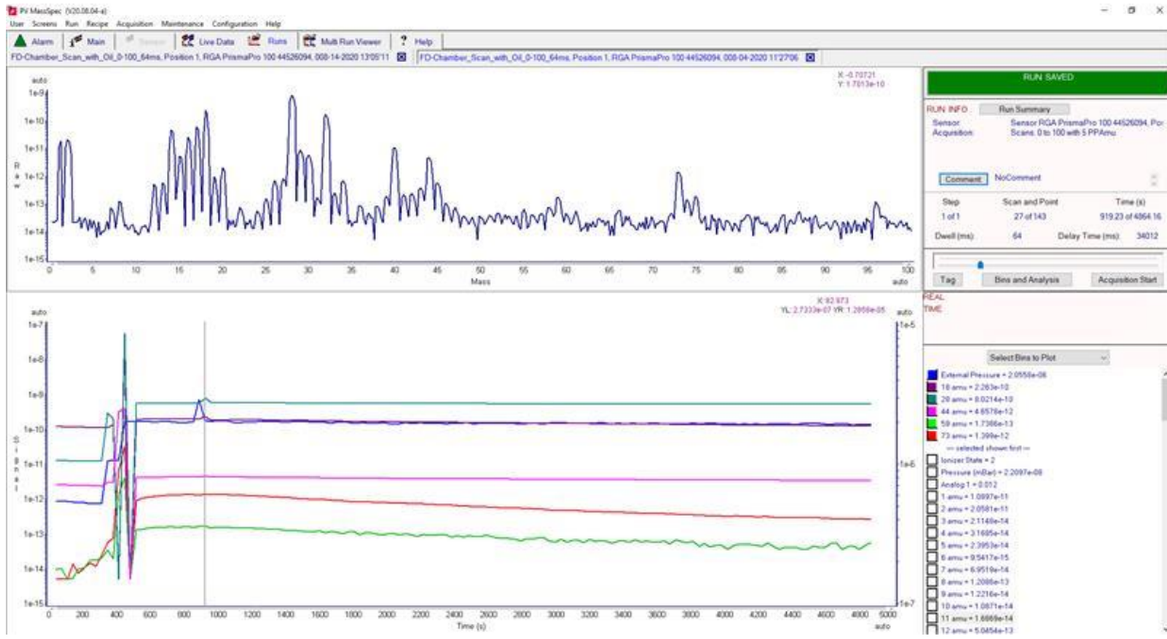
The repeating unit of the siloxane polymer

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

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



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

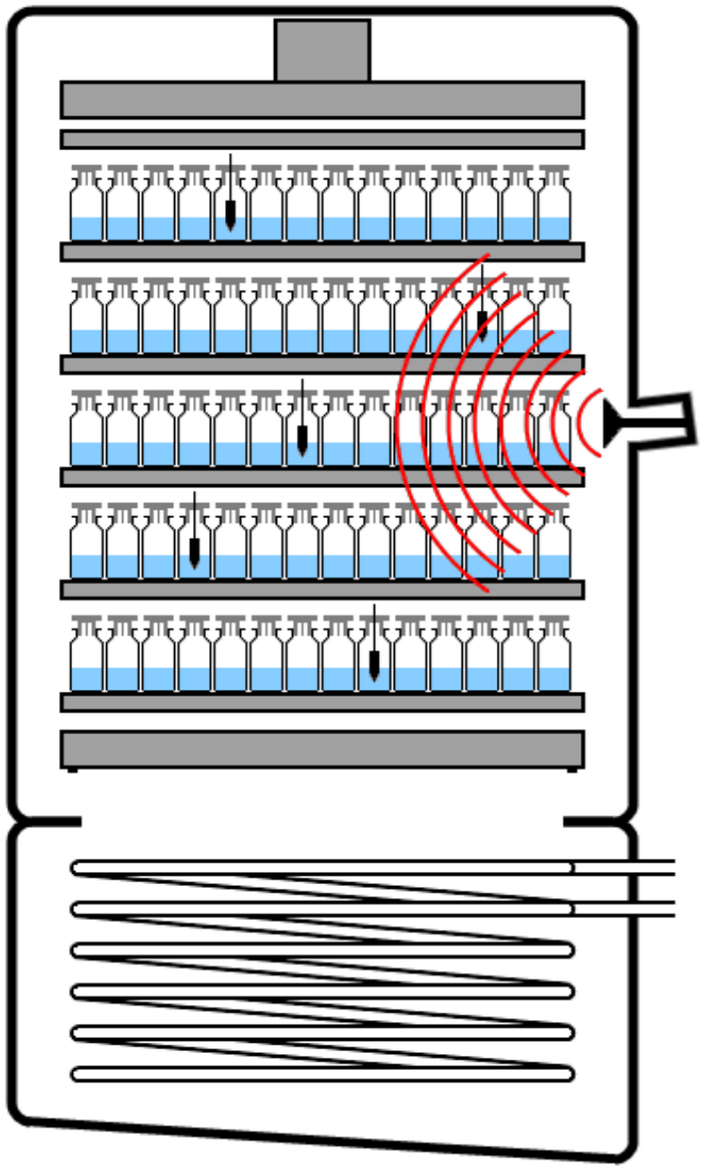
Cryologger

-85C to +140C

Wireless temperature measurement

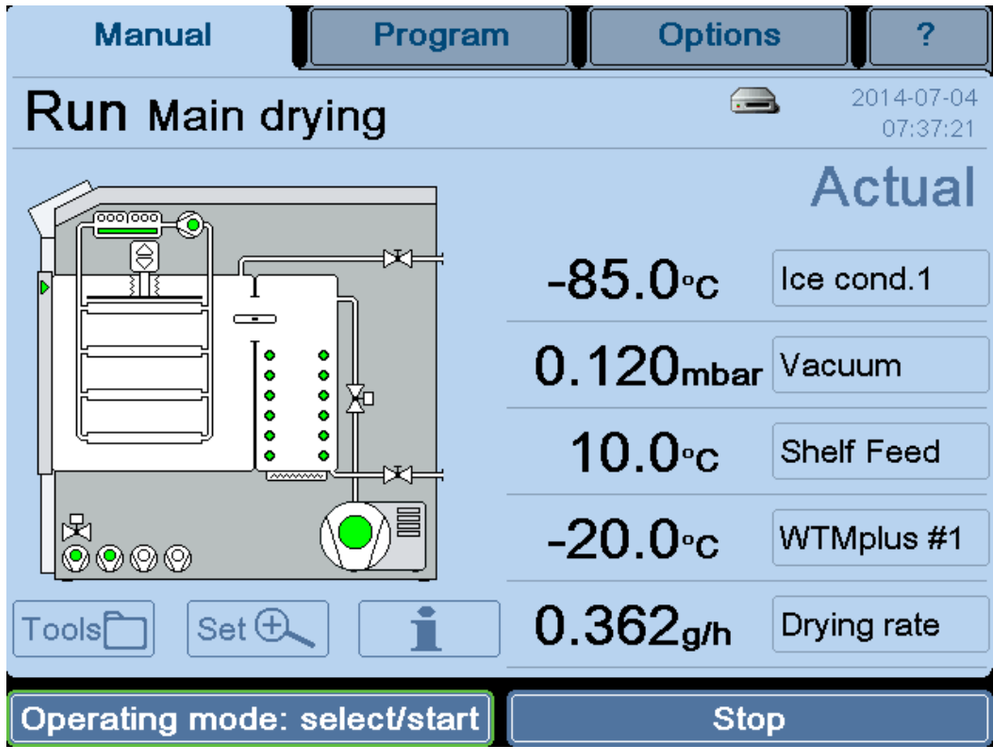
positioning equipment

Functional principle wireless Sensors

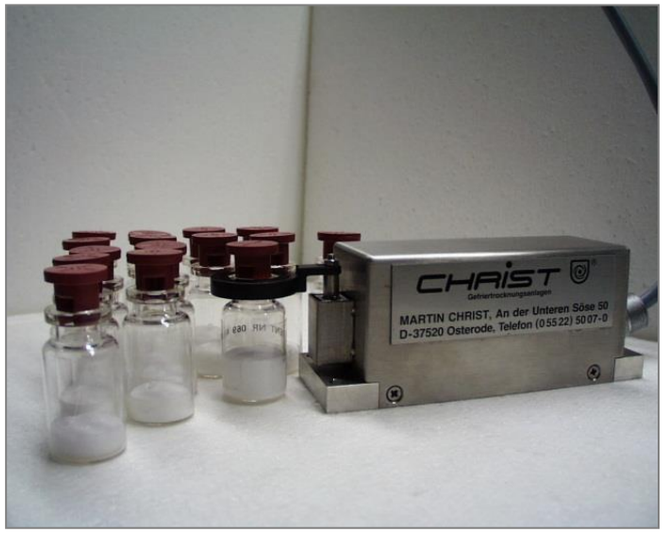


- energy supply of the sensors by means of a radio frequency within in the 2.4 GHz range, no battery or other energy storing device necessary
- intermediate storage of energy by stimulation of a quartz crystal
- high precision temperature-dependent detuning of quartz-oscillation frequency
- transmission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

Process control tools (sensor technology)

