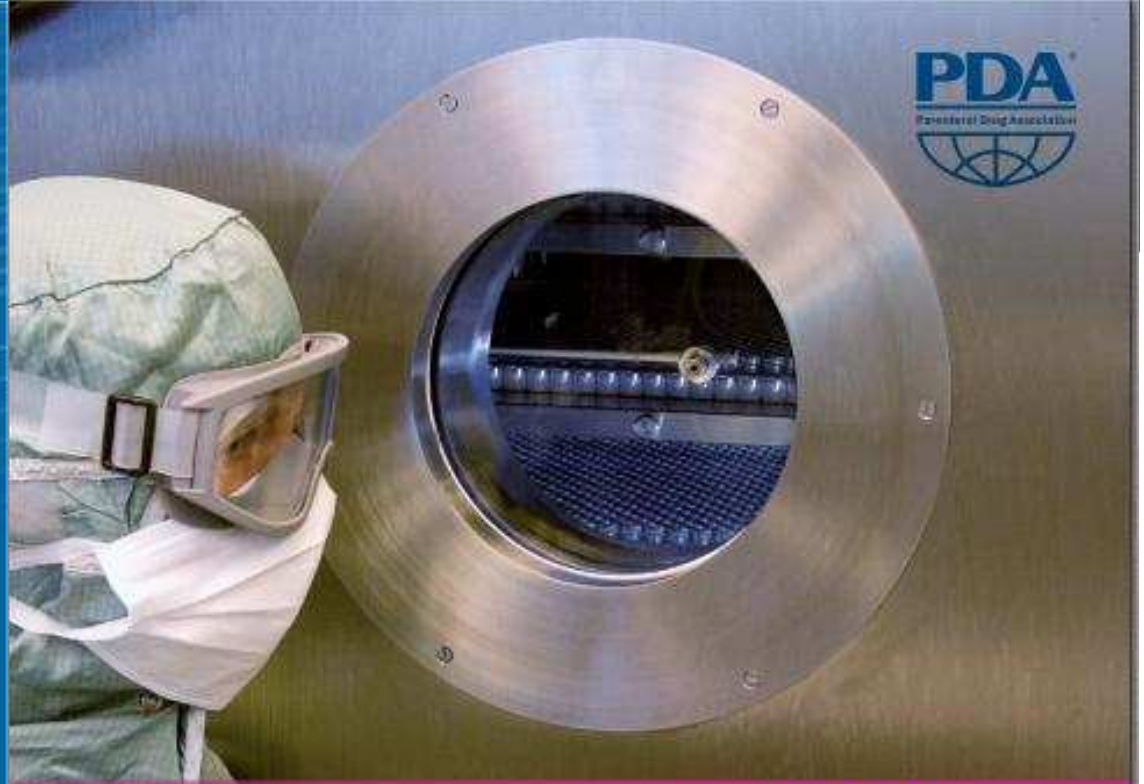
PDA

Connecting People, Science and Regulation



2018 PDA Europe

Freeze Drying in Practice

23–27 April 2018 | Training Course

23–27 April 2018

Martin Christ Gefriertrocknungsanlagen GmbH
Osterode (Harz) | Germany

www.pda.org/URL

Company portrait

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

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

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

Lyo Engineering

GMP is our passion!

Theory 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 population of questionable 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:

