Commissioning and Qualification of a Lyophilizer

Documentation and Qualification

PDA Europe
Development of a Freeze Drying Process

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Bayer

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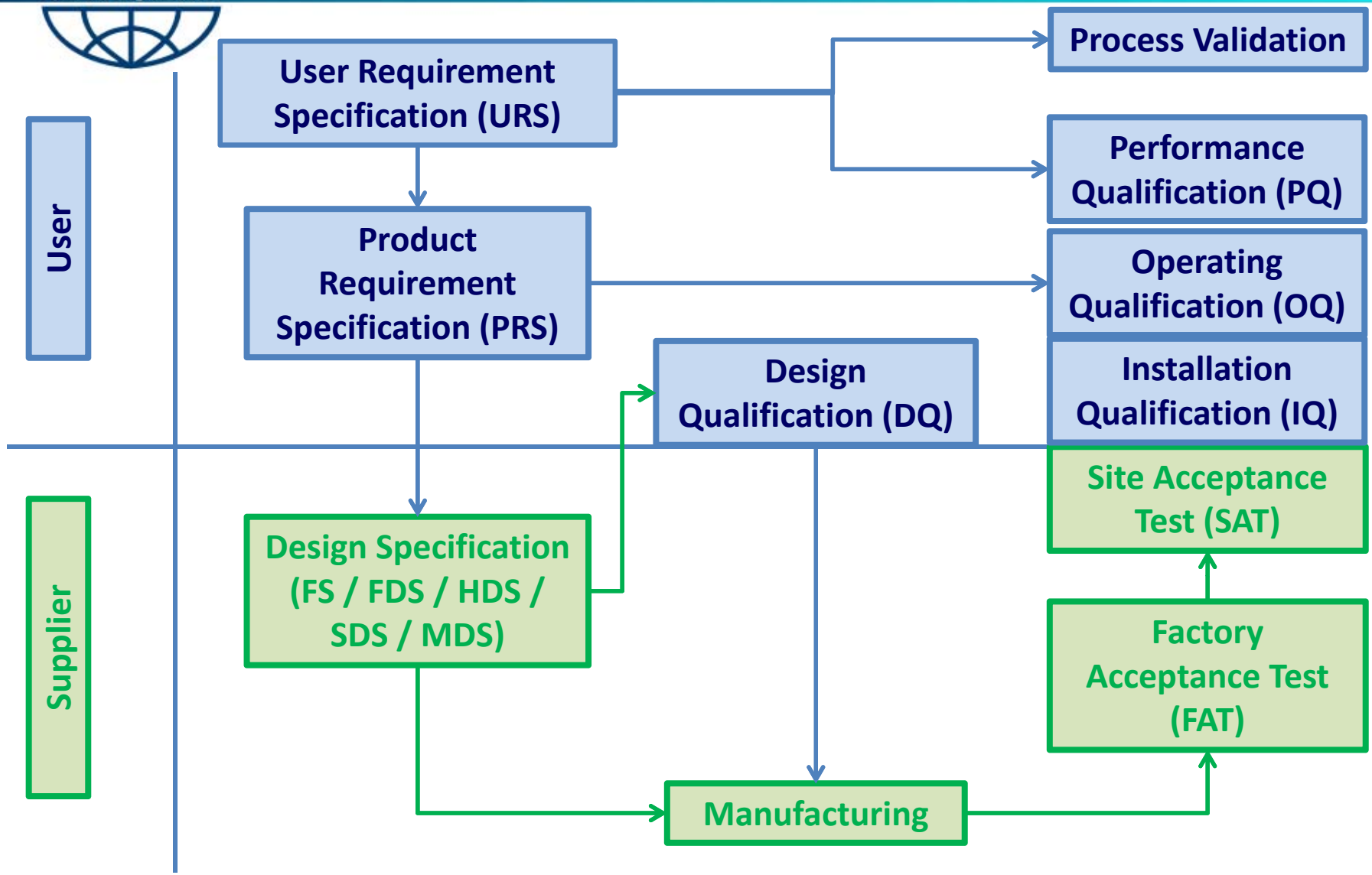
Volunteer for PDA