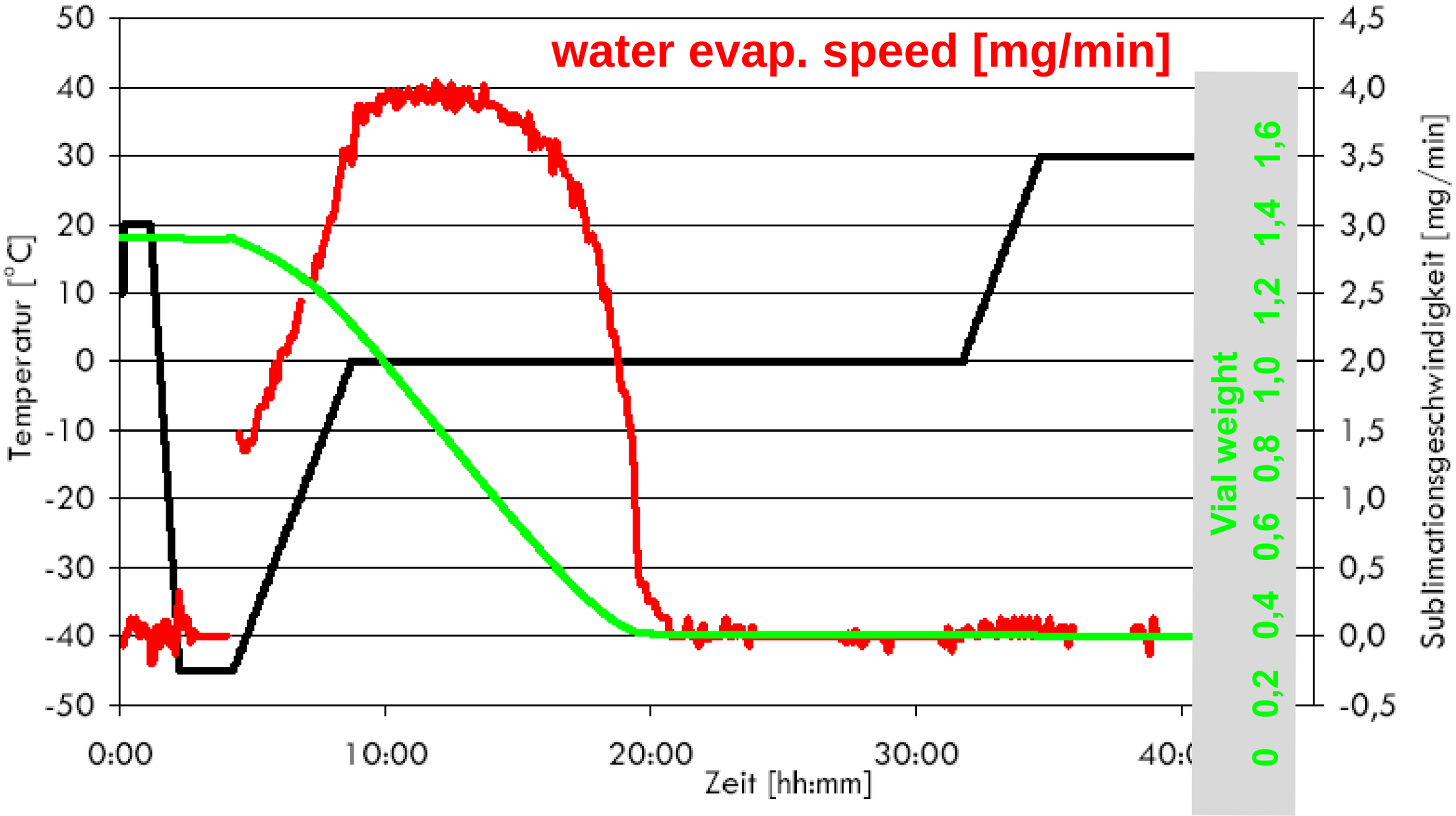


Measurement of drying rates



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



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

Pharmbiocon

Life Science Engineering

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

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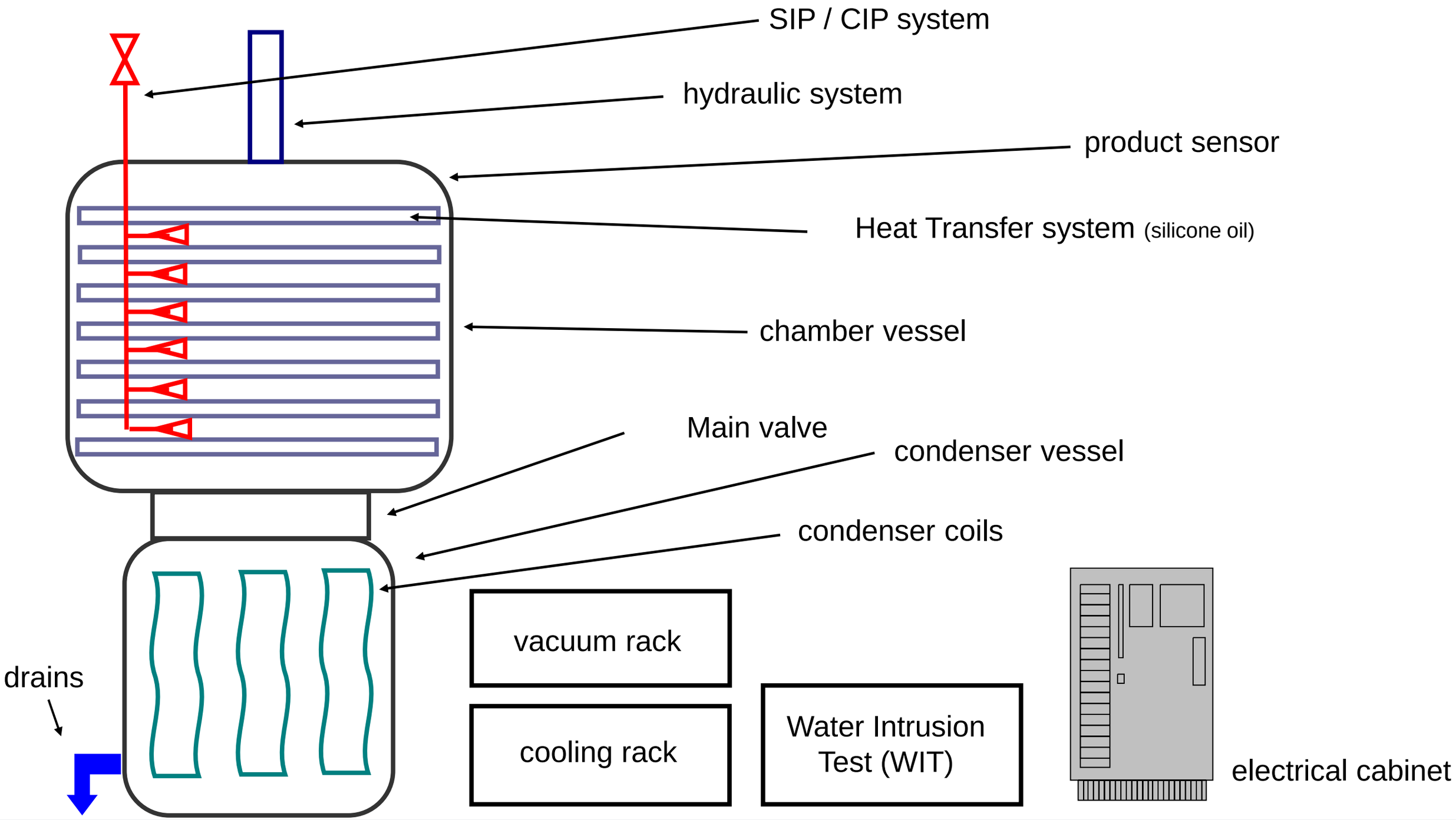
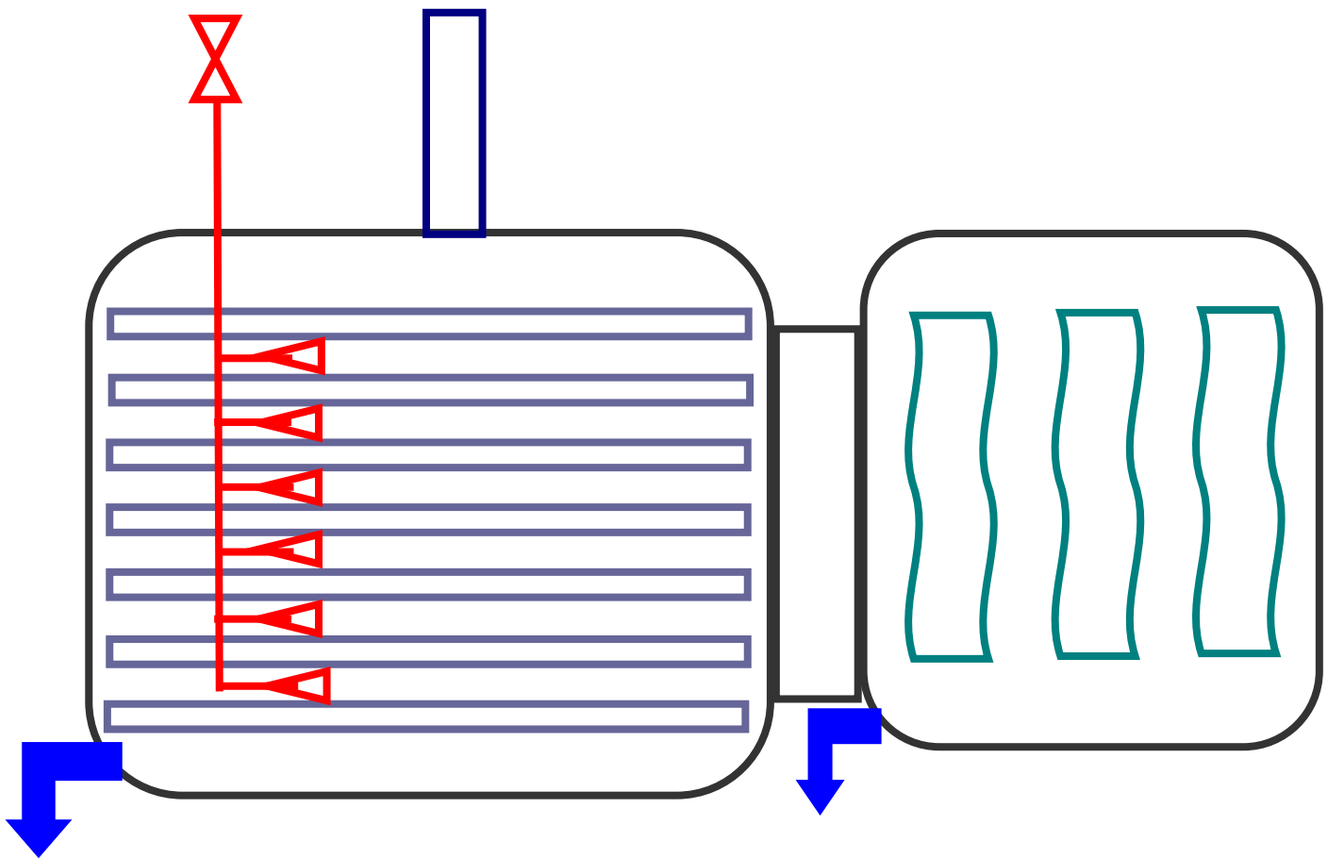
Theory 5:
Construction of freeze dryers

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

Lyophilisator



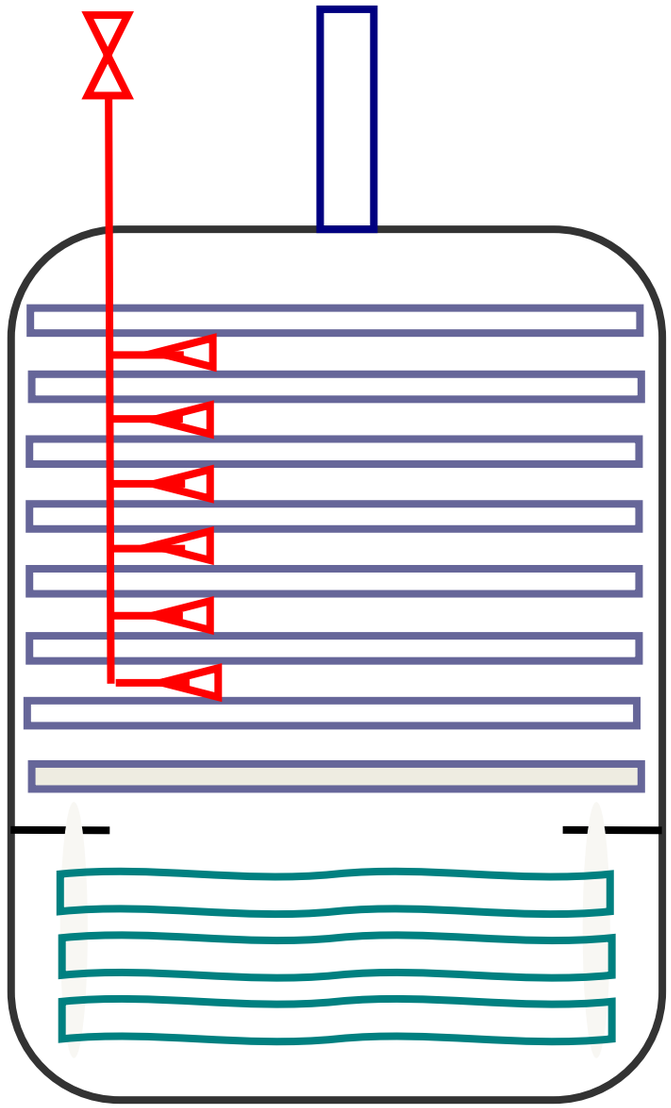
Lyophilisator



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

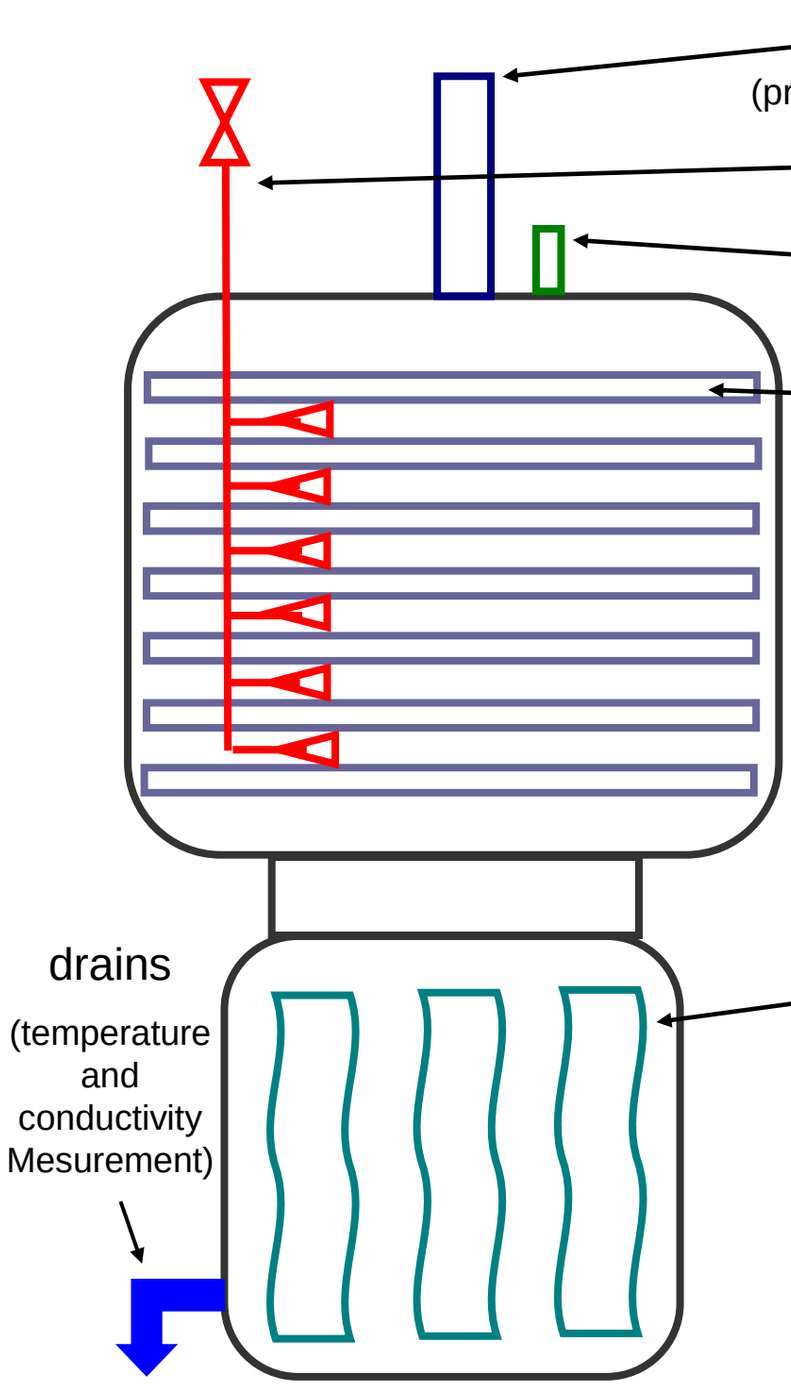
Lyophilisator



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)

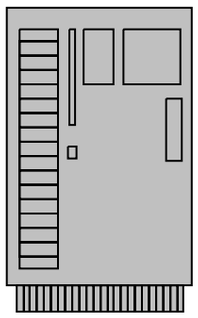
condenser coils (temperature sensors)

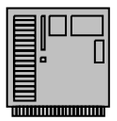
drains
(temperature and conductivity Mesurement)

vacuum rack
(vacuum sensors)

cooling rack
(temperature sensors)

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





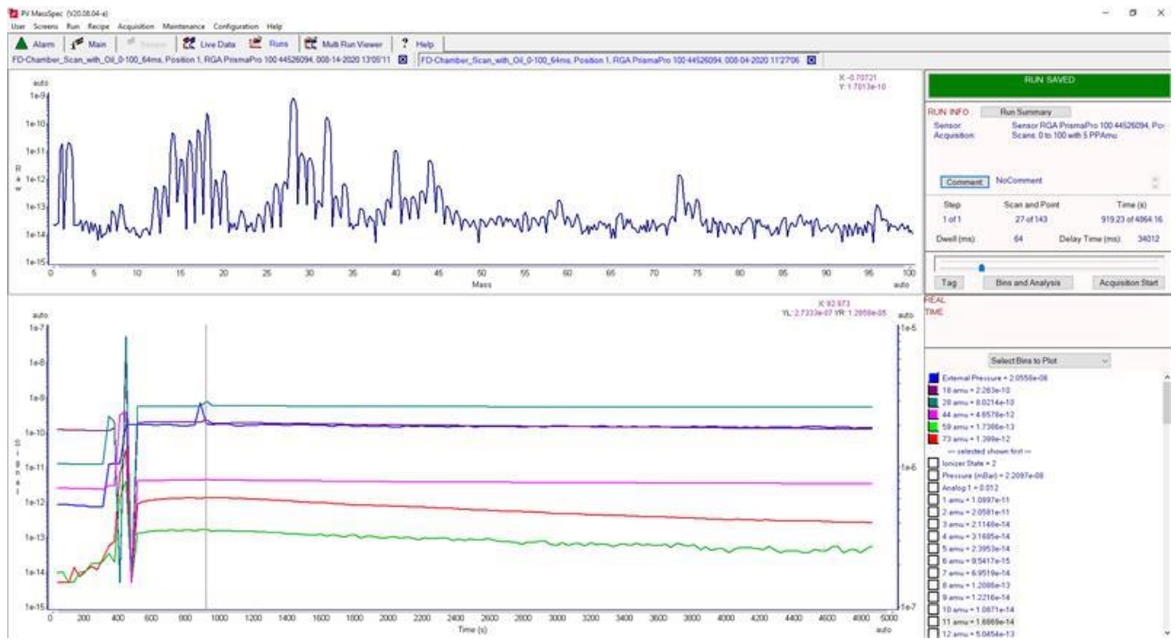
PC systems
(SCADA / operator panel)

power and communication systems
(PLT / PLS systems)

