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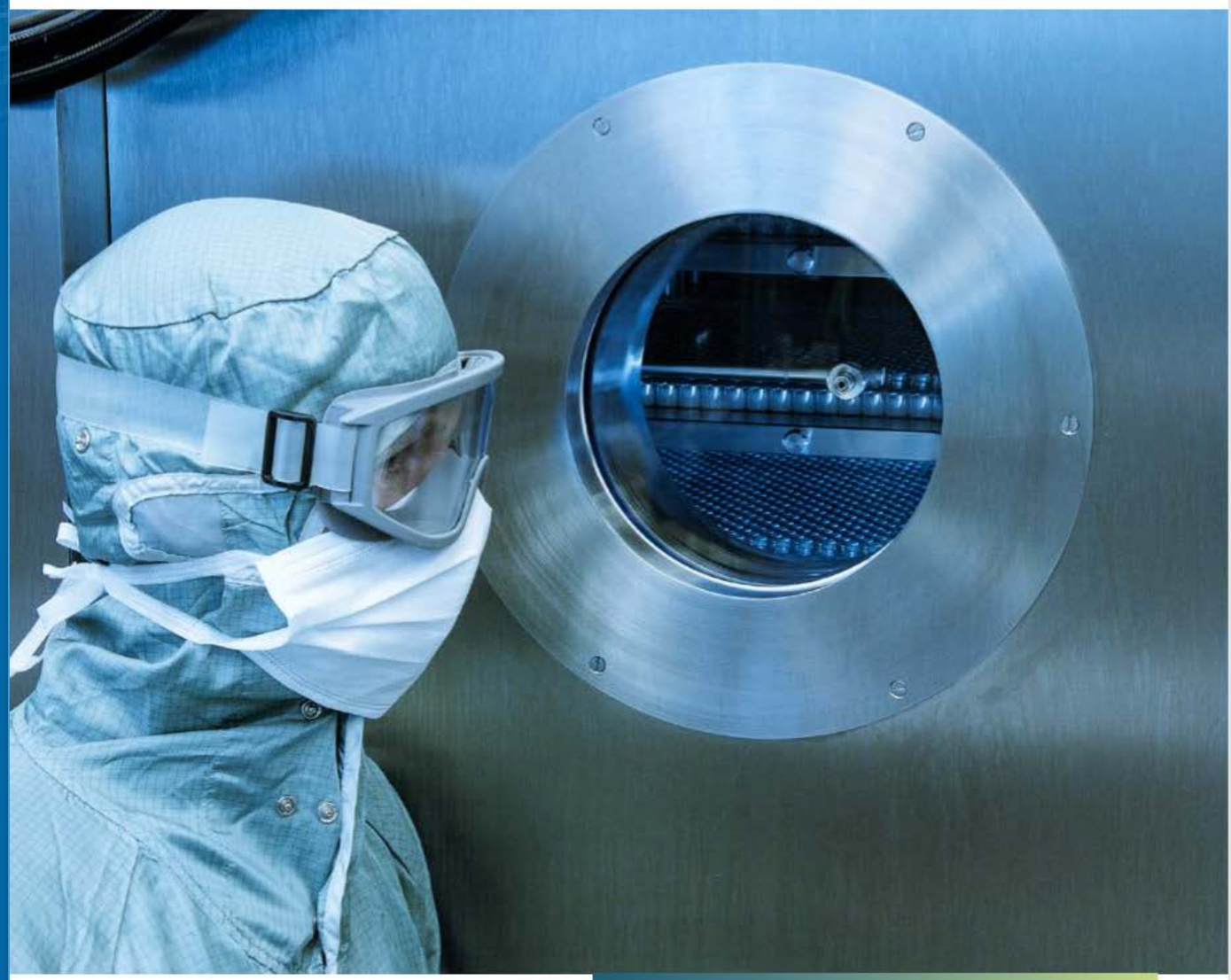
2019 PDA EUROPE TRAINING

Freeze Drying in Practice



25-29 MARCH 2019
OSTERODE (HARZ), GERMANY

CONNECTING PEOPLE SCIENCE AND REGULATION®

REGISTER BEFORE 16 DECEMBER 2018 AND SAVE!

Company portrait

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

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

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

Lyo Engineering

GMP is our passion!

Connecting People, Science and Regulation®

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:

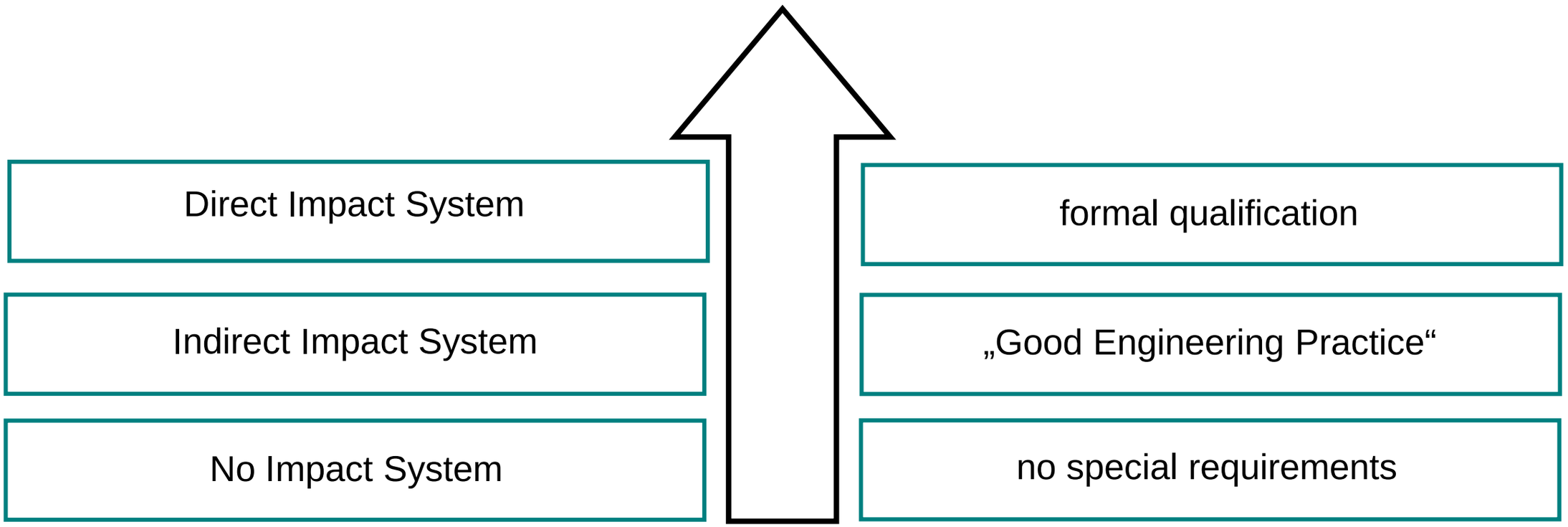
Policy of a GMP inspectors:

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“

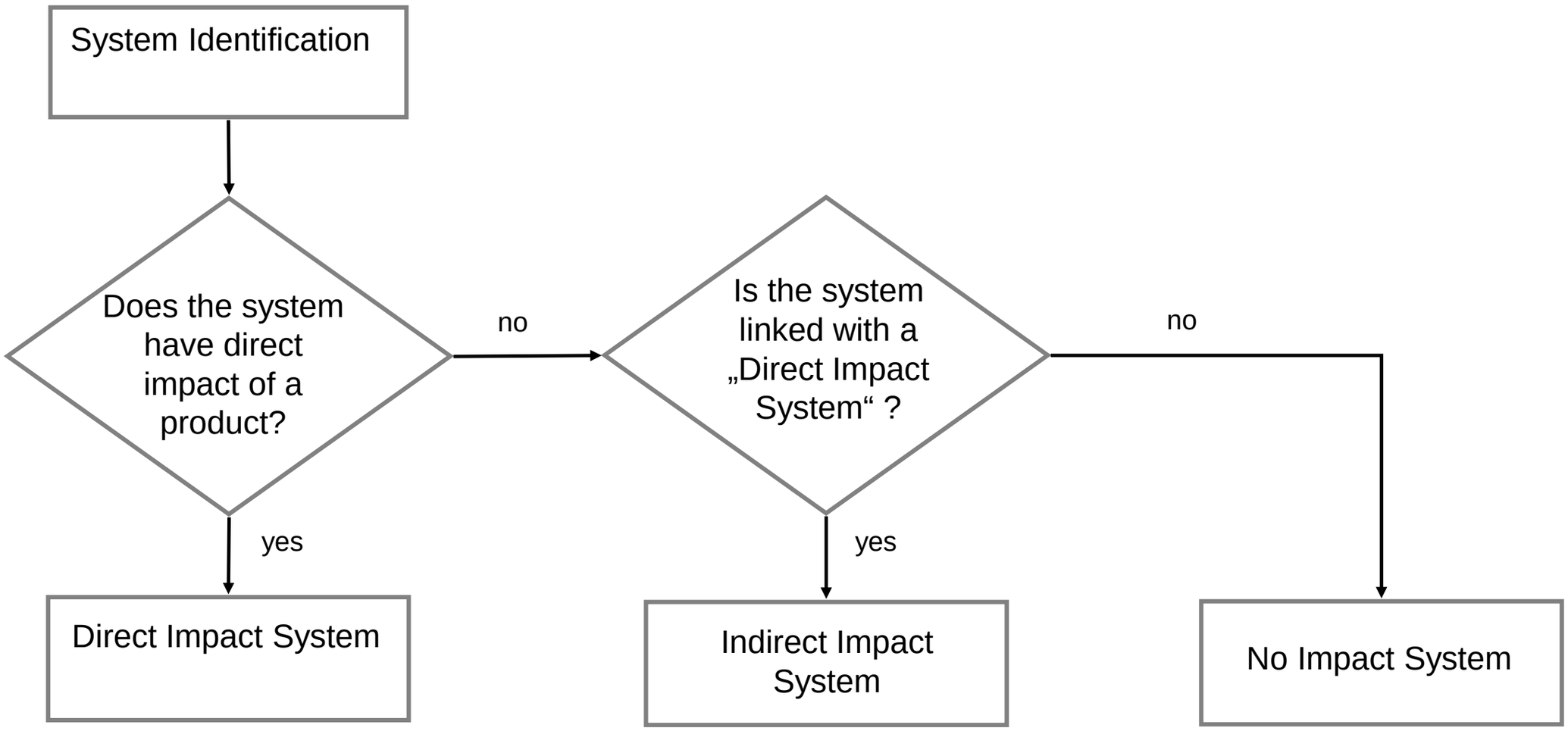
No Impact System

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?