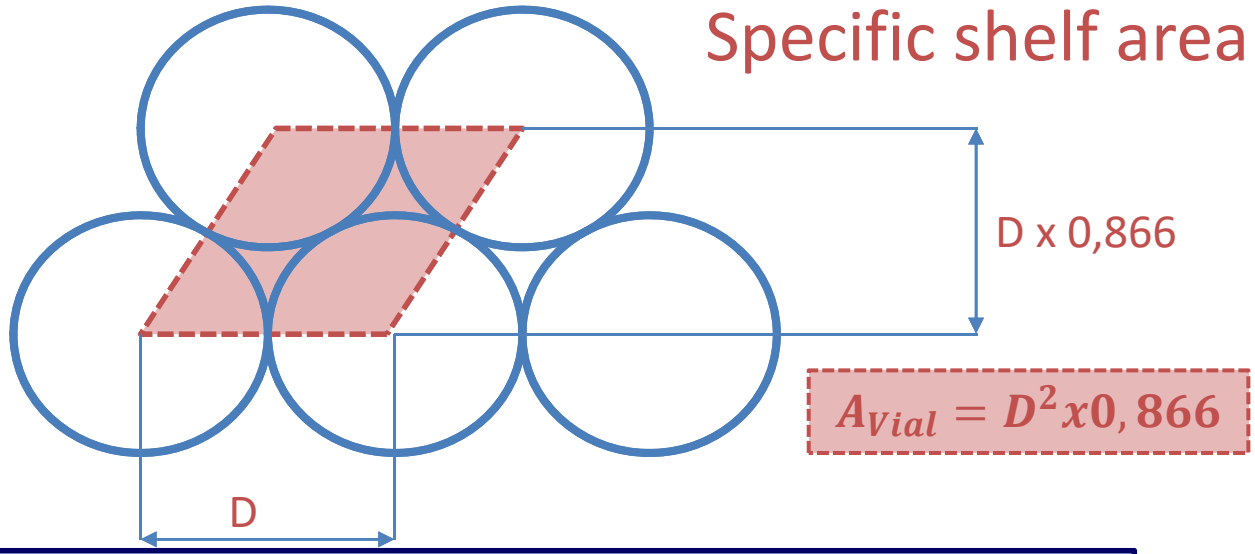
Project Chart of a Lyo-Installation



- Shelf System
- Chamber System
- Ice Condensor System
- Main Valve

Shelf System

The design always start with the shelf area:



$$A_{Shelf\ package} = N\ x\ D_{Vial}{}^{2}\ x\ 0,86$$

Rough formula to estimate the required shelf area

Parameter	QPhase
Shelf Area	IQ
Amount of Vials	OQ/PQ

Shelf System - Typical Vial dimensions

Diameter	Height	Stopper Diameter
16…23mm	30…60mm	13mm (d = 7mm)
20…30mm	40…75mm	20mm (d = 12,6mm)

Shelf Interdistance consists of:

- **Vial height**
- **Stopper height (~5mm / ~10mm)**
- **Sufficient Clearance for vapor flow**

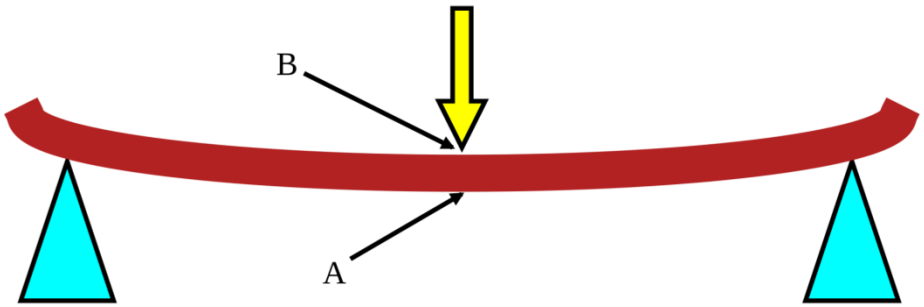
Mechanical stiffness vs. shelf weight

• Shelf is bended by load (and its own weight), the optimum form is a raised shelf at the center at unloaded conditions (becomes plain when loaded, complex manufacturing)

⇒ ***Most important during loading/unloading, a plane deviation of >0,5mm between loading/unloading system and loaded shelf will cause tumbling of D16-Vials (e.g. 2R).***

⇒ ***Maximum misalignment shelf vs. loading interface: 0,5mm***

⇒ ***Maximum shelf distortion: 0,8mm/m***



Parameter	QPhase
Shelf distortion (empty)	IQ
Misalignment	IQ

Mechanical stiffness vs. specific heat capacity

Better stiffness require more reinforcements of internal shelf structure, the associated increase of weight is proportional with an increase of specific heat capacity

⇒ ***A common standard is a specific heat capacity per shelf area of 90…120kJ / m² x K (Heat Transfer System). This can be determined by a heating curve.***