Lyophilisator

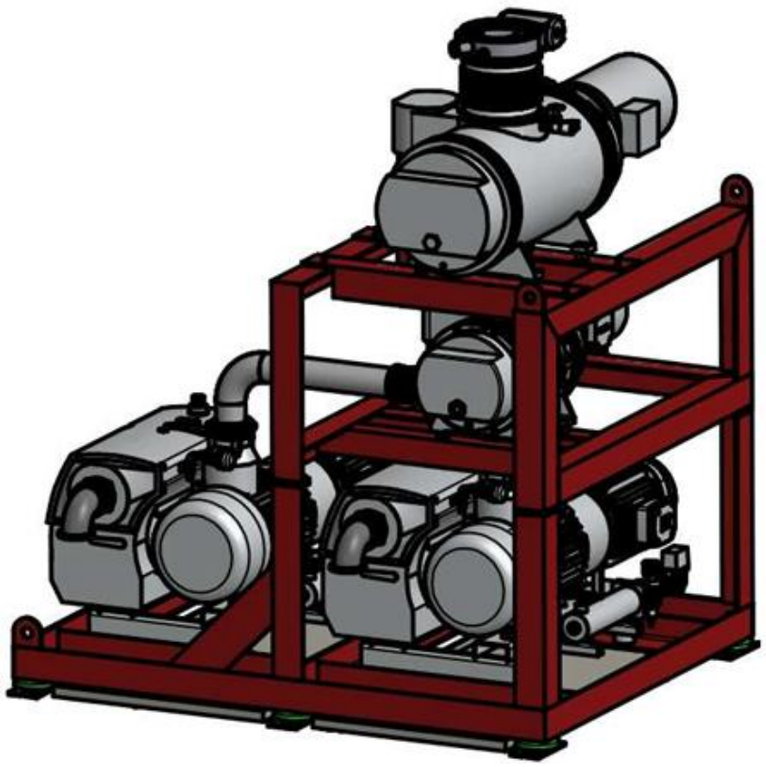
Special Sensor

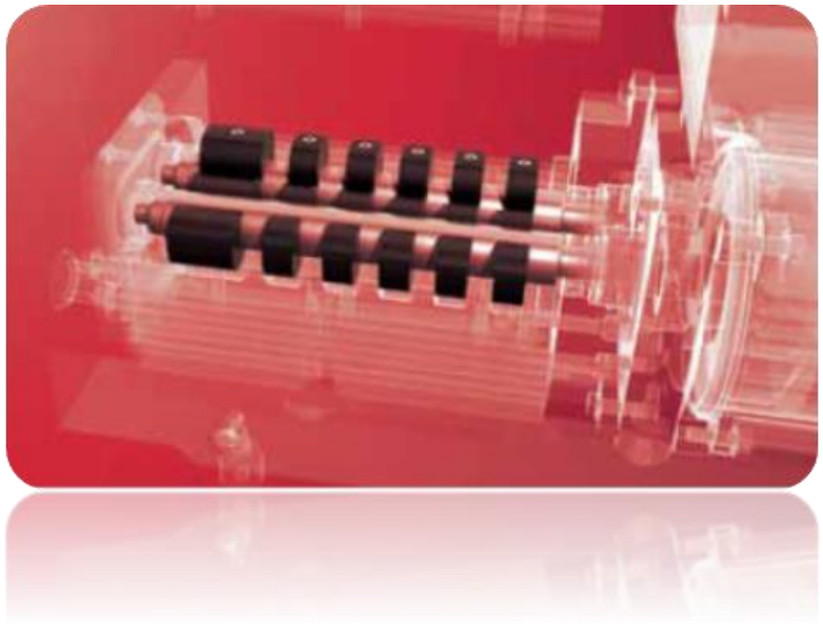
Mass spectrometer Sensors for silicone oil detection mounted in the Main Valve



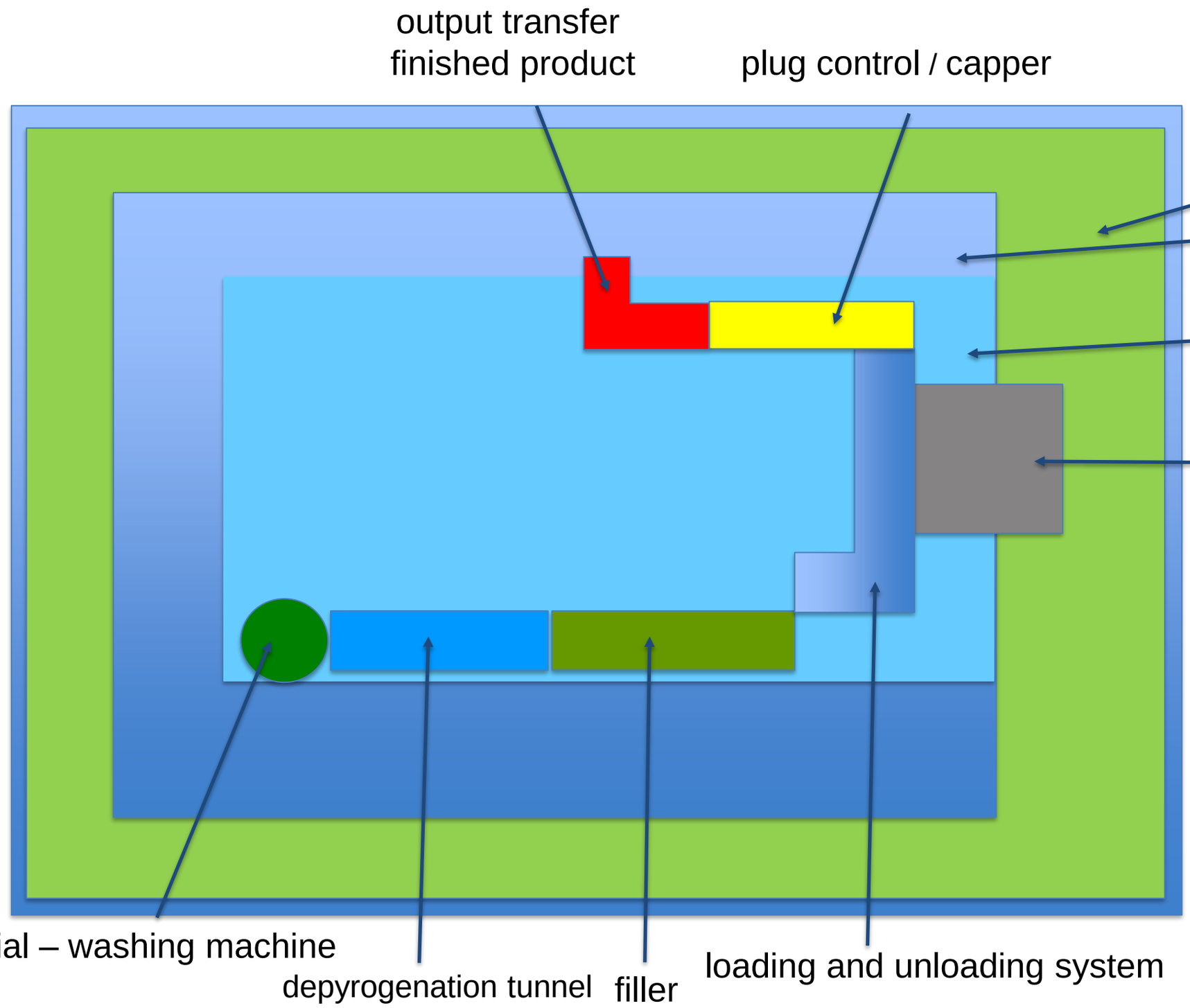
Lyophilisator

vacuum pump units



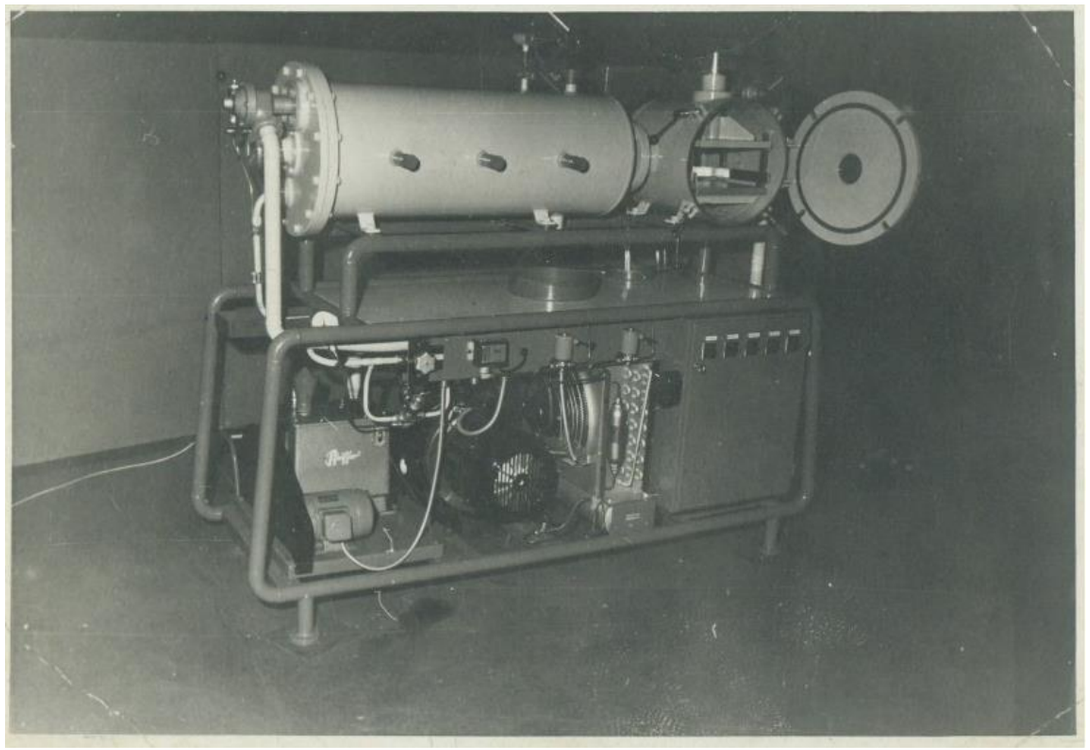


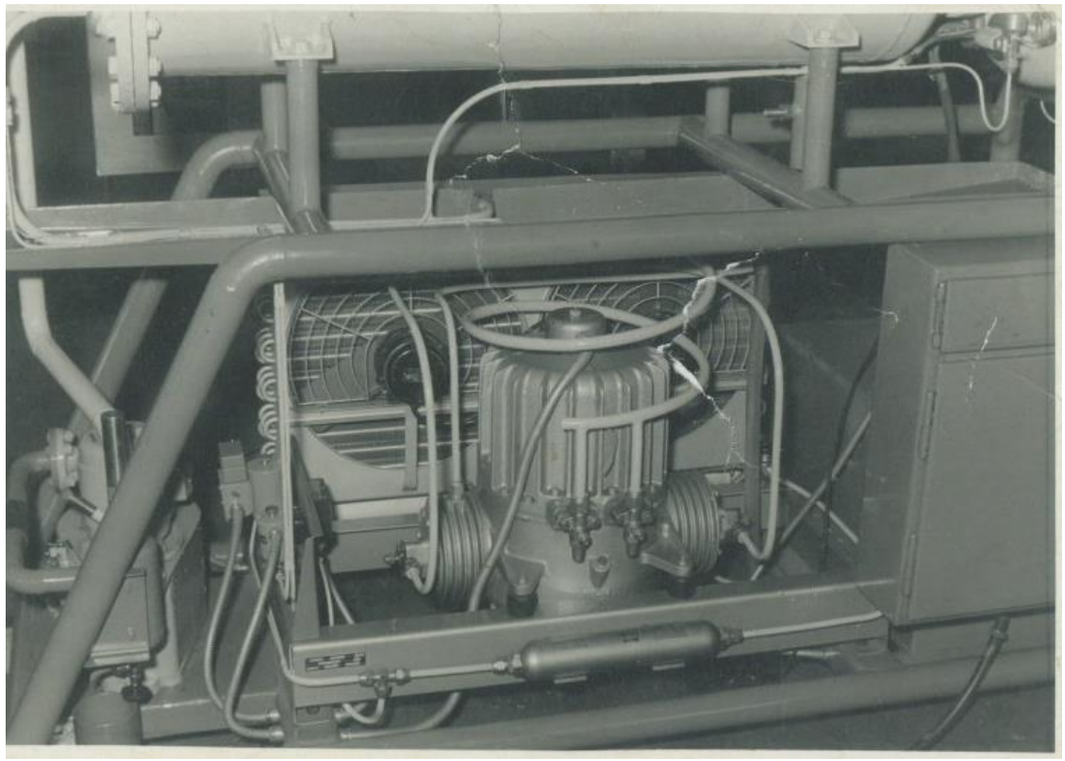
Exemplary construction of GT range



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

Old treasures





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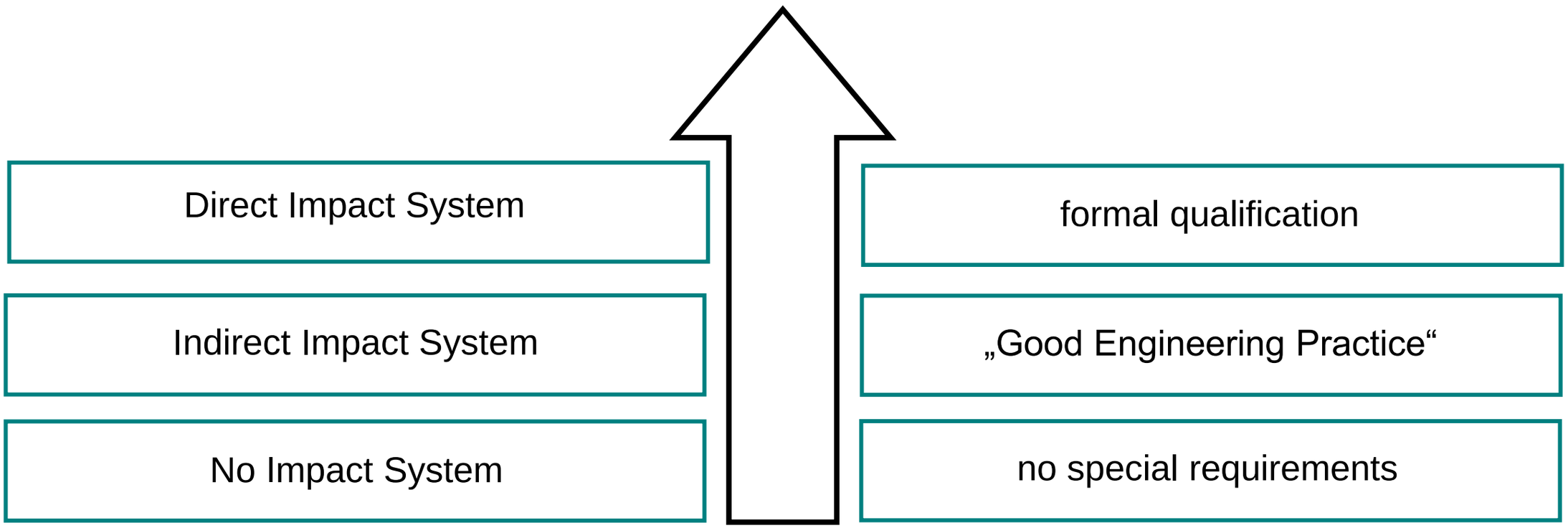
Theory 6:
Qualification/ requalification /maintenance