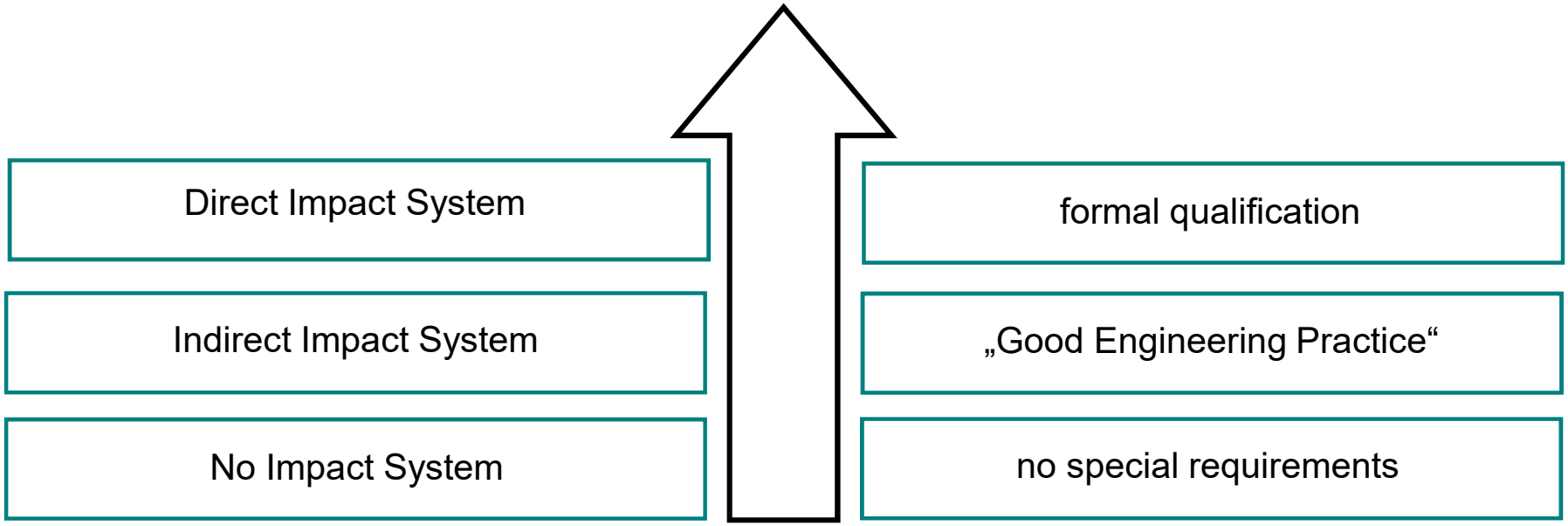
Policy of a GMP inspectors:

Everything that is not recorded in writing, is considered as an attempted fraud 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

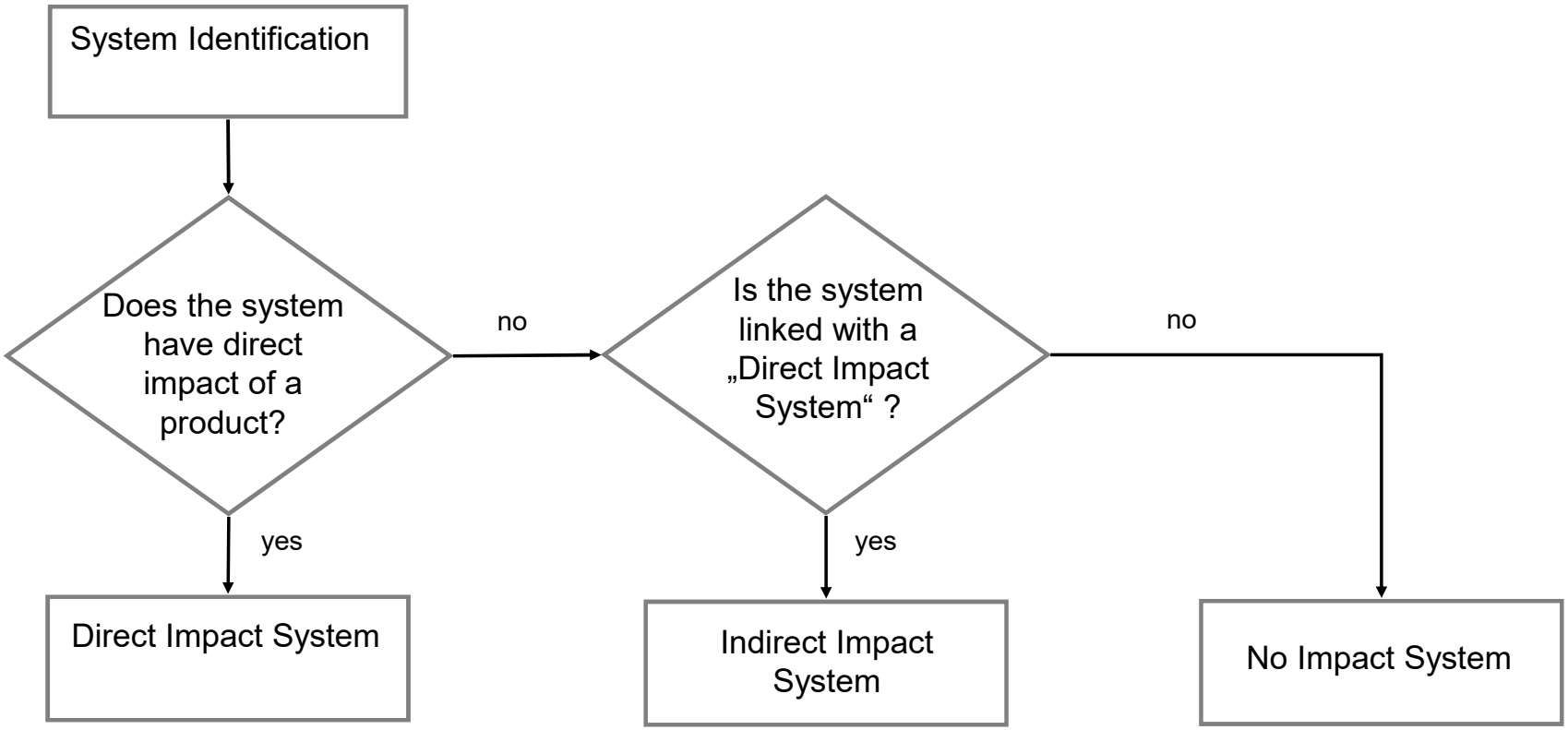
A“Indirect Impact System“ is not expected to have direct impact on product Quality,
but typically will support a „Direct Impact System“