Parameter	QPhase
Heating Curve	OQ

Mechanical stiffness vs. heat transfer coefficient

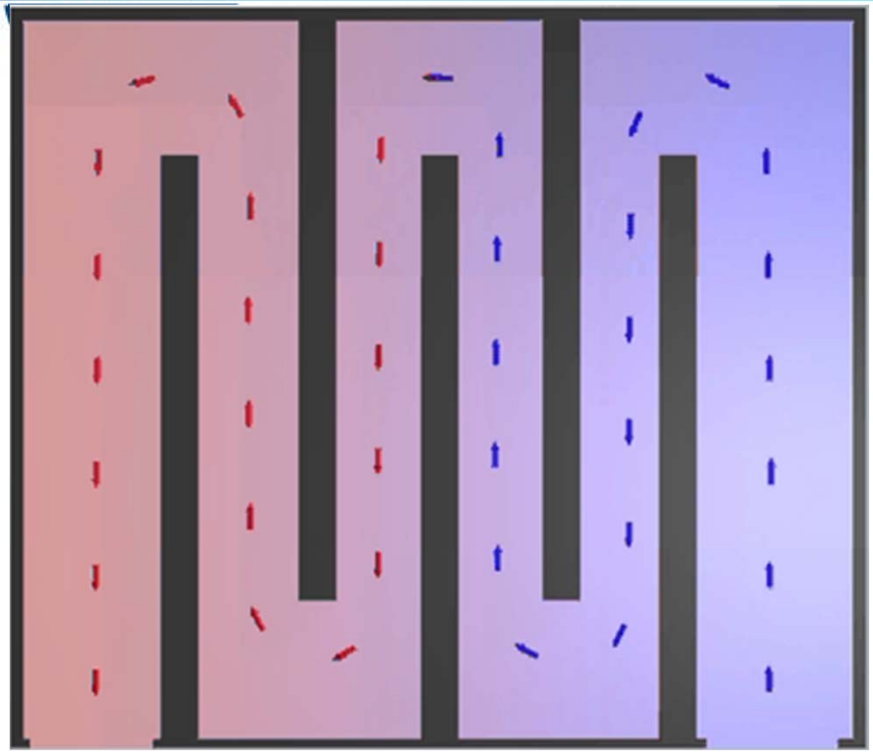
• The direct heat conduction from silicone oil to shelf surface is of minor interest, but not meaningless

• The scalar field of heat conductivity of the shelf surface is important (normally not qualified), especially under dynamic conditions

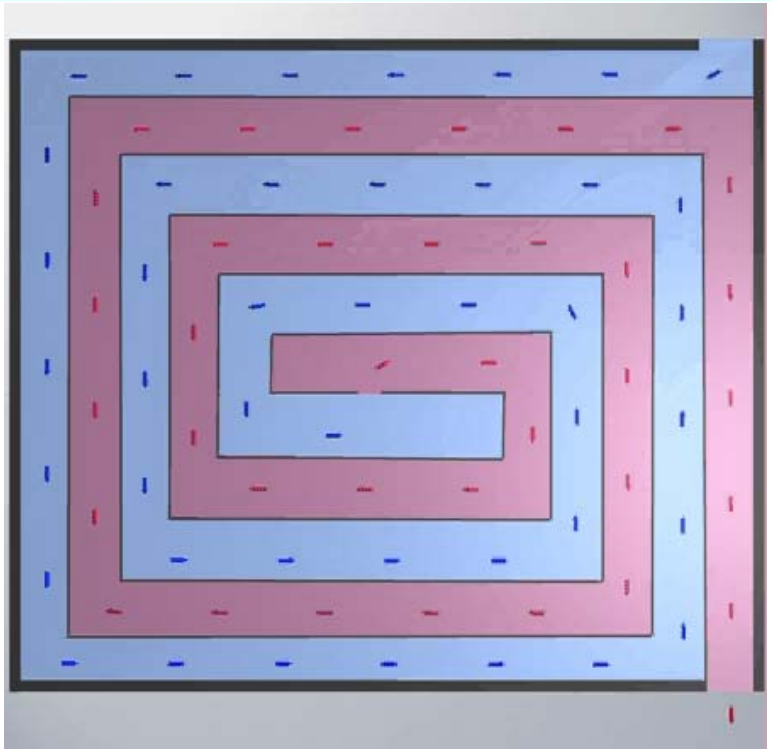
⇒ ***A common value is 50…250W / m² x K (silicone oil to shelf surface)***

⇒ ***A homogenious temperature distribution should not vary for more than +/- 1K (better 0,8) from Silicone Oil Temperature Average (Inlet/Outlet) at empty conditions under atmospheric pressure***