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

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“

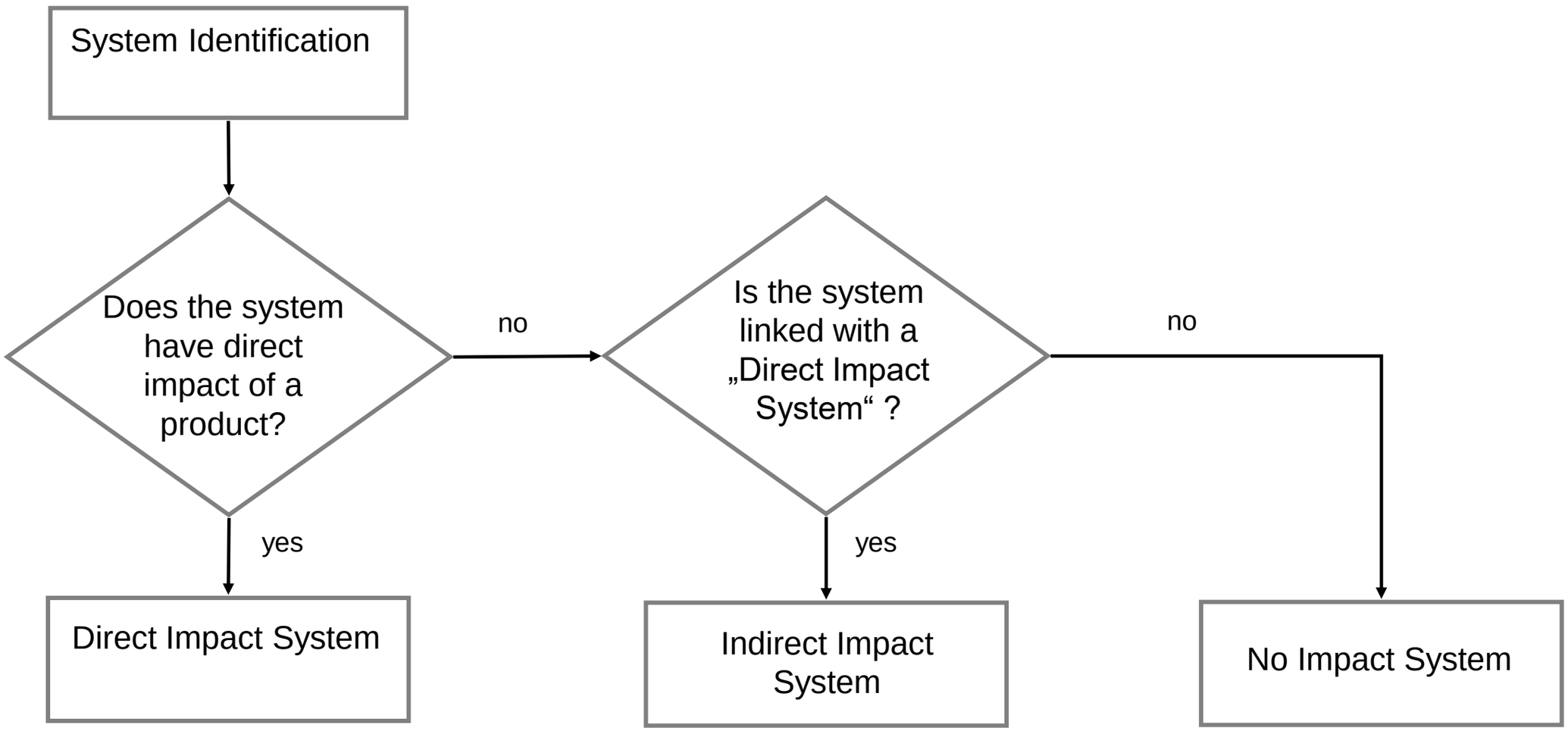
No Impact System

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:

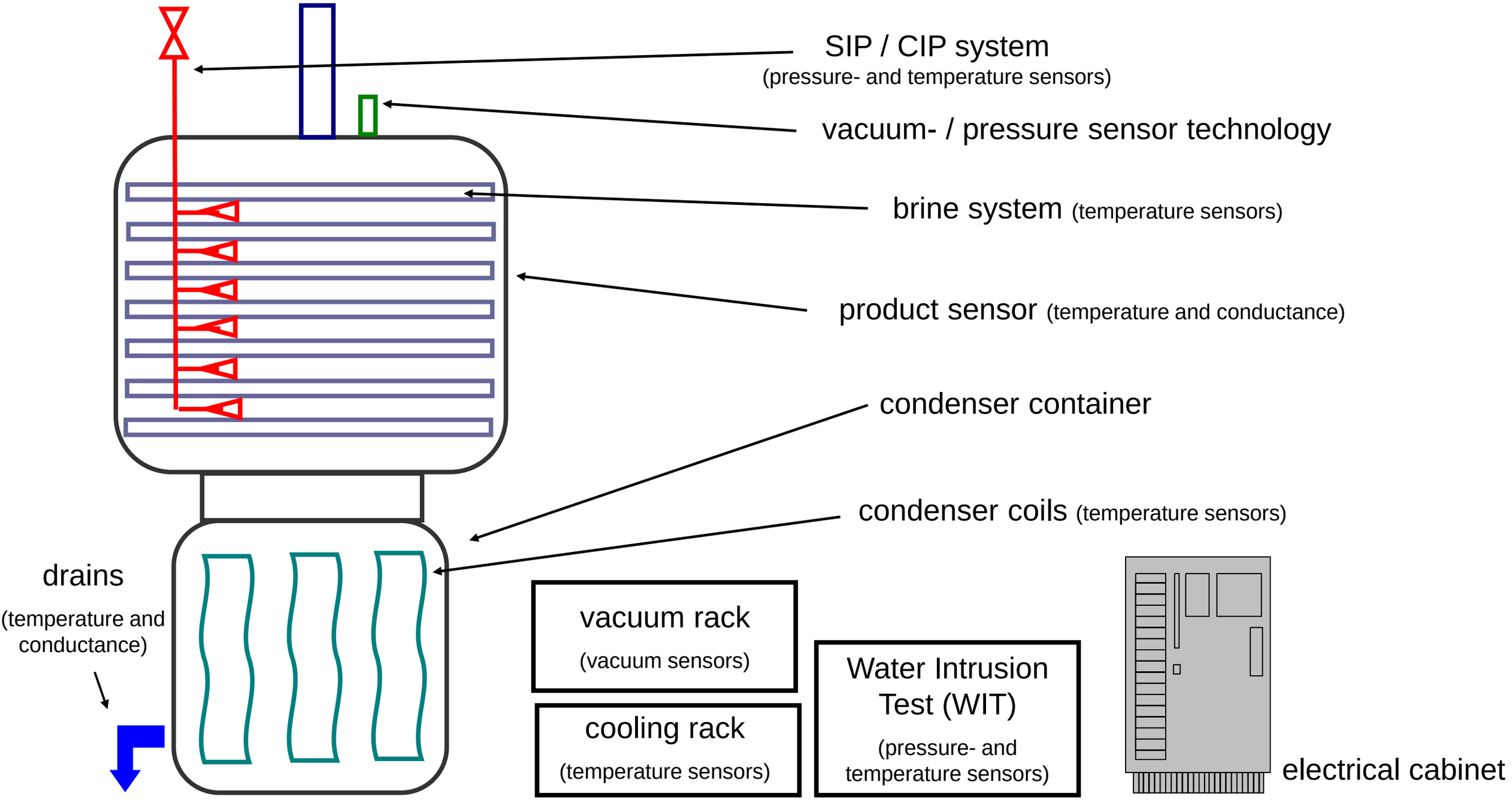
<u>What is qualification:</u>

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.

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)

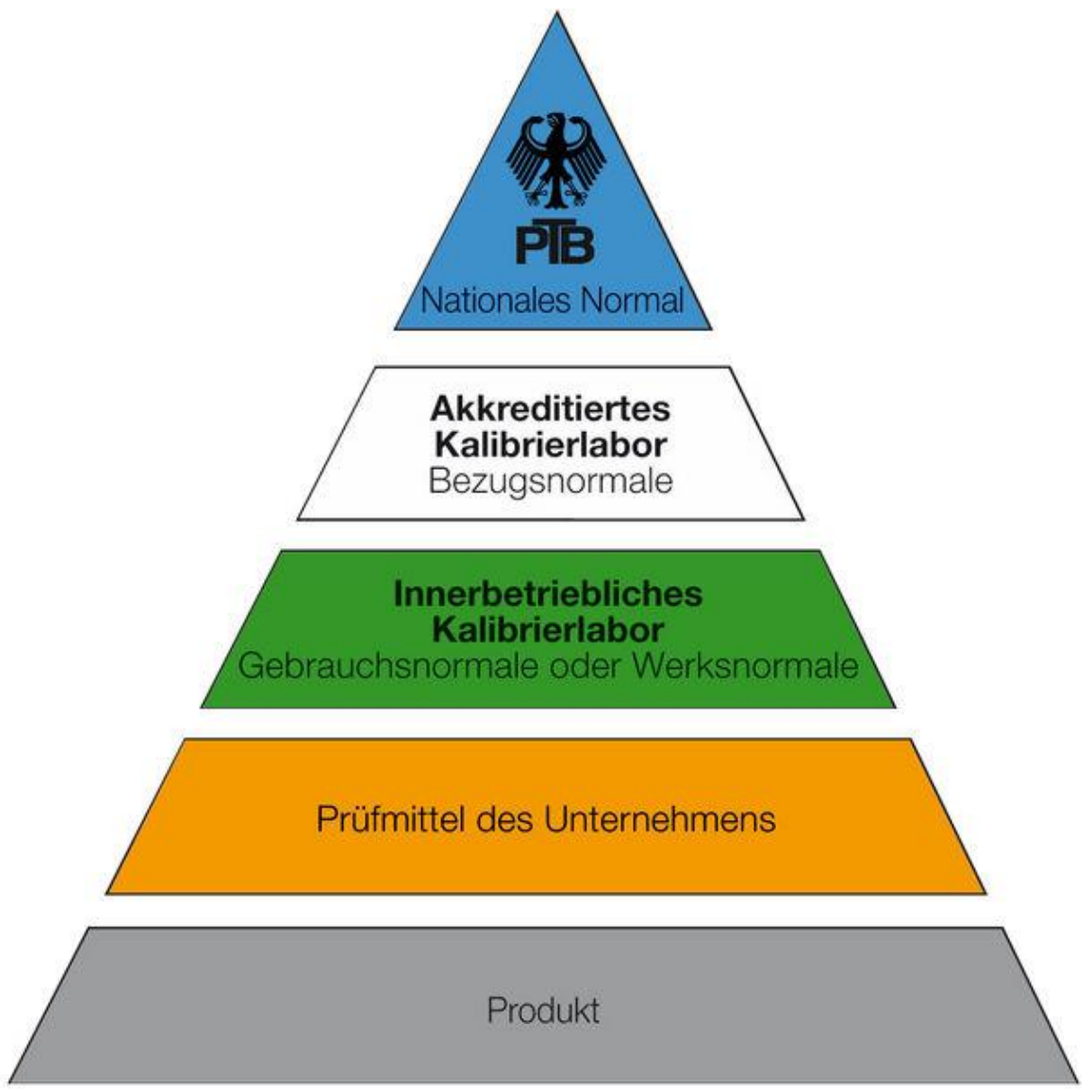
A official verification is also a calibration, however official verification may only be carried out by government Institues (NIST).

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.

Calibration / Official Verification / Adjustment

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



e.g. German NIST Organisation

Three general rules for calibration

1. Acceptance Criteria must be clearly defined.

2. Reference value (unit) must be defined.

3. Measurement method must be specified with all boundary conditions, which have an influence 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.

Good calibration practice

A master SOP describes the basic procedures of a calibration.

The calibration method reflects the state of technic,

The calibration method 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.

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.

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.

Special Test - 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

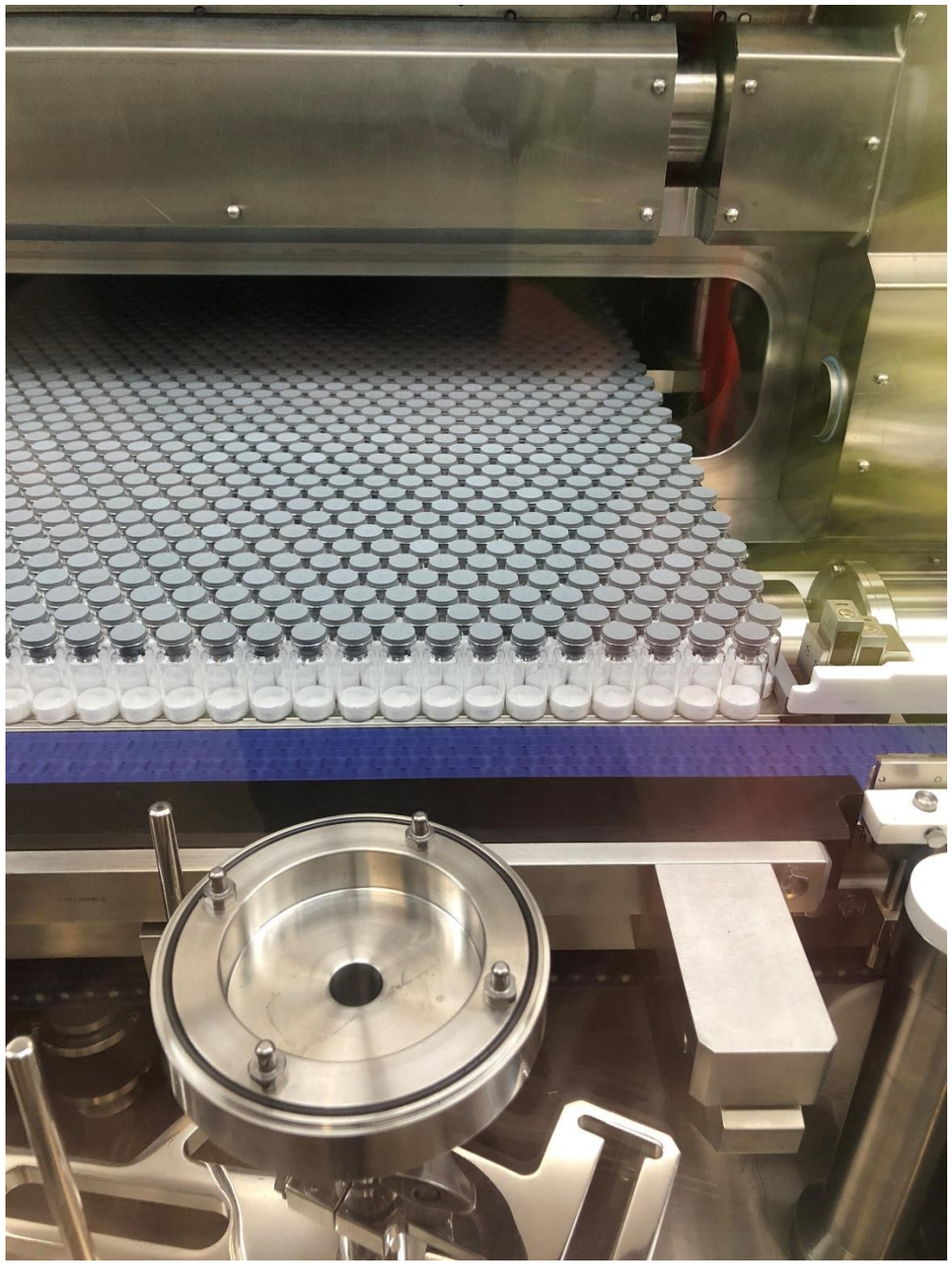
Condenser

Condenser Stresstest - Vial

View from the Top of the Ice Condenser.