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:

What is qualification:

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

What is validation:

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:

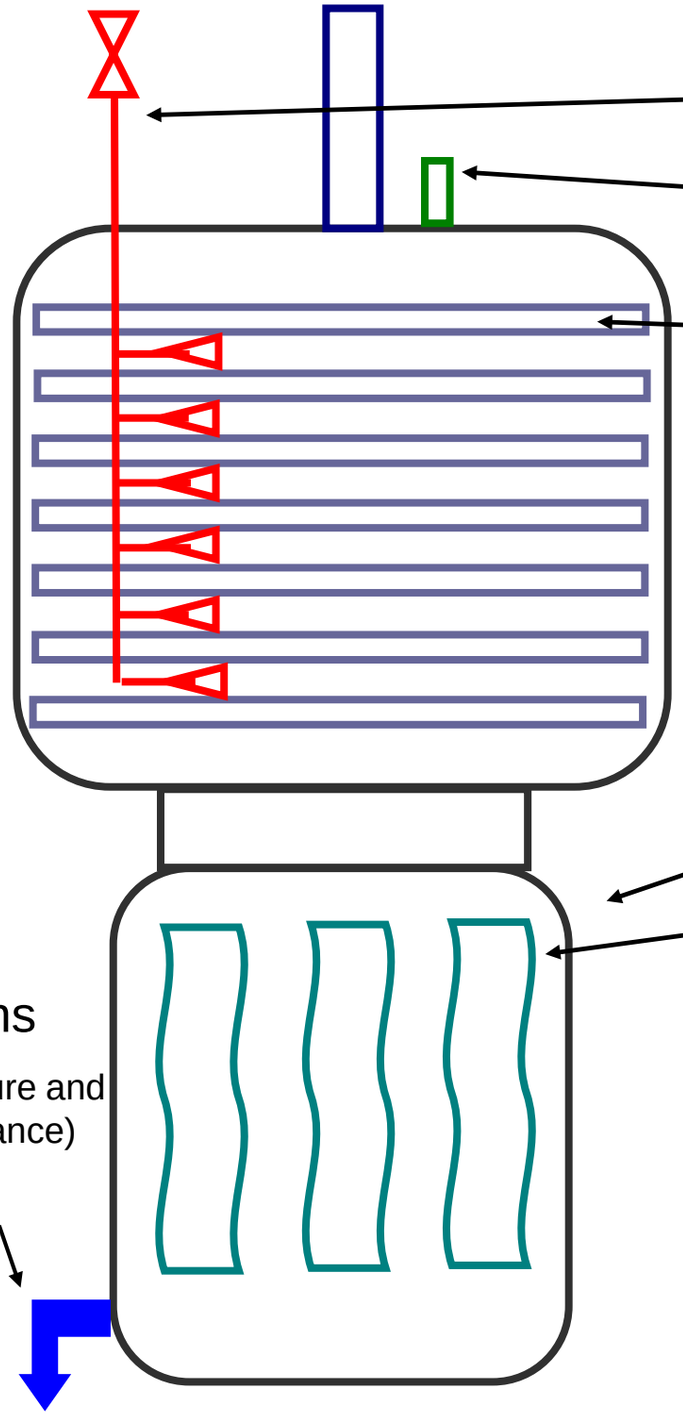
Do no modifications at validated machines, if the responsible persons (Head of Production, QA, etc.) have not release the Change.

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

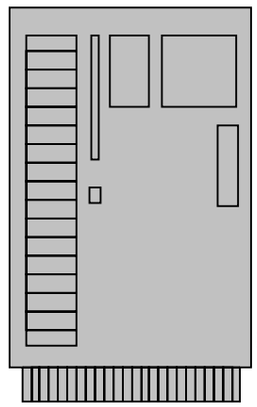
condenser coils (temperature sensors)

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)