Shelf System – design concepts

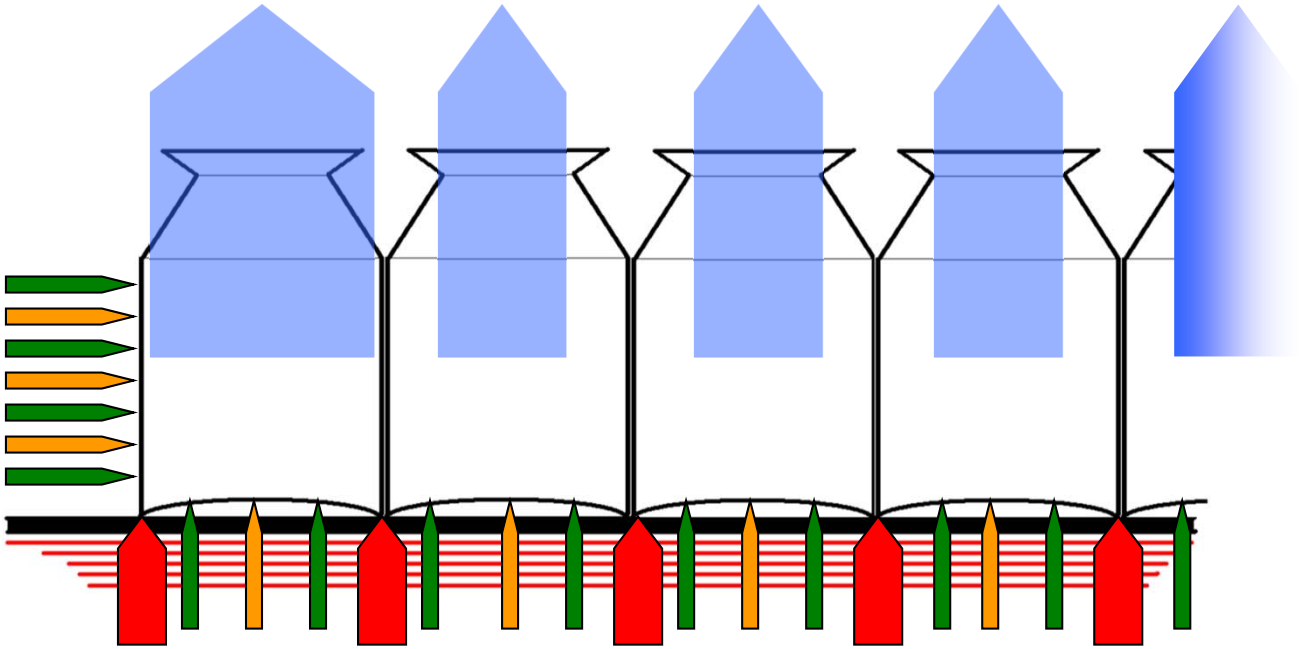


- Simple and robust construction
- Common Standard at most suppliers
- Usual compromise to fulfill modern requirements



- Very complex design and sophisticated manufacturing process (soldering & welding)
- System is said to have a better heat distribution under load

Reasons for the Edge effect



Conduction

Radiation

Convection

Sublimation

Shelf System – temperature mapping

- To provide a homogenous temperature distribution for the heat transfer at freezing and sublimation, some technical issues have to be considered
- Due to technical imperfections shelfs have a thermal inertia and inhomogeneous heat transfer conditions
- Not every vial can be placed at center position, different flow conditions occur. Those issues have to be taken into account for recipe development and validation

Parameter	QPhase
Shelf Mapping	OQ

- The sensors impact the results also
- Sensors should be selected with minimum influence to the test results

⇒ The decision of the right sensor equipment may decide about fail or success of your Shelf temperature validation!