Condenser Stresstest - Vial

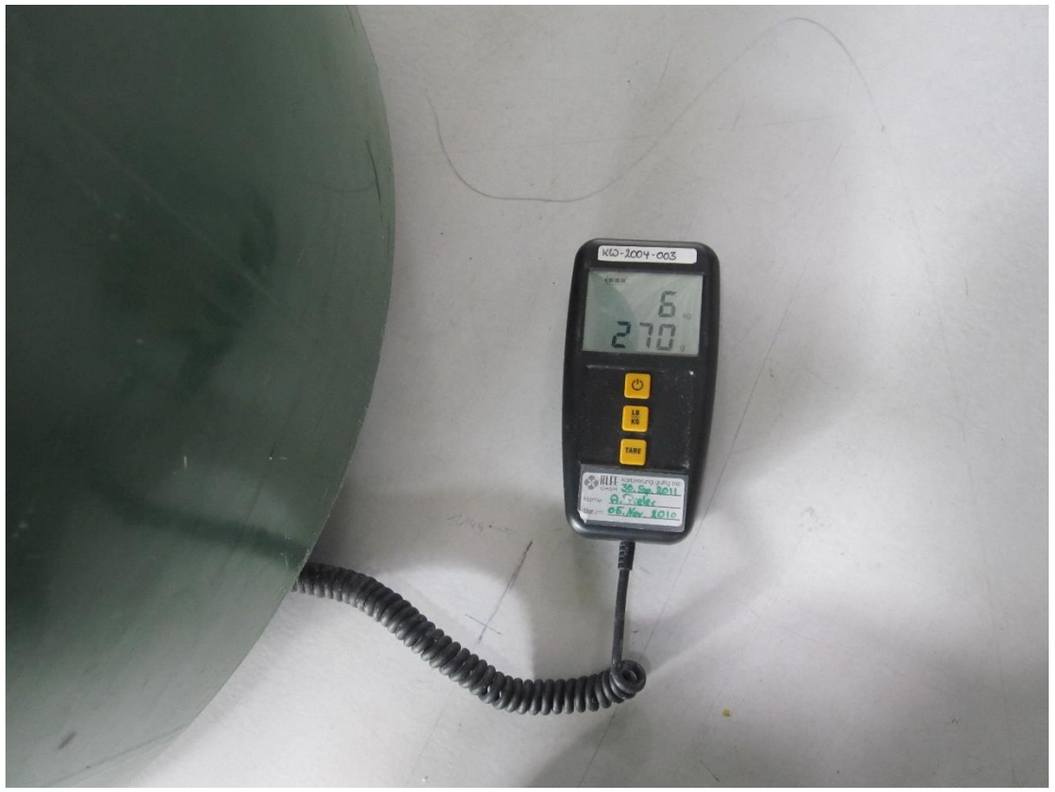
Row by Row Unloading of Freeze dried Vials



Lyo qualification – typical Test

Condenser Stresstest - Frames

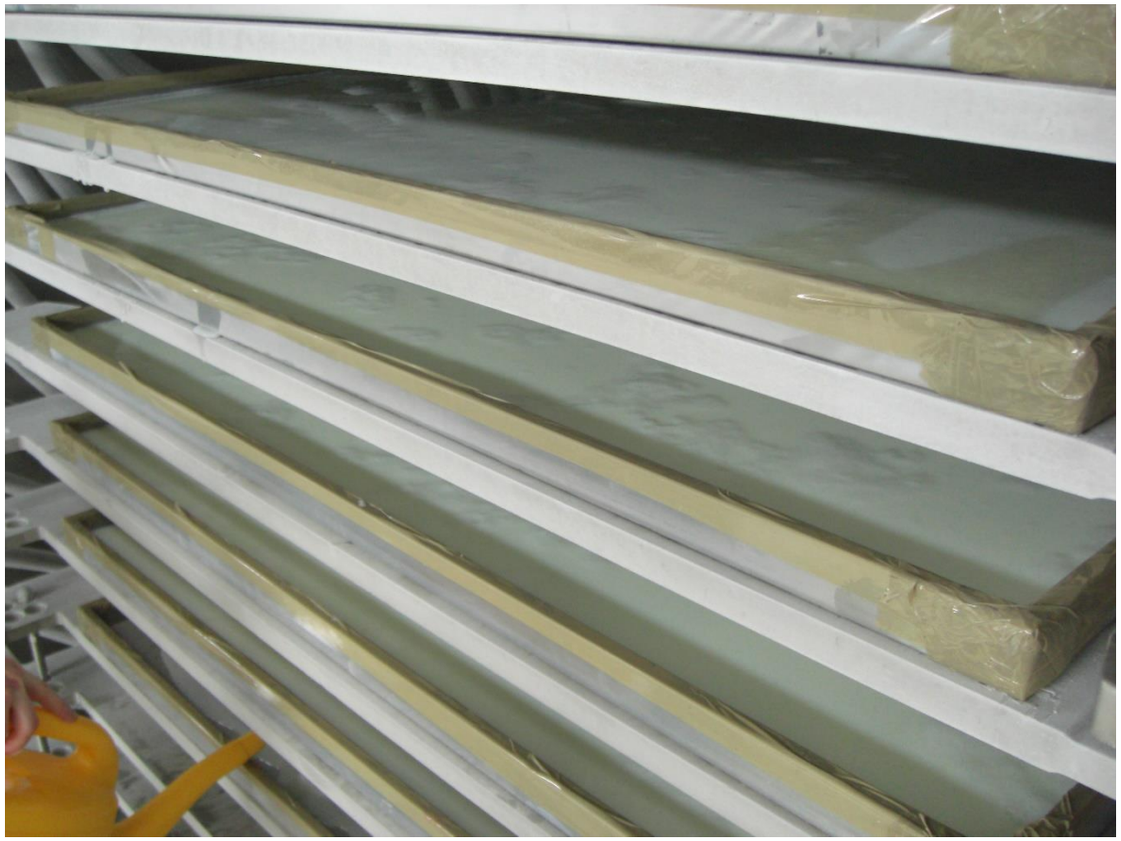
Weight of Solution

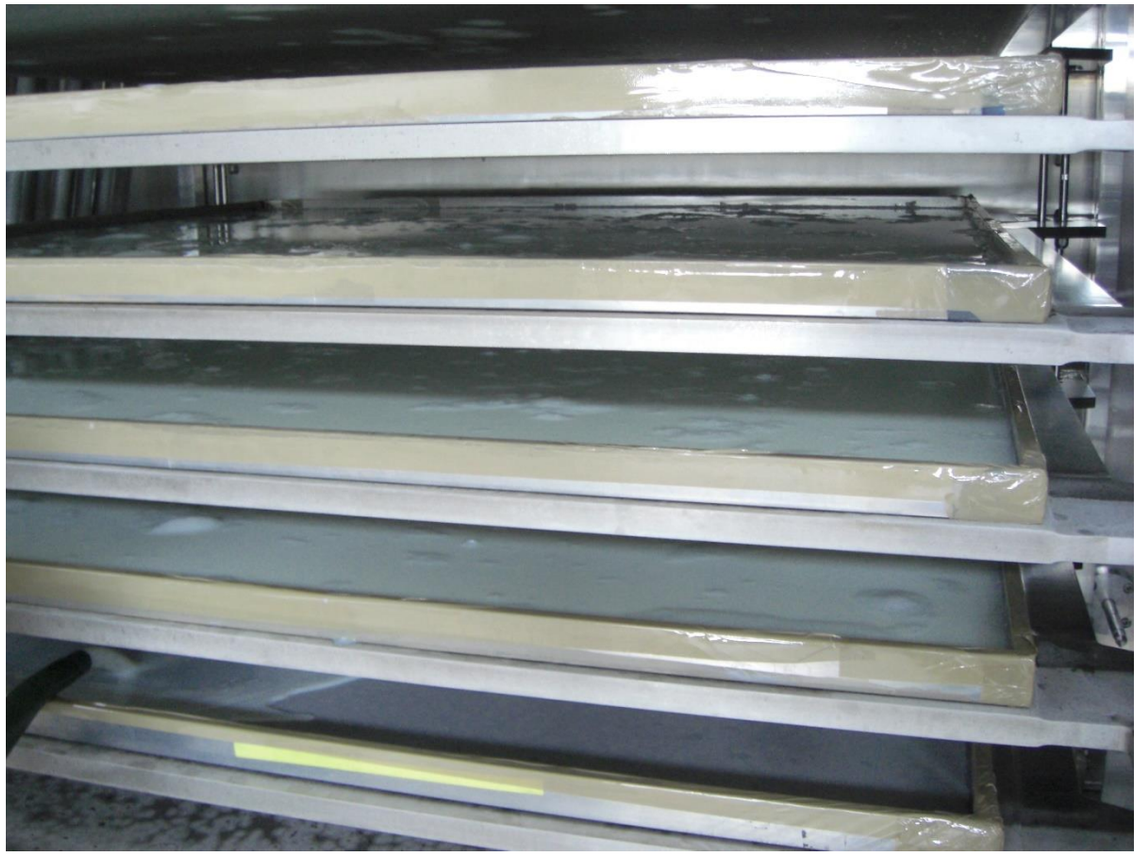


Filling the Frames

Condenser Stresstest

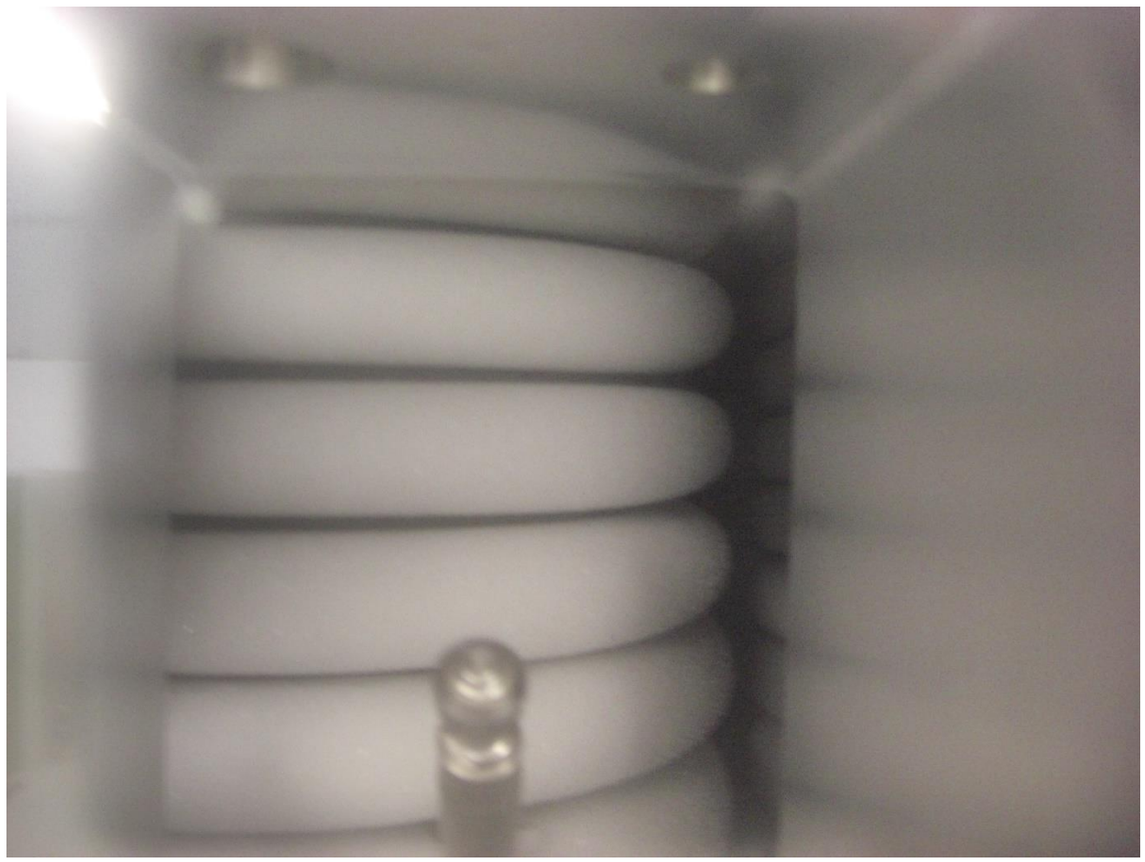
All Frames should be filled similar to avoid different Sublimation on the shelf stack