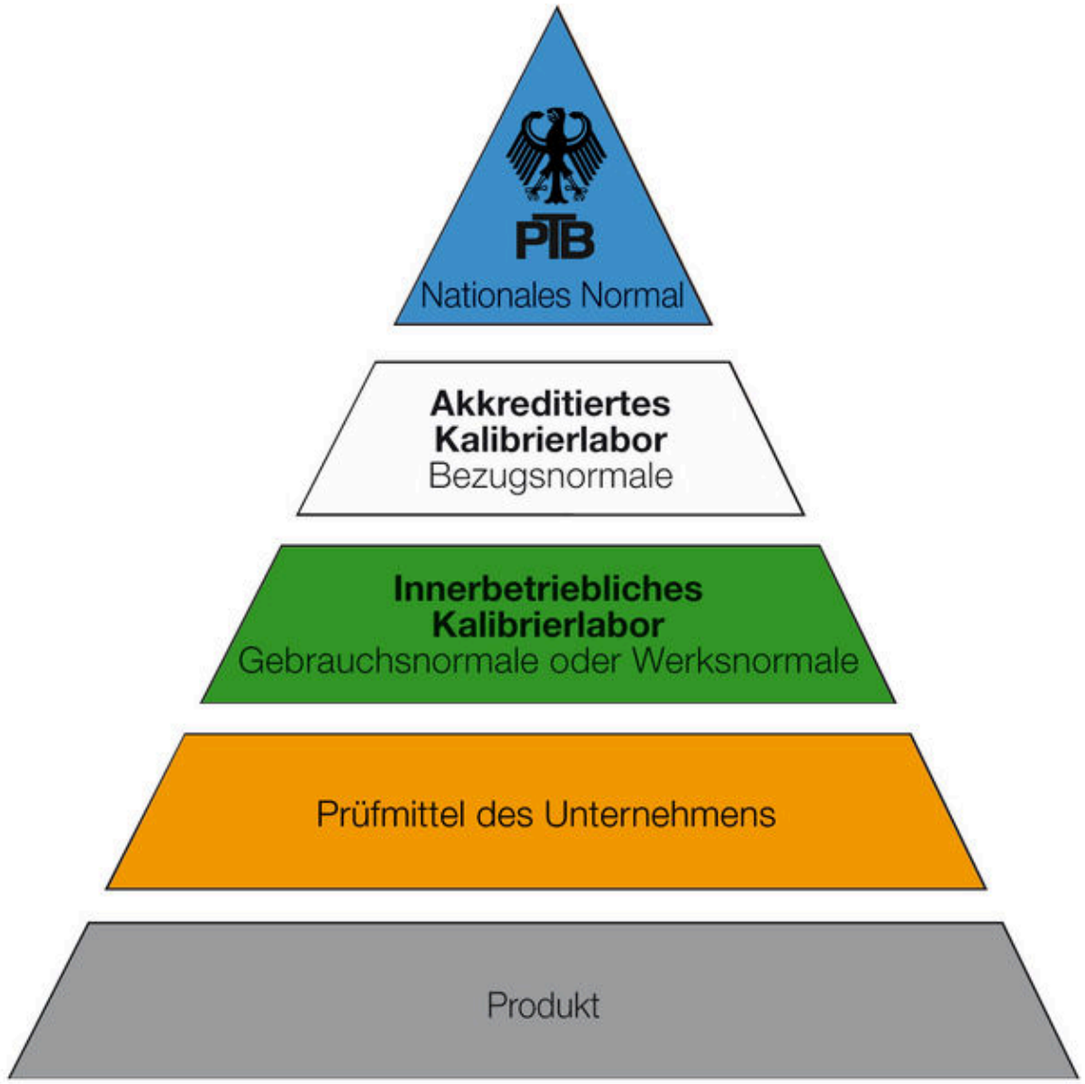
A official verification is also a calibration, however official verification may only be carried out by government Institues (NIST).

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.

Calibration / Official Verification / Adjustment

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.

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)