No Impact System

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

Basic Quality Risk Management

Impact Assessment Process



Lyo qualification

The different 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 any of theses phases this one is qualified and subject to the procedure of Change Control.

Lyo qualification

Qualification is the documented evidence, that the facilities are constructed as they have been specified.

What does it mean?

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

IQ – It is verified that the machine corresponds to drawn scheme, layout, circuit diagram, etc.

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

PQ – The performance is in compliance with the specifications e. g. 3 mapping runs in a row, milk test, etc.

Lyo qualification

Facilities 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

Once again in comparison:

What is qualification:

Qualification is the documented evidence, that the facilities are constructed, installed and performed as described in the specifications.

What is validation:

The validation is the documented evidence that the procedure or the process of facilities leads to the anticipated result.

Lyo qualification

Change Control process serves to 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 responsible person (customers)
- partial steps of validation (DQ-PV) are obliged after their end of Change Control

Lyo qualification

A not well-run change management may leads to loss of production approval.

If the pharmacist produces product with a not valid machine and place it on the market, he make himself liable to prosecution. In the worst case scenario, this can mean that a human lives is been destroyed.

For us it means:

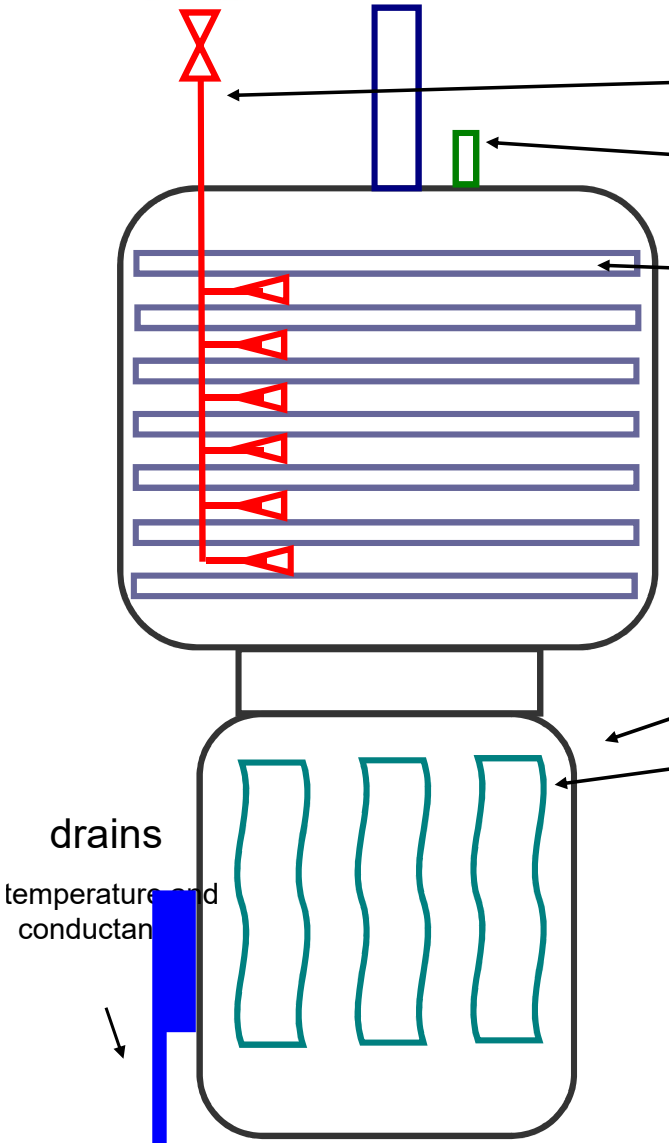
Fundamentally no further modification at validated machines may be made, if the customer did not release this modification.