Condenser Stresstest

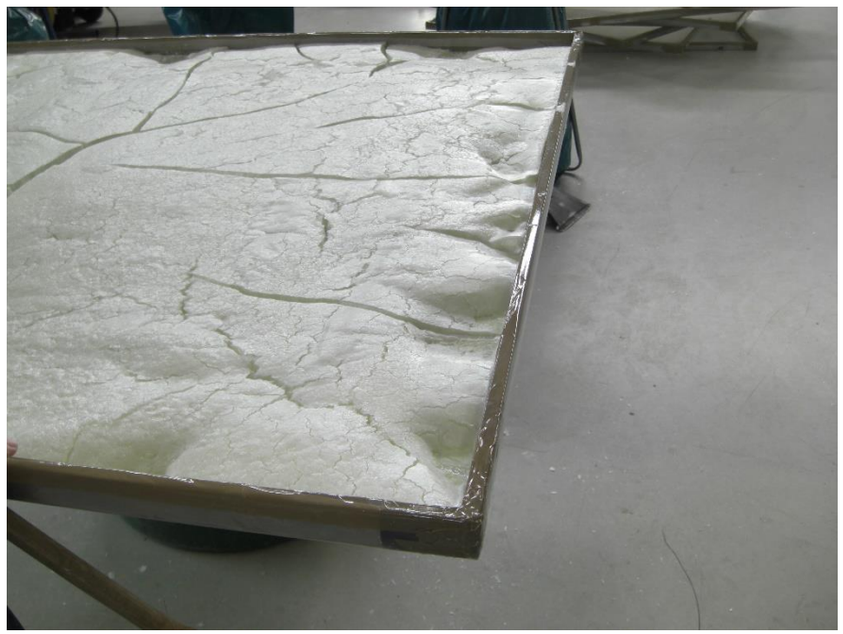
View into the Condenser during Process

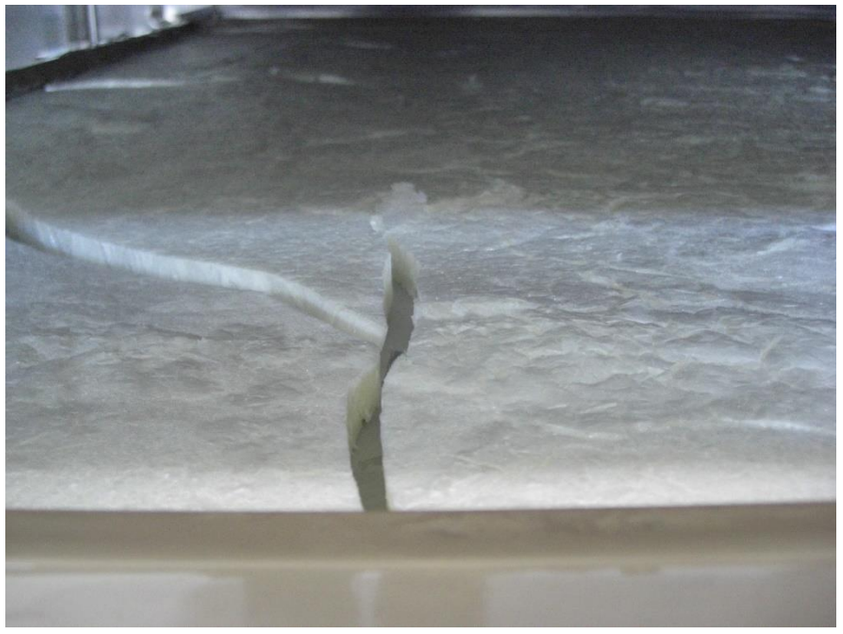


Lyo qualification – typical Test

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:

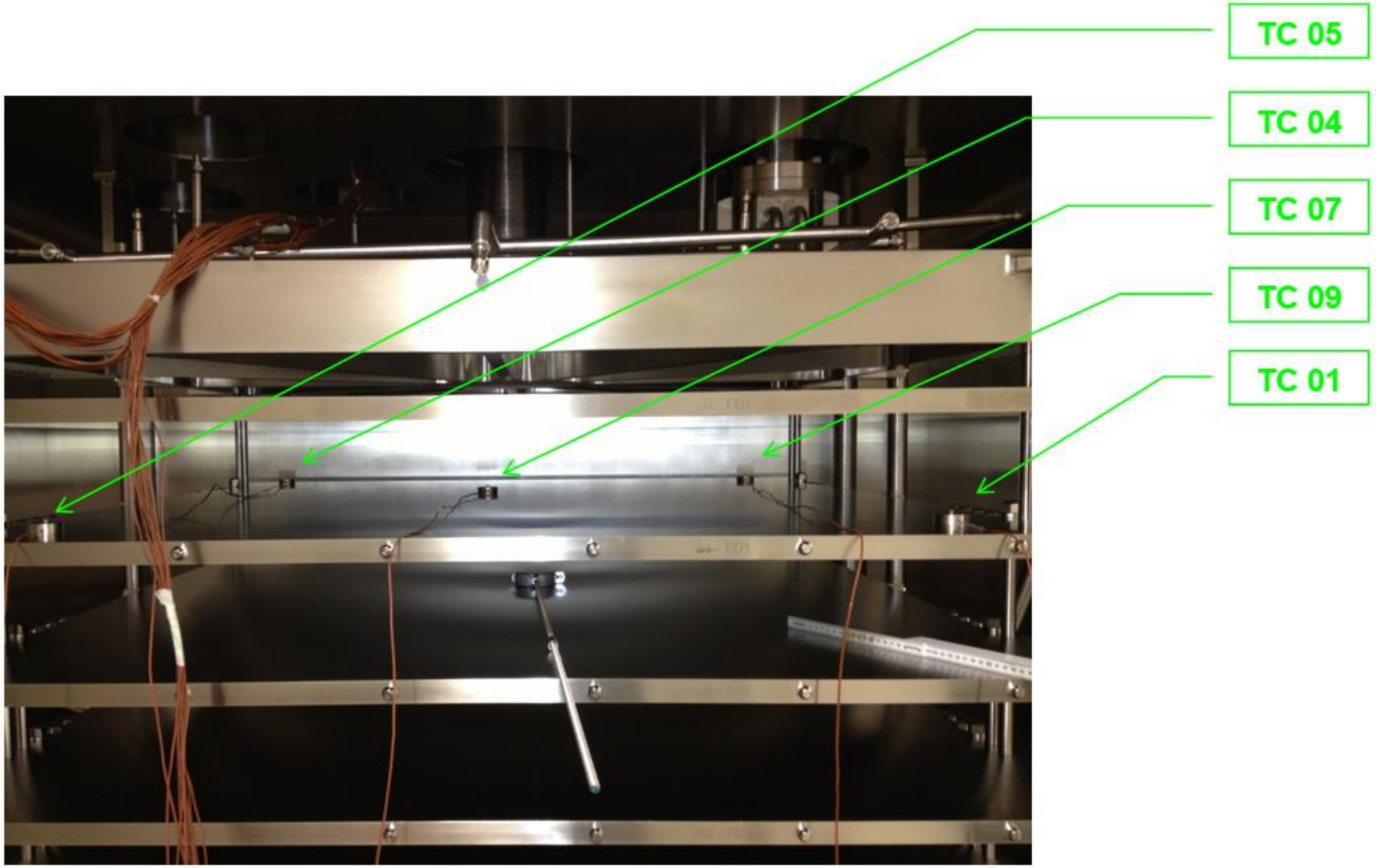
- that each shelf is inside the Spec e.g. +/- 0,5°C
- that the hole shelf stack is inside the Spec e.g. +/- 1,0°C
- that the controller System for Silicon oil works correct (Calibration is done)
- that the Heat Transfer System is filled correct (no air inclusions)

Shelfmapping

Positioning of Shelfmapping Sensors

Lyo qualification – typical Test

Shelfmapping



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

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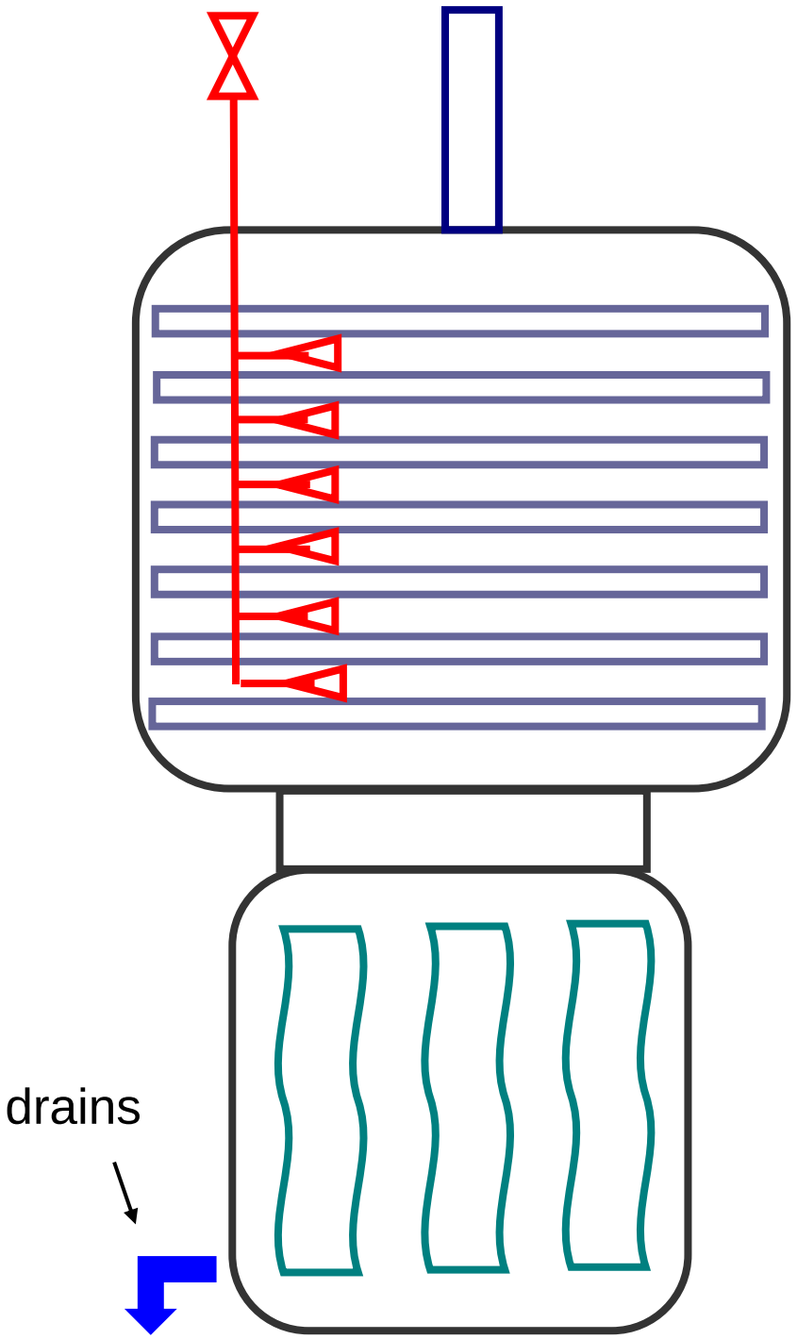
Cleaning and sterilisation

Theory 7:
Cleaning and sterilization / In Process Testing

- CIP / SIP systems
- acceptance of CIP / SIP systems
- cleaning validation
- sterilisation qualification
- turnaround process
- In Processtesting during Lyophilisiation

CIP / SIP systems

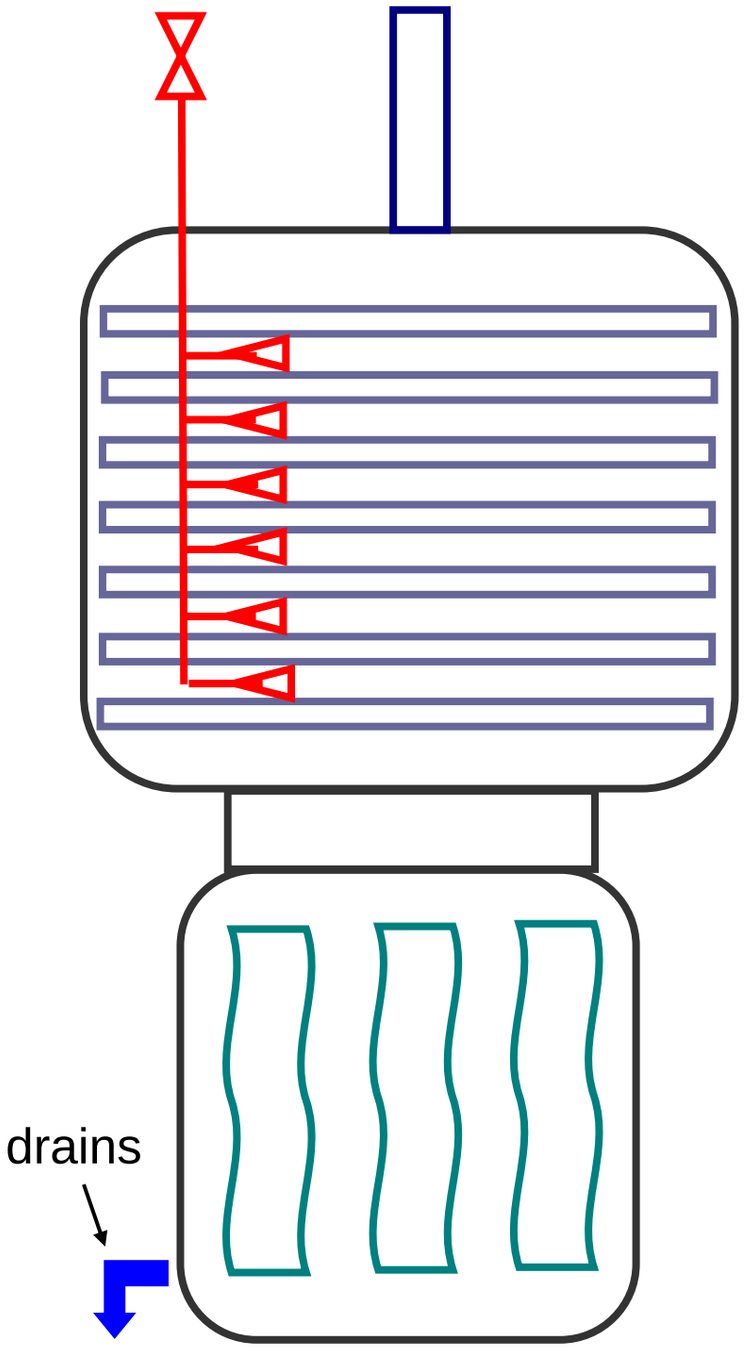


The aim of a CIP / SIP system is to clean the system and to sterilize the Freeze Dryer according to Specification.

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.