Condenser Stresstest – In Vials

Chamber

Main Valve

Sublimation

Condenser

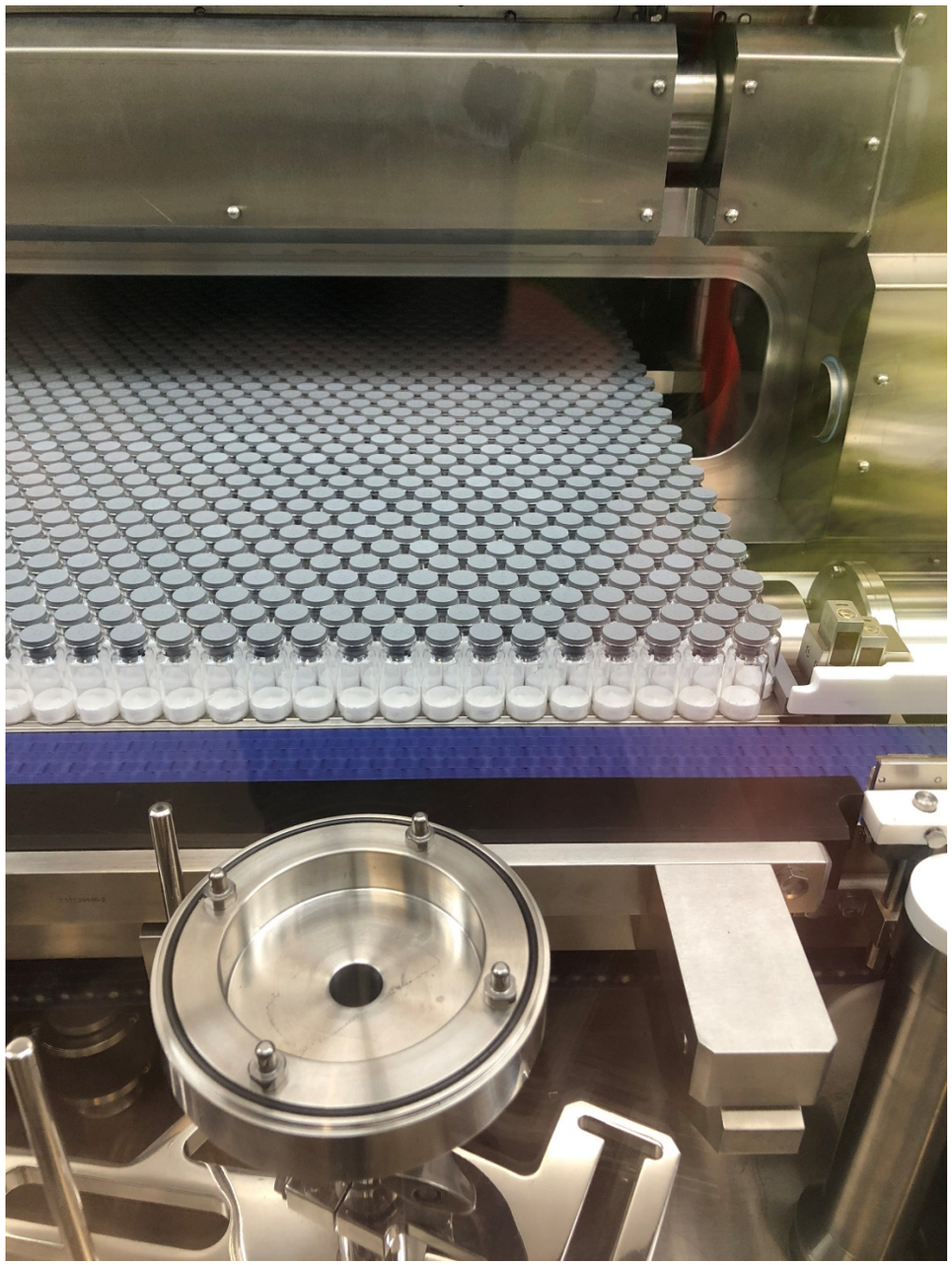
Condenser Stresstest - Vial

View from the Top of the Ice Condenser.