There is no regulatory standard available for shelf mapping

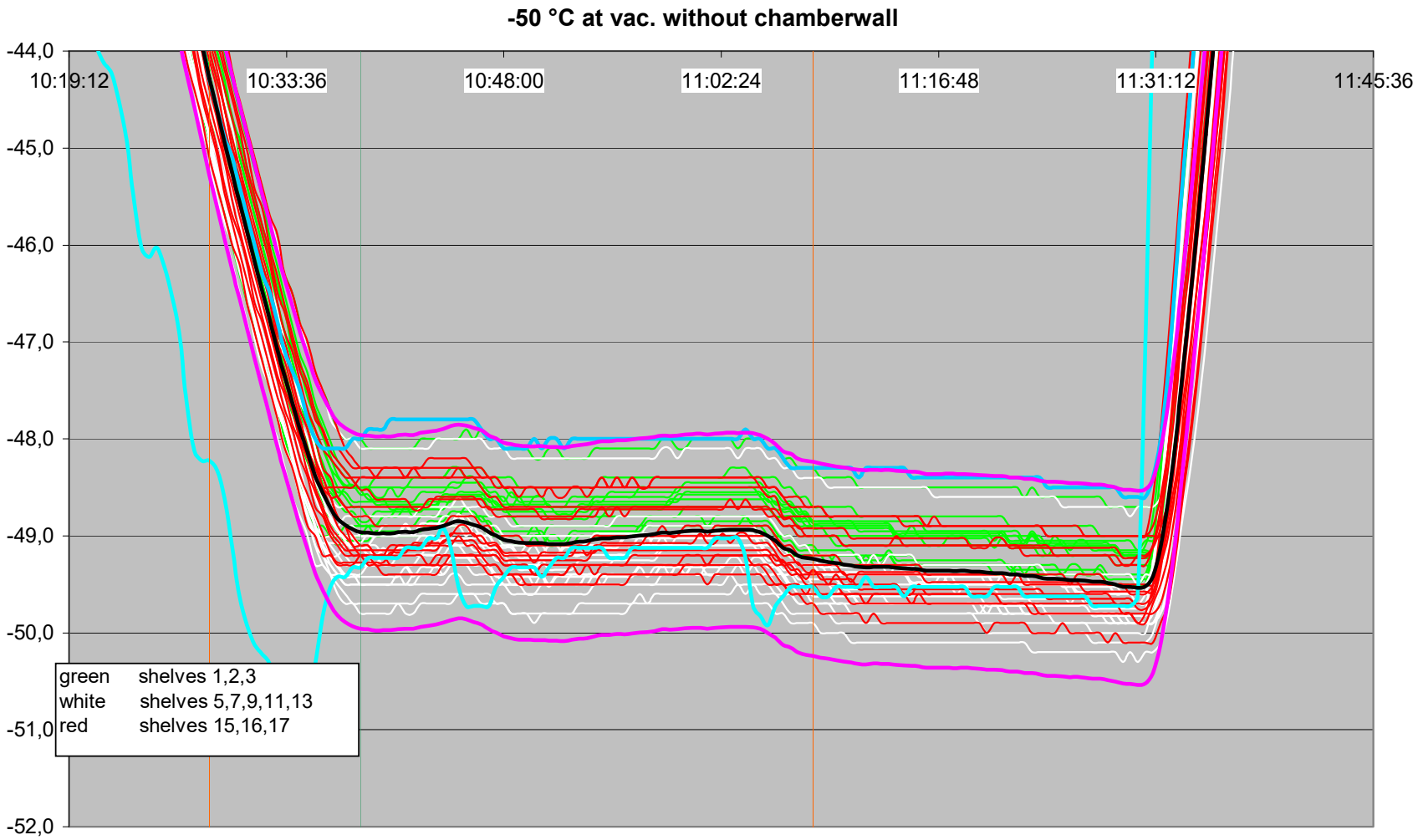
The right validation procedure depends on the freeze dryer design

Shelf System – temperature mapping

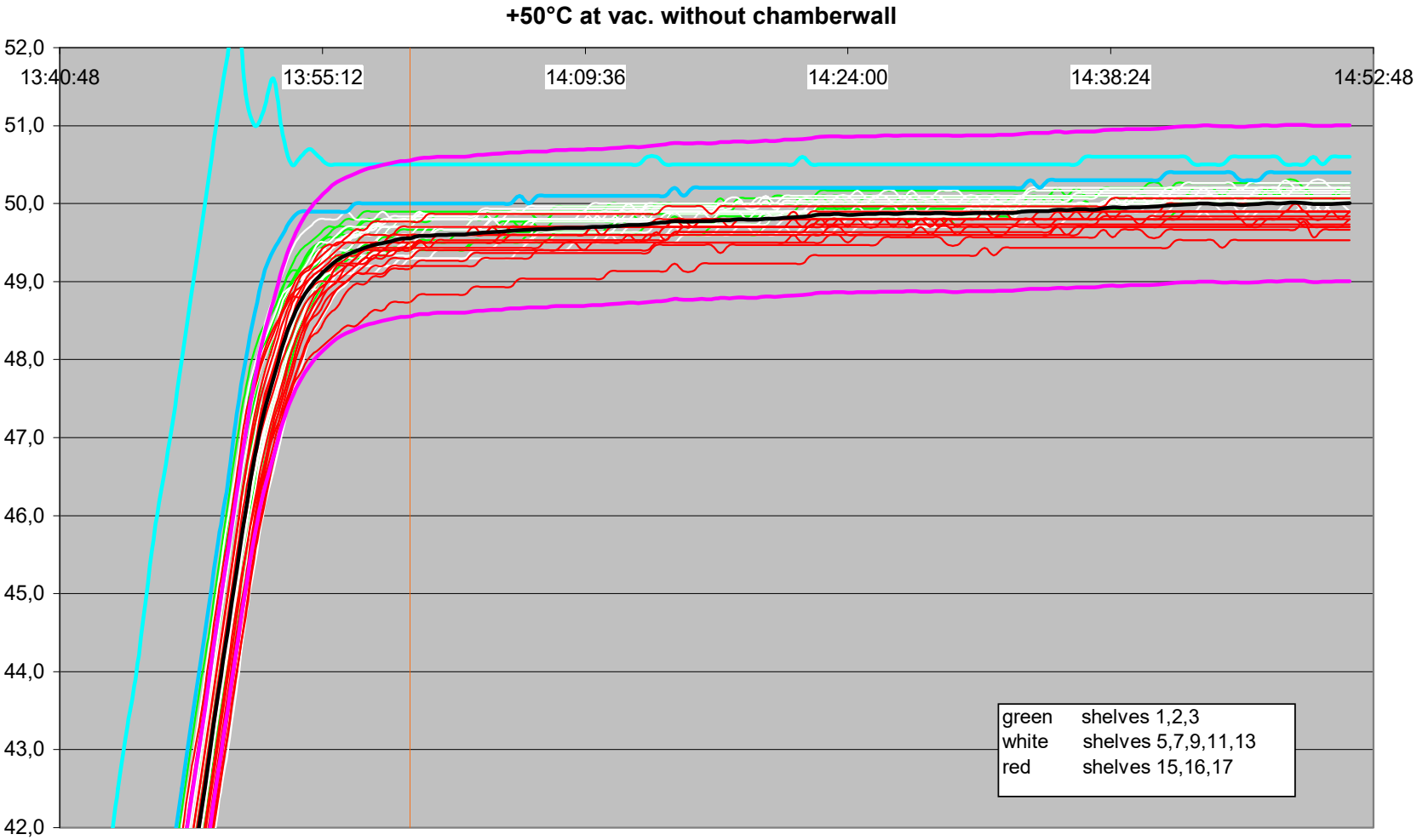
- The wiring of the sensors require a vacuum tight conduction through the chamber wall
- The qualification should be performed at vacuum AND atmospheric conditions to be closer to the later operation at sublimation