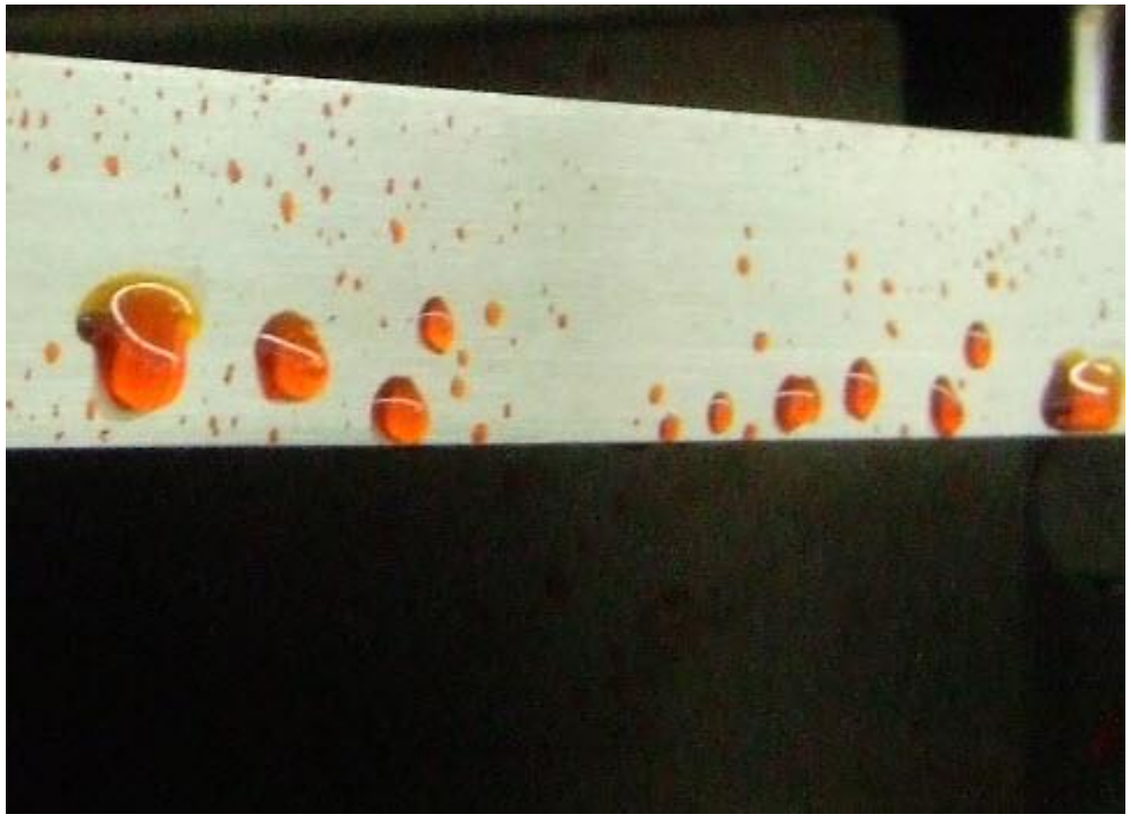
CIP / SIP systems ensure sufficient and qualitative supply of media for machines.

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

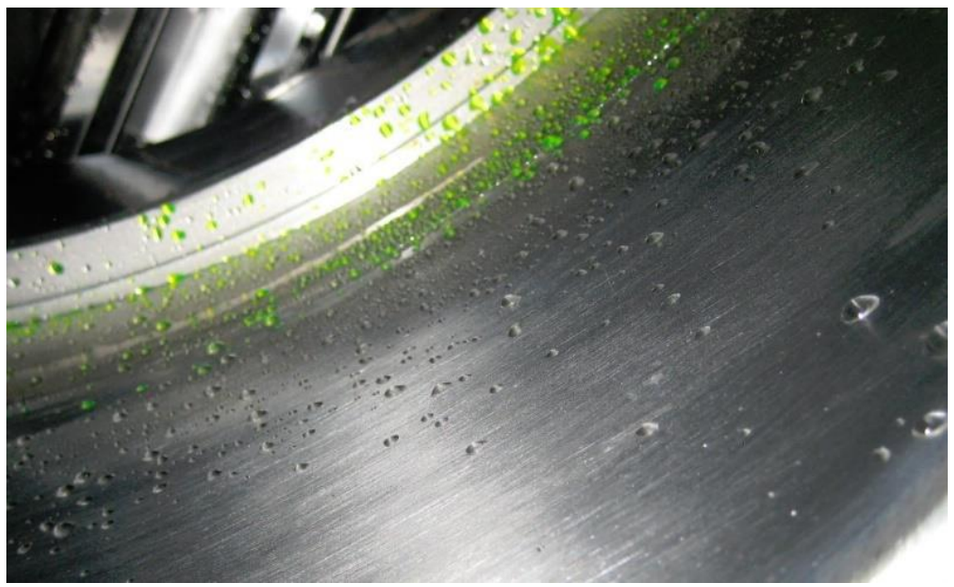
The riboflavin test can used as proof of solid design of a the FD.

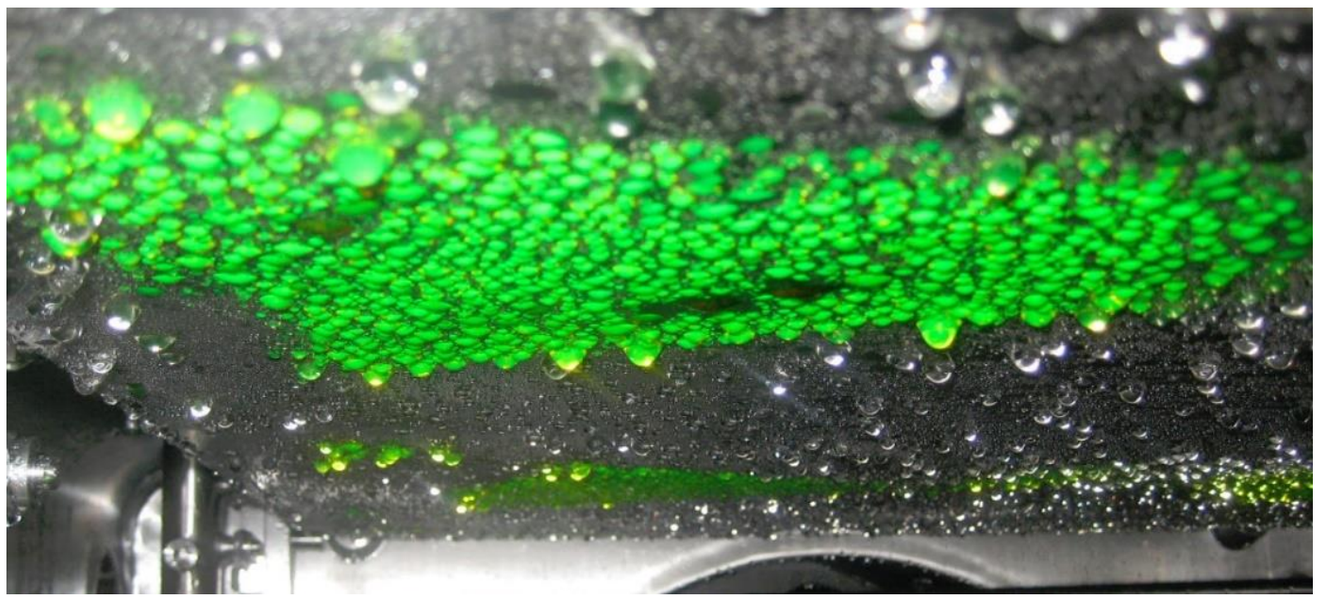
- the riboflavin test shows potential weakness of the CIP system (spray shadows)
- demonstrate cleaning success
- spray shadows can help to setup the CIP System

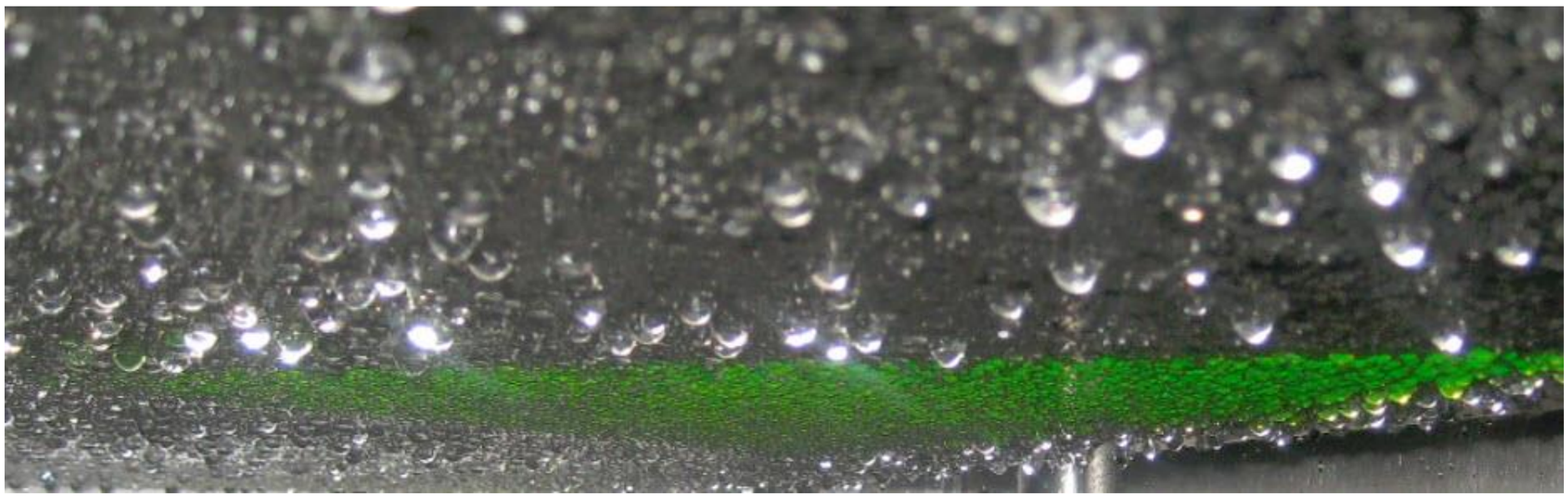


CIP / SIP systems

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

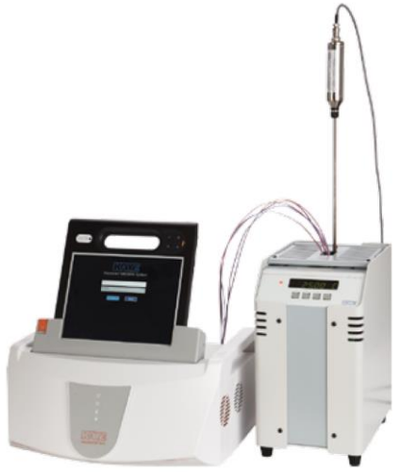
The qualification of sterilisation generally takes place with external equipment (recorder). The recorder e. g. can be a wired system with thermocouples (online measuring system) or a wireless system (logger).

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

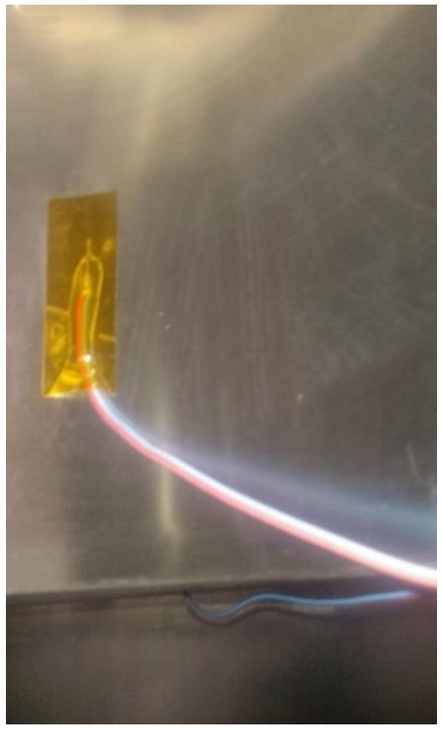
Qualification pout / absolute pressure tube

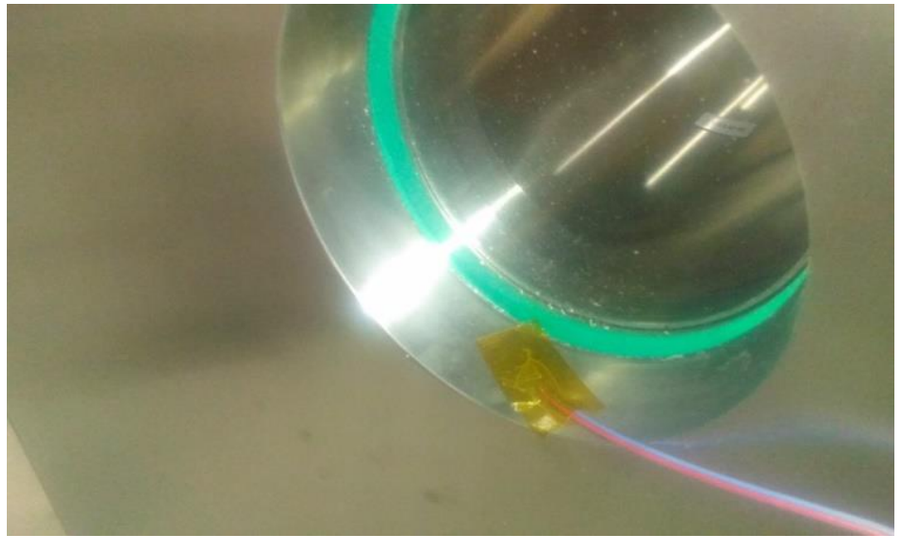


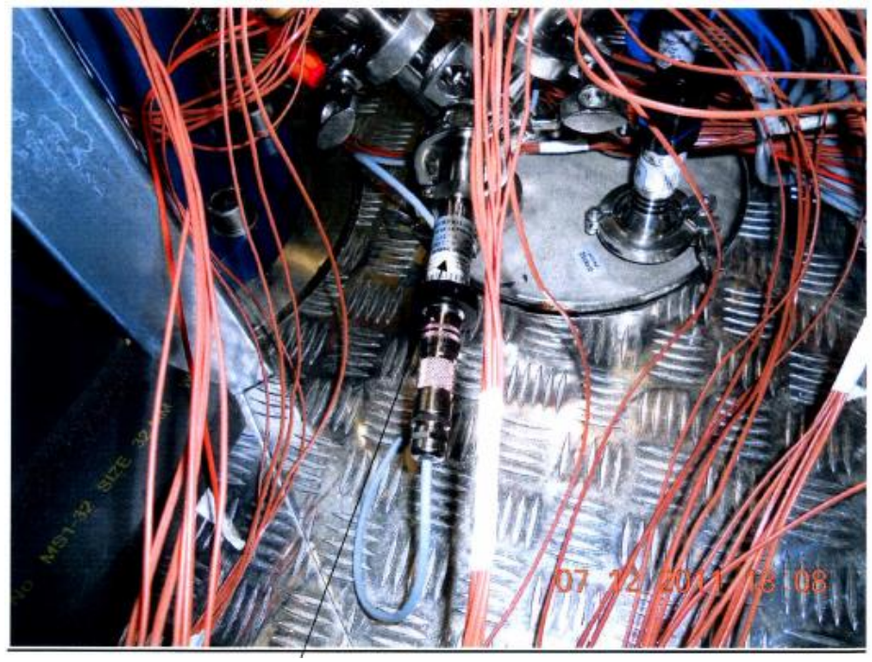
Construction of a recorder system including a temperature standard