Lyo qualification – typical Test

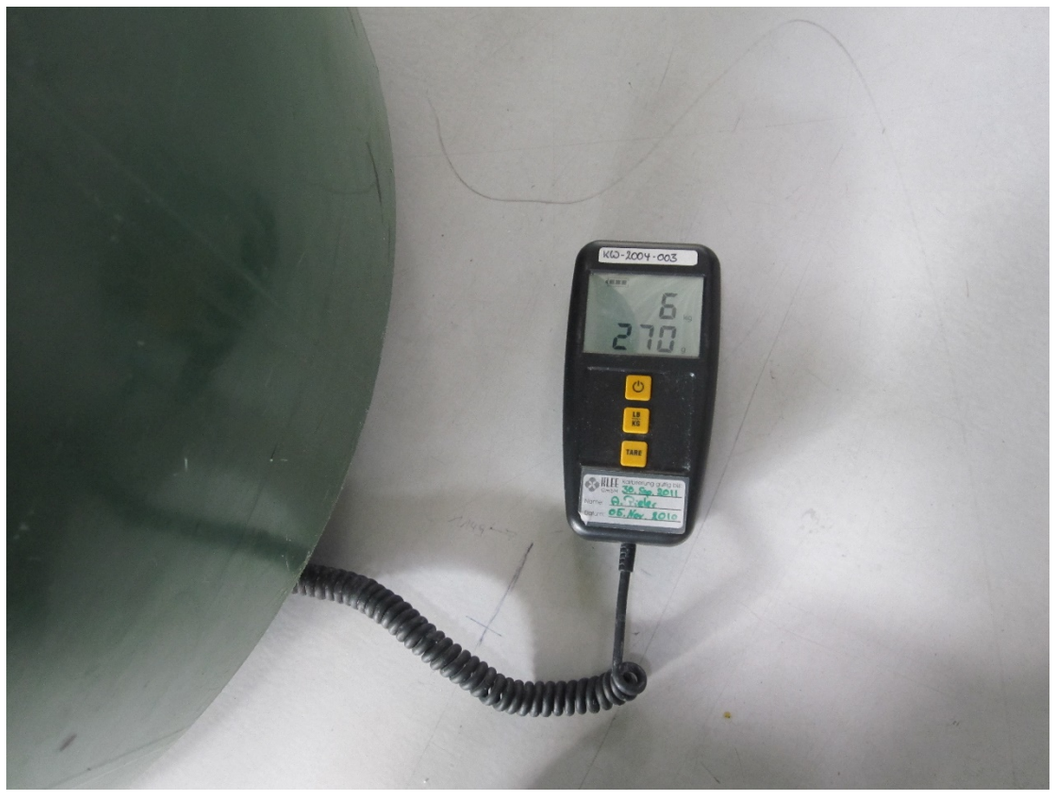
Condenser Stresstest - Vial

Row by Row Unloading of
Freeze dried Vials



Condenser Stresstest - Frames

Weight of Solution

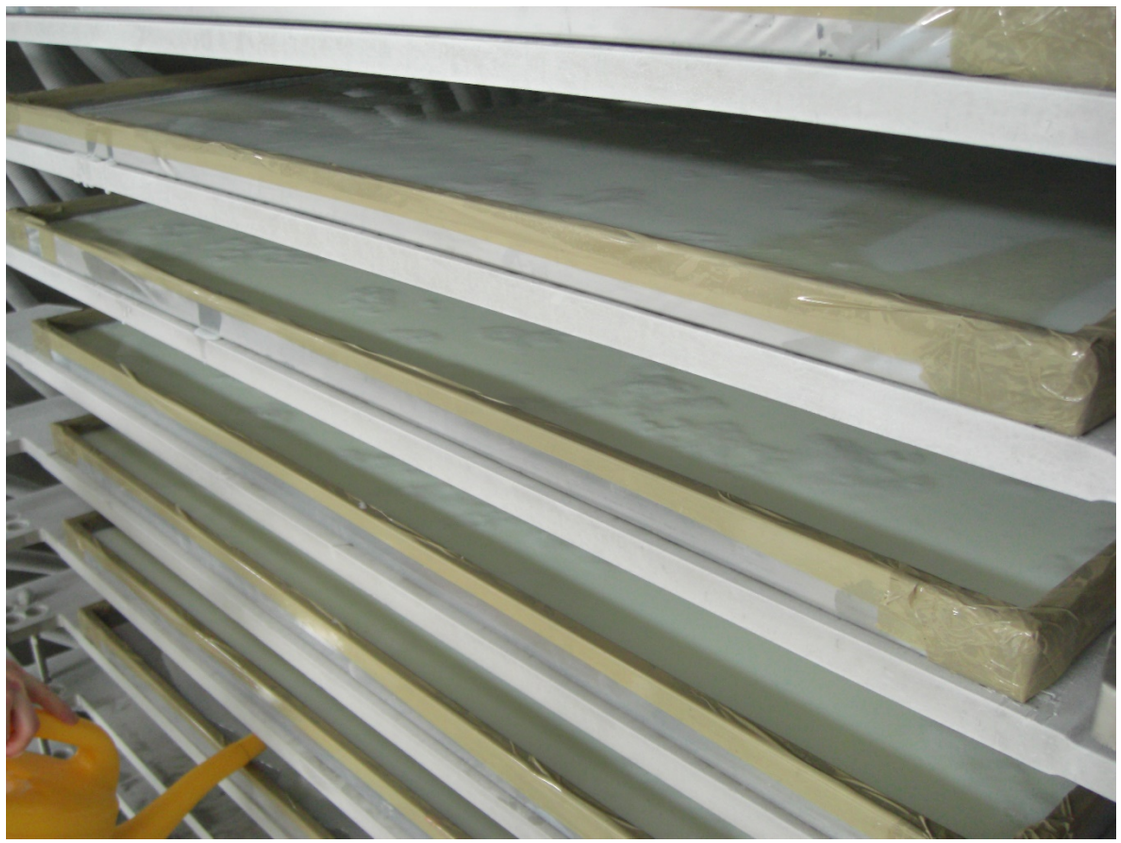