Sensor holder *(GE-System)*

Shelf System – temperature mapping



Shelf System – temperature mapping



Material properties vs. process conduction

- GMP-processing requires Stainless Steel (AISI 316L)
- Loading process generates particles
  ⇒ ***Surface quality <0,5µm or better***
- Stopper contact require rough surface
  ⇒ ***Surface quality of shelf bottom ~1,5µm***
- Non-GMP-Lyos use Alu-Shelves
  ⇒ ***Inertial Heat capacity can be reduced to ~20%***
  ⇒ ***Heat conduction is increased ~5x better***

Parameter	QPhase
Material Certificates	IQ
Roughness check	IQ

Movability vs. Robustness

- Movement of shelf package is required for stoppering and loading / unloading

⇒***Plain Bearing of movable shelf-parts is difficult for available materials under GMP-conditions***

- Some supplier require additional shelf tilting to maintain full cleanability of shelves

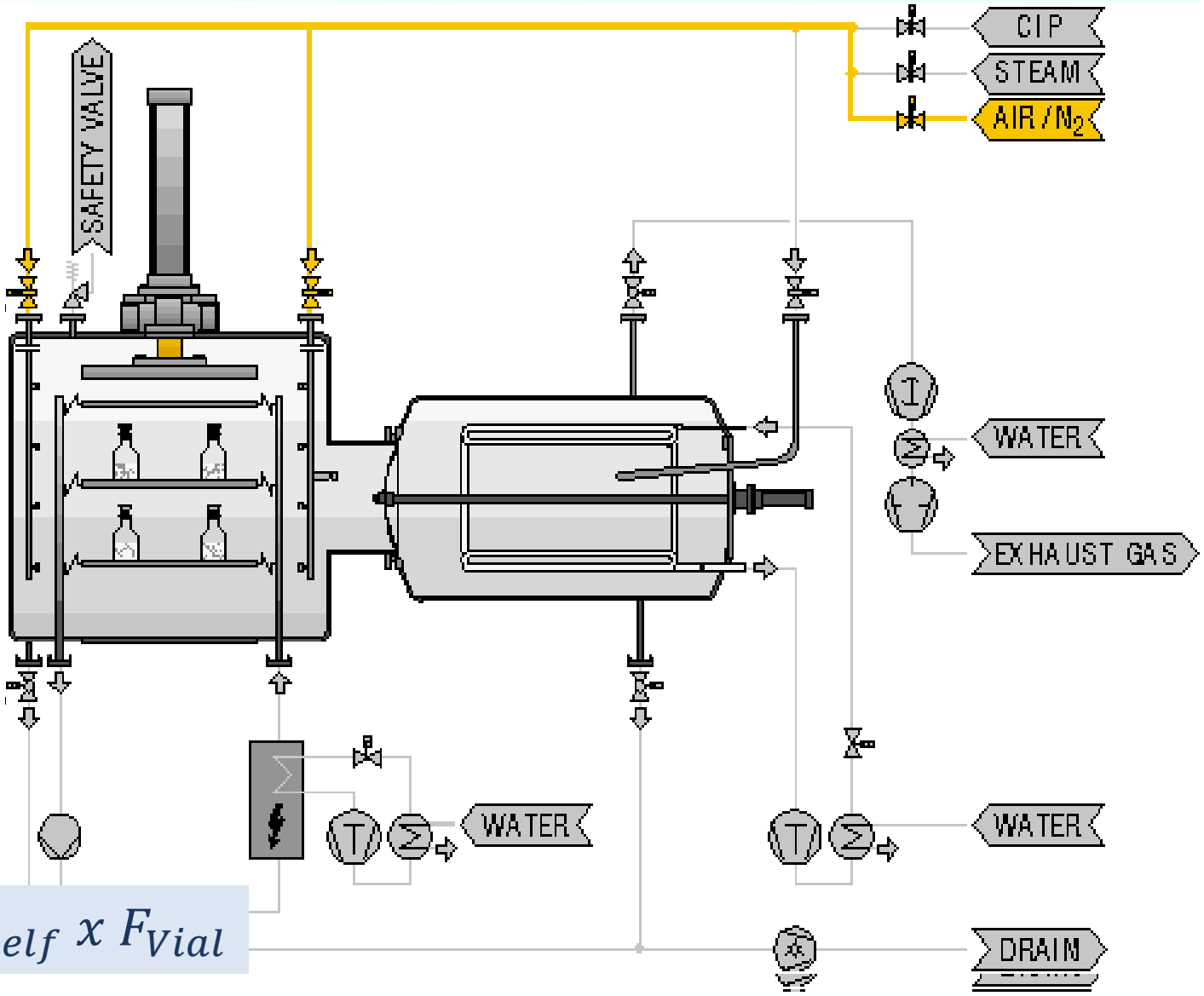
⇒***Very complex and vulnerable shelf system***