CIP / SIP systems

Examples:



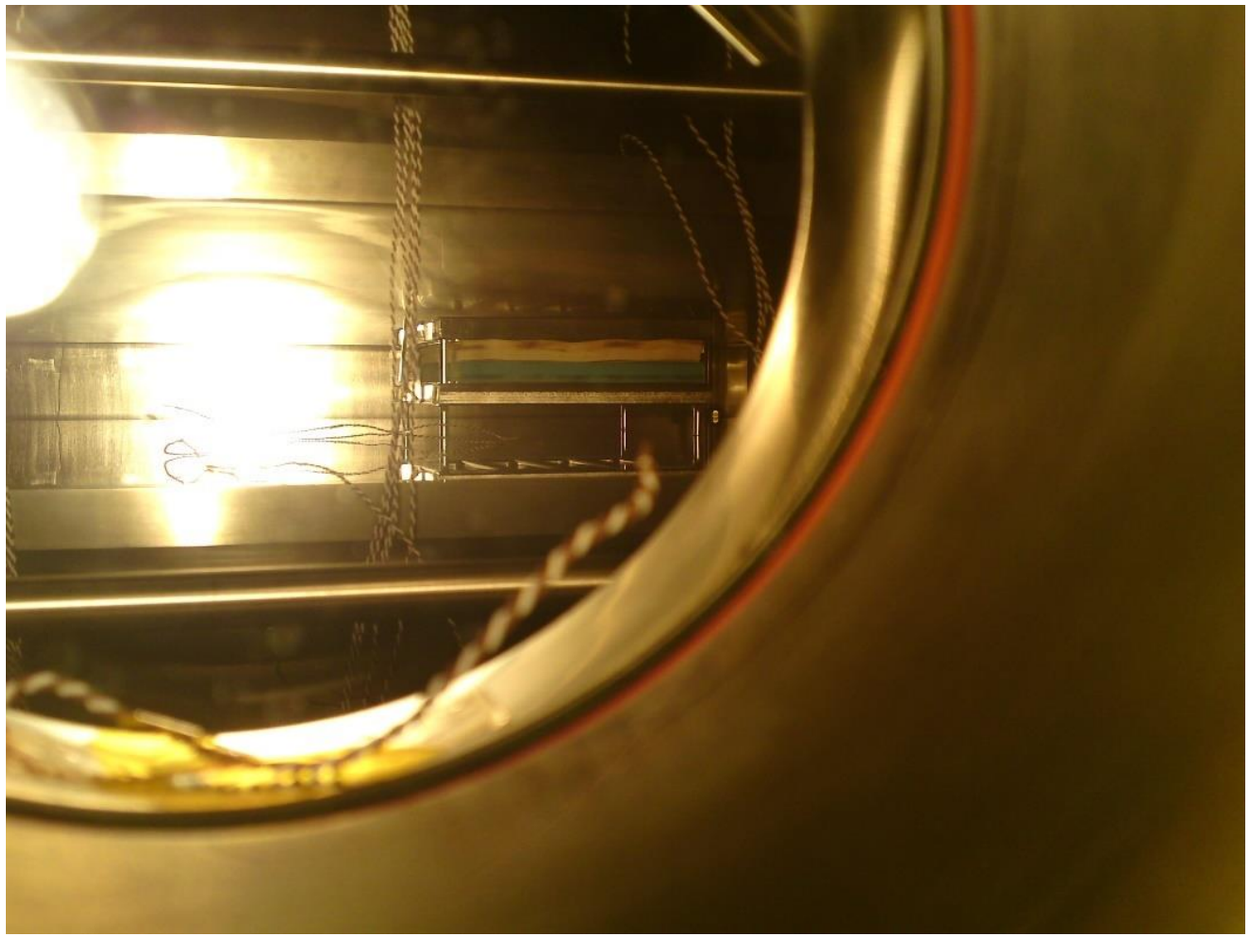




CIP / SIP systems

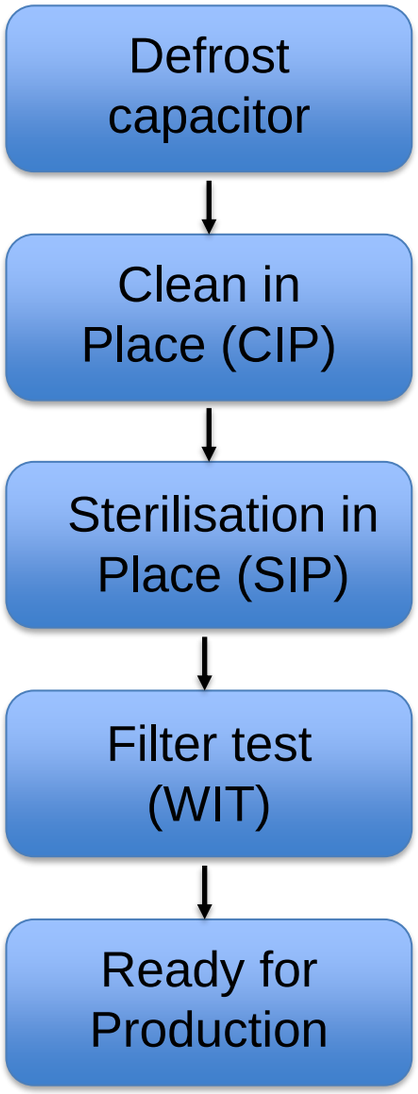
Special Tests for sterilization process are:

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



CIP / SIP systems

Turnaround - process:



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

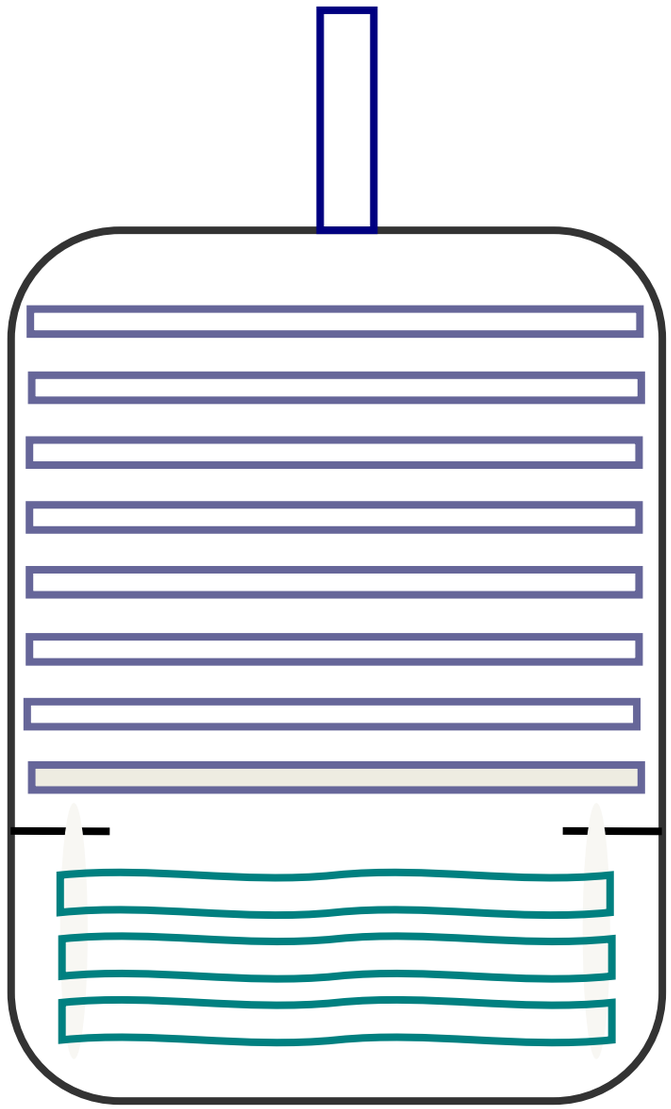
The turnaround time is the time from the end of production (unloading GT) till the start of a new production.

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).

In Process Testing – Lyo Process

Pressure Rise Test



Pressure Rise Test is done by the End of the Main Drying

Used Sensors: Vacuum Sensors

Function:

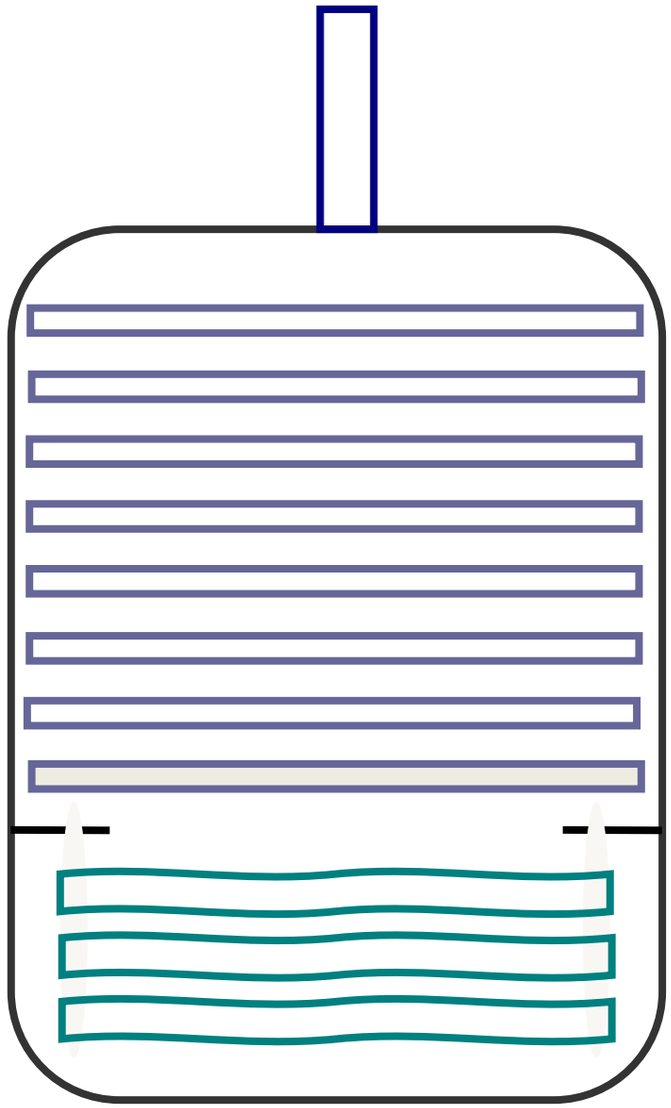
- Close the Vacuum Valve
- Observe the Pressure
- Define Acceptance Criteria e.g. 10µbar
- Define extension Time e.g. 15min
- Define how many repeats are accepted till a Mayor Alarm occurs.

Description:

If there is any more Sublimation ongoing, the Pressure in the System will rise. In case the Pressure rises above the define Acceptance Criteria the FD extend the Main Drying for a define Time. After the extension Time a PRT will be proceeded again, if the PRT still fail the FD extend the MD again.

In Process Testing – Lyo Process

Emergency Cooling



Emergency Cooling

Used Sensors:

- Temperature Sensors
- Vacuum Sensors

Function:

- Observe the Condenser Temperature
- Define Critical Temperature -40°C

Description:

If the Sublimation is to high, the Temperature in the Condenser will rise. When the Condenser reach the critical Temperature the shelf stack will be cooled to avoid Batch lose. After the Process is stable again, the shelf stack starts again to head up.

Note:

The Emergency Cooling is an Emergency Function not a normal Process Function to control a Process!!!

Annex 1 Issues

A. In Annex 1 8.123 “Lyophilizers that are manually loaded or unloaded with no barrier technology separation (RABS) should be sterilised before each load. For lyophilizers loaded and unloaded by automated systems or protected by closed barrier systems (Isolator), the frequency of sterilisation should be justified and documented as part of the CCS.”

Question:

If a lyophilizer is manually loaded or unloaded but uses barrier technology (RABS) for isolation, can the sterilization before each loading be exempted if a risk assessment justifies it?

What is the rationale for the sterilization frequency?

What are the key considerations for the risk assessment?

Depending on the kind Product. For non Steril Processes / Products a Risk assessment can be carried out. The Risk assessment should reflect all Tasks which are typical for the Product like Patient Risk, Contamination, how the cleaning is carried out, etc. For Products which are biological active or toxic like cytos a Sterilization is must have. That means, after each Lyo run a CIP and a SIP should Take place.

Annex 1 Issues

B. In Annex 1 8.124 “The integrity of the lyophilizer should be maintained following sterilization and during lyophilization.”

Question:

How can this be ensured?

The main Goal is, to do Maintenance as recommended from the FD Supplier.

After a SIP, an automated Leaktest should be carried out as a part of the Turnaround Processes

Mass spectrometer Testing, once a week or after each Batch.

Should integrity testing be performed before the start of the lyophilization cycle and after its completion?

The recommendation is, to do it as a final step after the turnaround cycles before starting the new Batch.

For example:

Automated Leaktest after each Batch as final Test before starting the new Batch

Once a Week, MS Measuring of the dry and clean FD.

Annex 1 Issues

C. In Annex 1 8.124 “The frequency of vacuum/leak integrity testing of the chamber should be documented and the maximum permitted leakage of air into the lyophilizer should be specified and checked at the start of every cycle.”

Question:

How the frequency of integrity testing and the leak rate be determined?

An automated leak test (incl. leak rate test) should be a part of the SIP Cycle.

Recommendation: 0,02 mbar+l/sec as system leak rate. Be sure that your FD Supplier have this Acceptance criteria in his FD System implemented. Some FD Suppliers have as Standard leak rate 0,1 mbar+l/sec.

What are the key considerations for the risk assessment?

What is the rationale for the frequency and specifications?

Both Topics depends on which kind of Product do you have in your FD, how sensitive is your Process, etc.

Annex 1 Issues

D. In Annex 1 8.125 “Lyophilization trays should be checked regularly to ensure that they are not misshapen or damaged.”

Question:

Is there a standardized checking method?

A visual Inspection should be carried out, latest at Shutdown / Maintenance. To check if the shelfs or the guiding rods have a deforming a stainless steal roler can be used together with a feeler.

How are the criteria for deformation or damage established?

Acceptance Criteria for Shelf flatness is 1mm / m

Bumps from i.e. Vials between the Shelfs should be visual checkt, in case of deep Pumps it can be that the Shelf can not be maintend. In That case the Shelf must be changend.