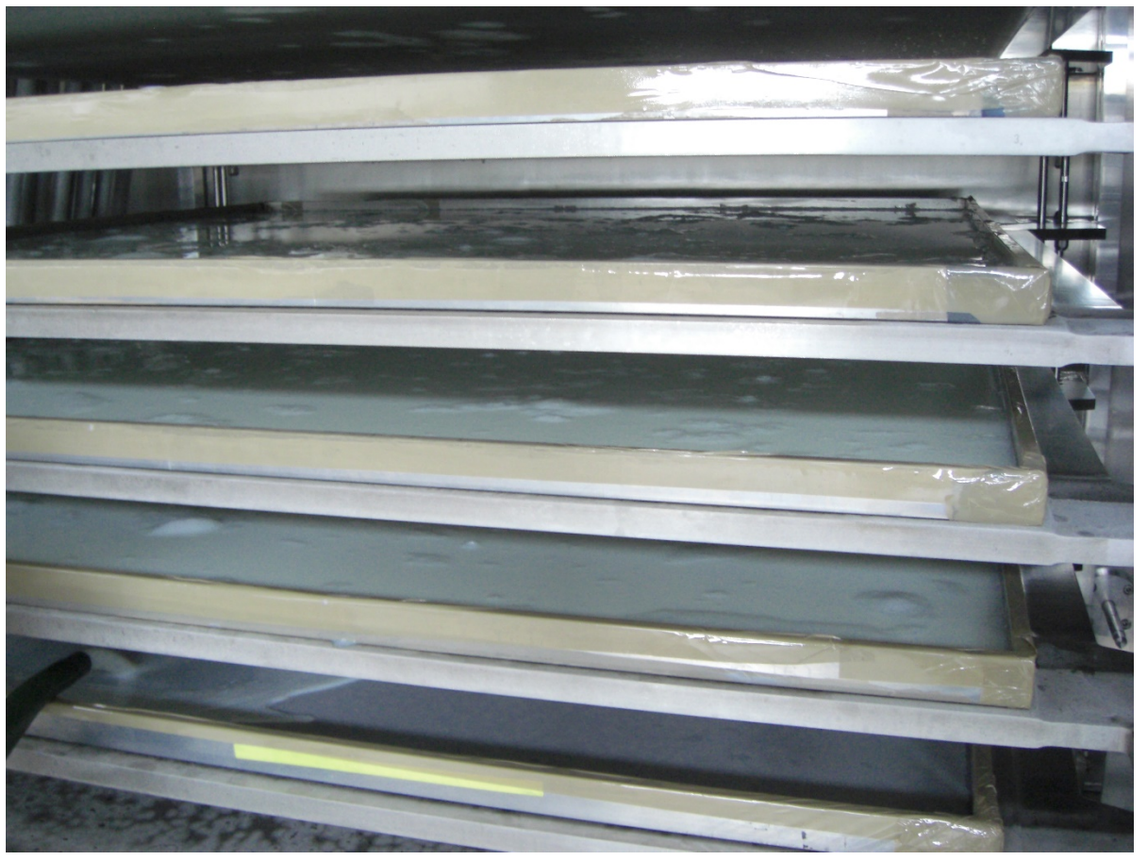
Filling the Frames

with a High Performance watering Can

Condenser Stresstest

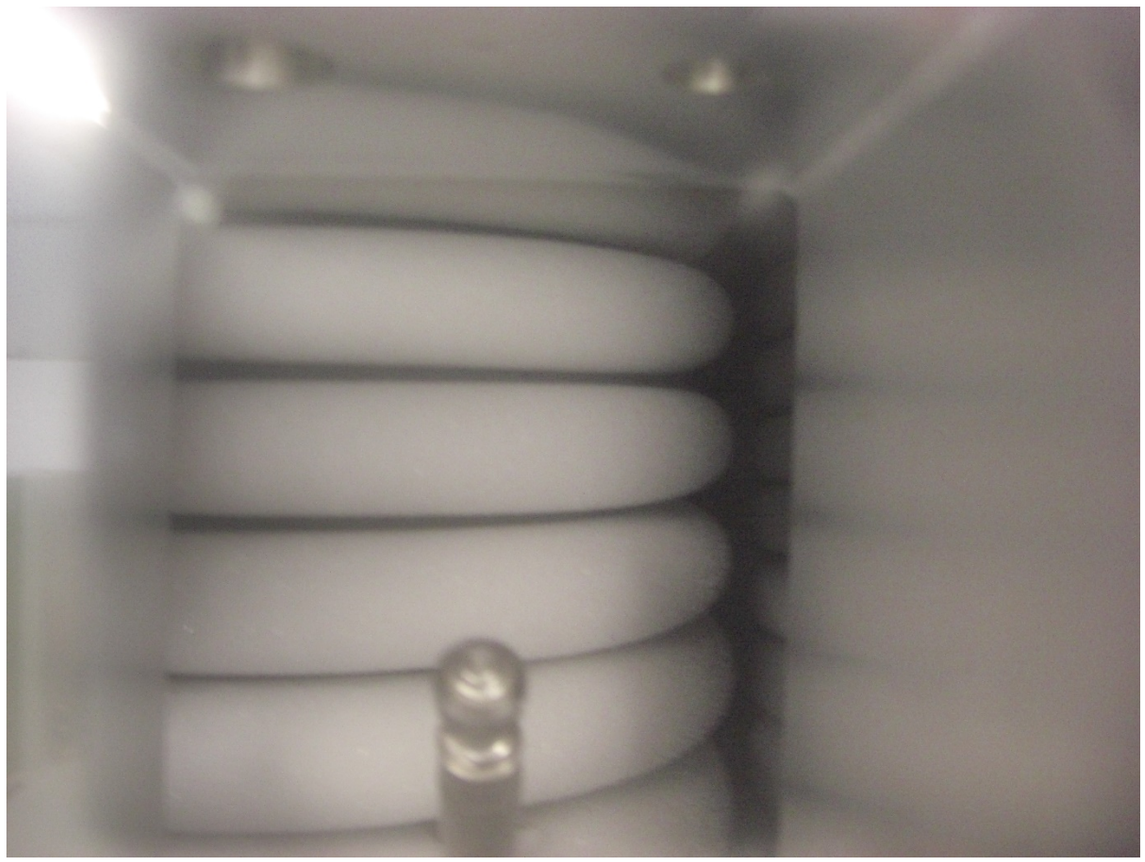
All Frames should be filled similar to avoid different Sublimation on the shelf stack