In an emergency (product in chamber) a written confirmation is sufficient including signature of customer, in which he 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)

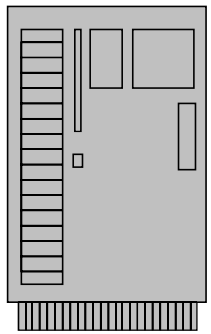
drains

temperature and conductan

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 determination and recording of the difference between the displayed value and the true value, without any technical intervention.

Official verification

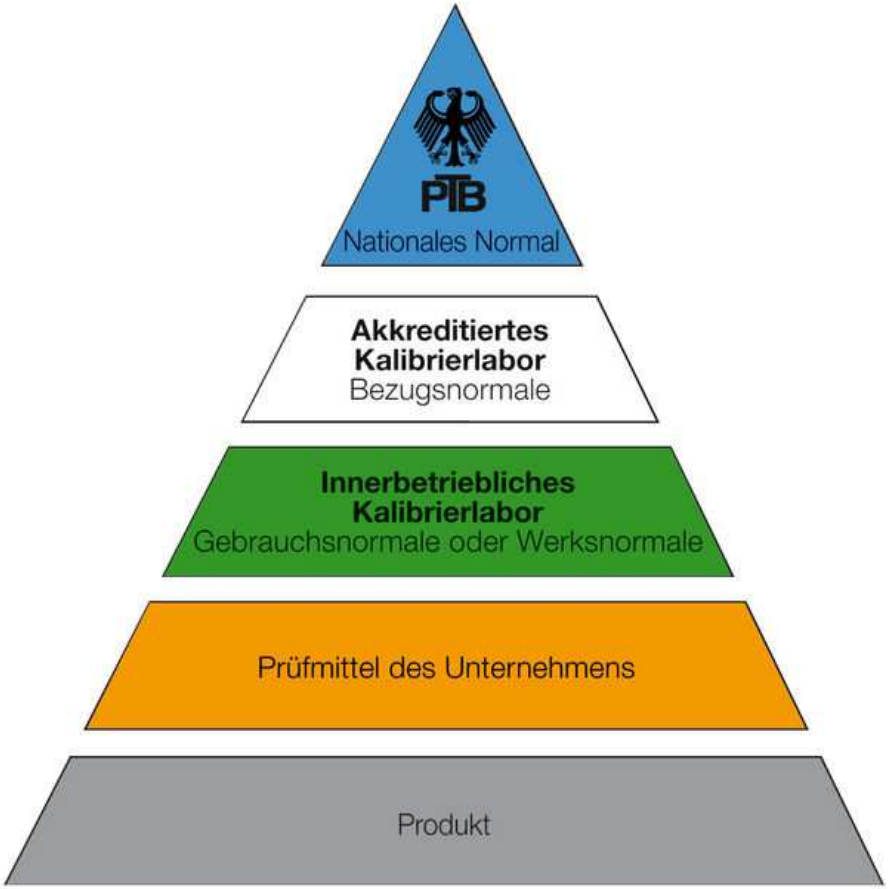
Official verification is also a calibration, however official verification may only be carried out by appropriate government institutions (PTB). Official verification is regulated in article 73 of German Basic Law. The federal government pass legislation on Weights and Measures as well as time determination.

Adjustment

Adjustment is s a technical intervention 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.



Three general rules for correct measurement

1. Measured variable 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.

measurand	→ temperature
unit	→ °C
measurement method	→ composition proceedings with reference e.g. in a liquid bath

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.

Testing devices are adapted to the calibrated sensor according to measurand, operation site, measuring range, design and accuracy.

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 faults or failures have an influence of the product quality.

Process- and system critical instruments:

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

GAMP:

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

Safety-critical instruments:

Safety-critical instruments are instruments which faults of failures have an influence of system readiness.

Uncritical instruments:

Uncritical instruments are instruments which faults or failures have no influence of product quality, machine- and process functions or system security. There are only intended to provide information.

Calibration / Official Verification / Adjustment

Specifications:

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

Calibration of temperature measurement systems, used for validation, must be performed at a temperature that is within the range of sterilisation temperature.

Lyo Engineering

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