Shelf System – Working principle

Enables shelf movement for loading, stoppering and unloading

Required Stoppering to be calculated:

$$F_{Stoppering} = N_{Shelf}\ x\ F_{Vial}$$



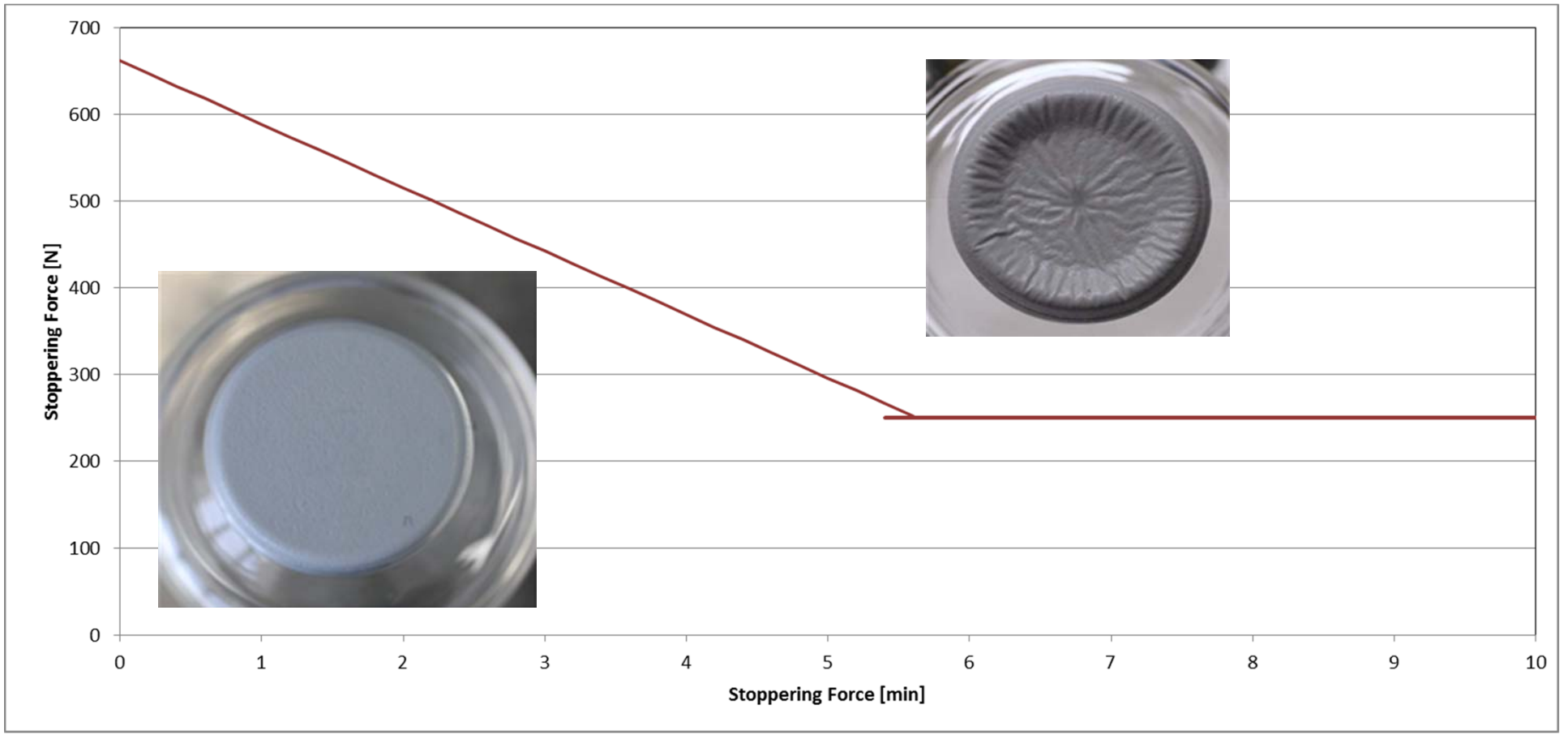
Shelf System – Hydraulic Unit

- **Shelf package movement for constant level loading**
- **Automated Stoppering at the end of the cycle with stoppering force from recipe**