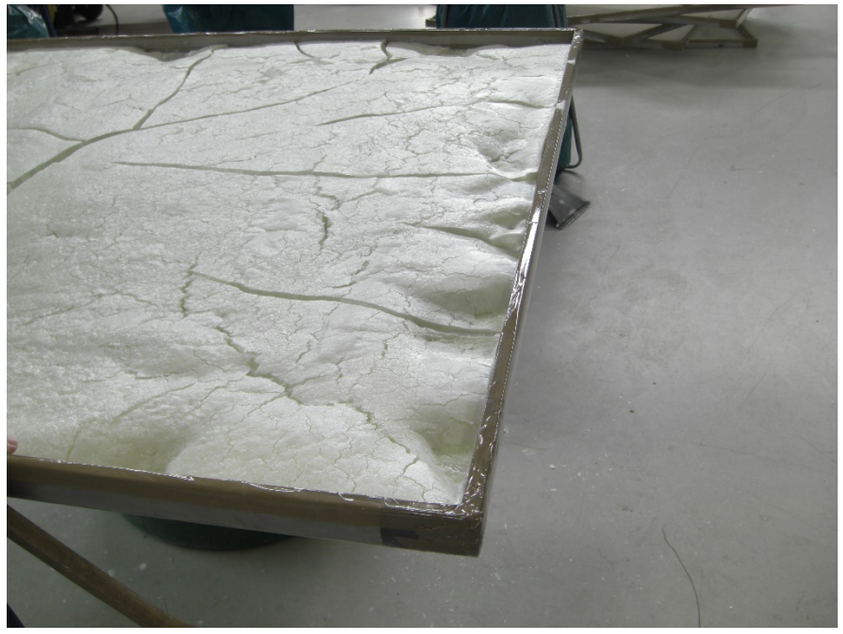
Condenser Stresstest

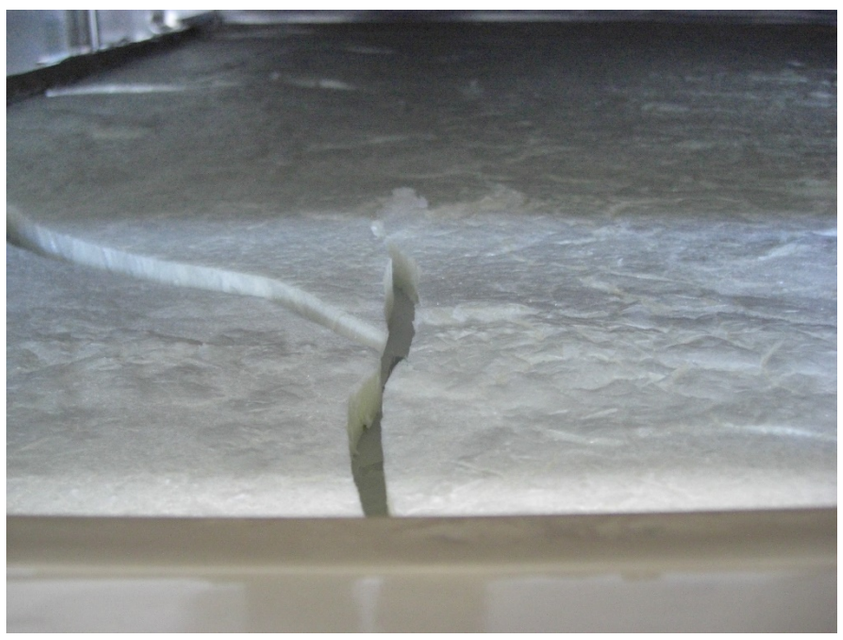
View into the Condenser during Process



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:

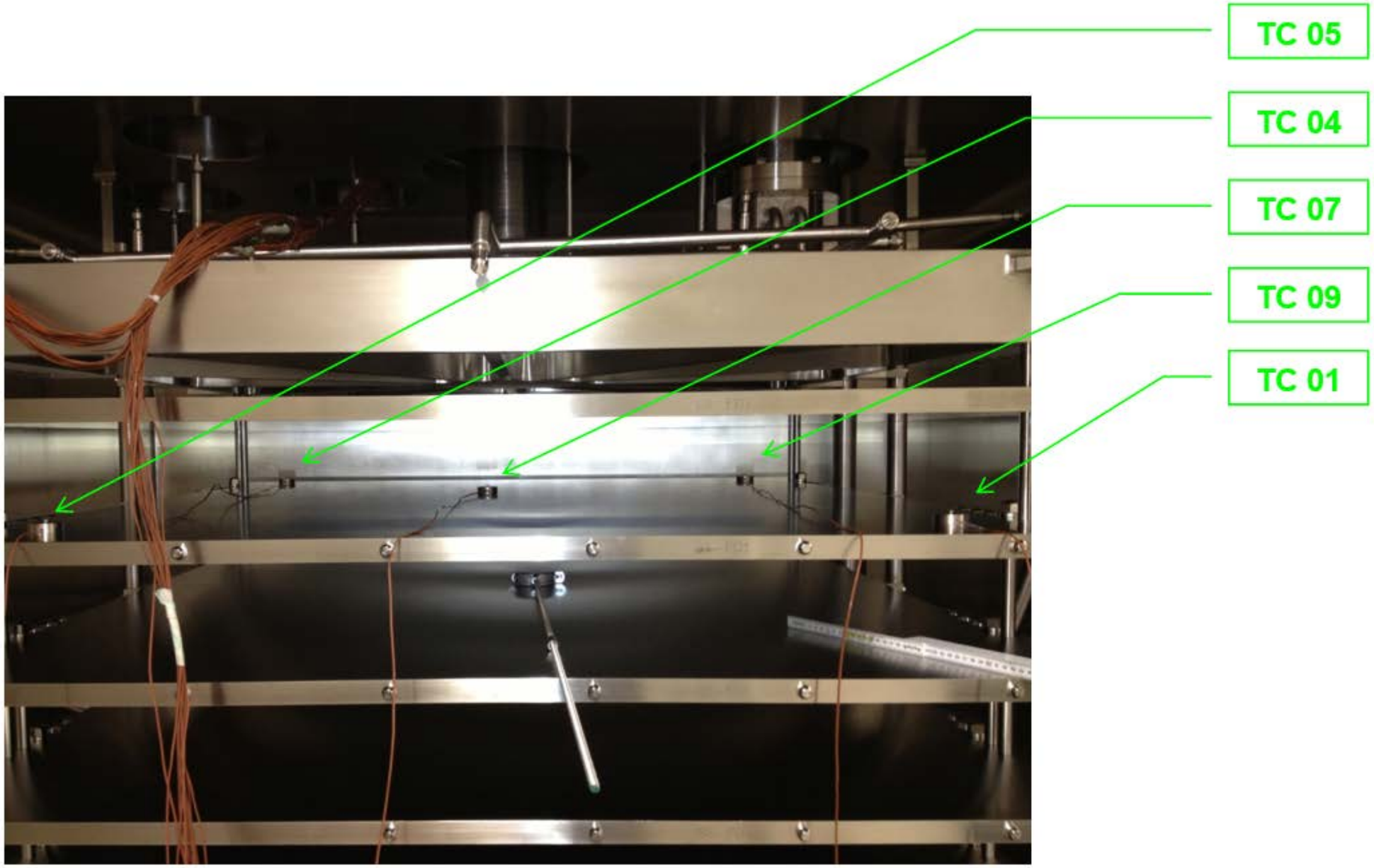
- that each shelf is inside the Spec e.g. +/- 0,5°C
- that the hole shelf stack is inside the Spec e.g. +/- 1,0°C
- that the controller System for Silicon oil works correct (Calibration is done)
- that the Heat Transfer System is filled correct (no air inclusions)

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

Lyo Engineering

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