- **Position indicator for high repeatability *(1µm accuracy is state of the art)***

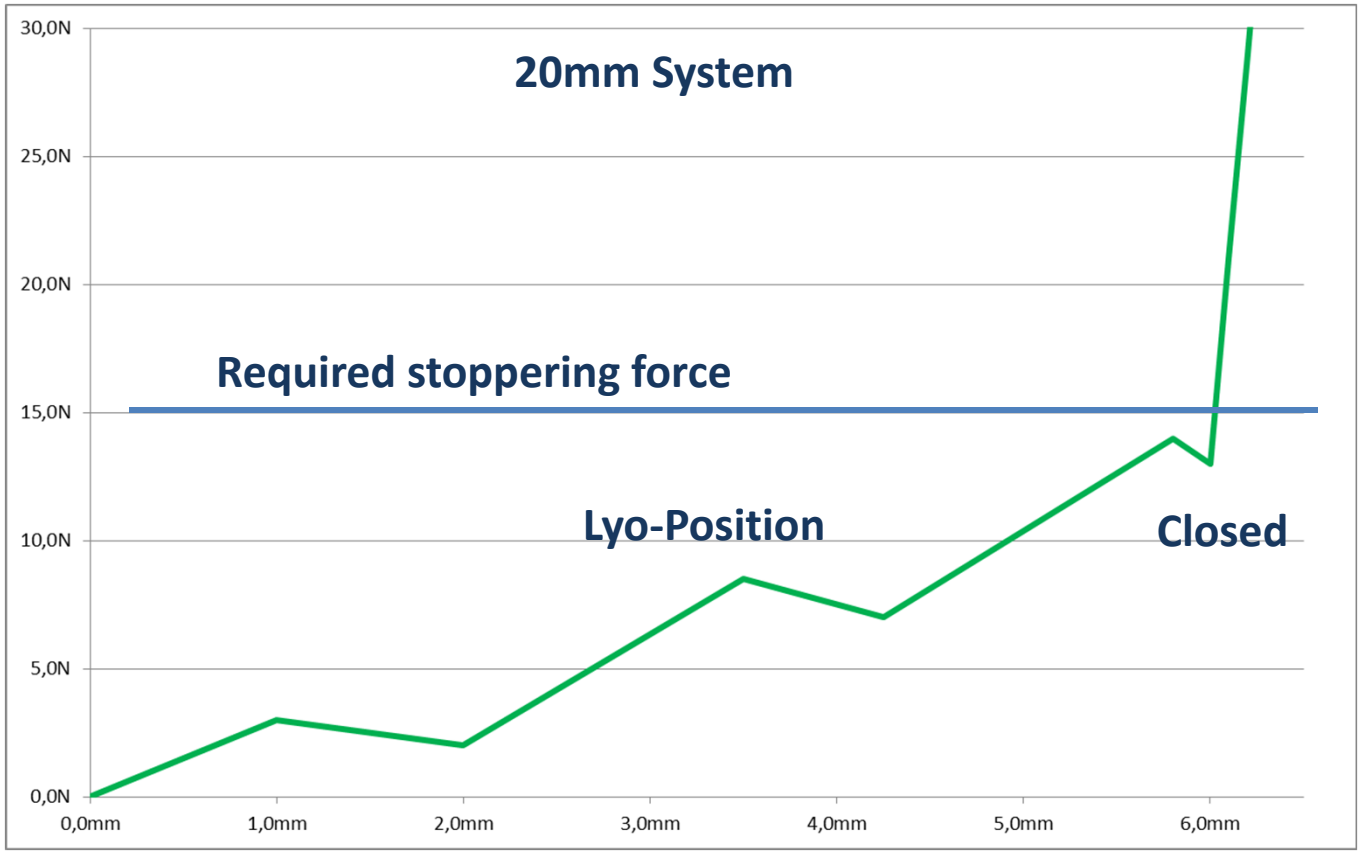
A common standard for performance design is 0,1 N / mm² [Stoppering Force / Shelf area] e.g. 10tons for a 1m² shelf. Further requirements must be specified at the beginning of the project

Parameter	QPhase
Hydraulic Force	DQ
Loading level	DQ & IQ
Loading test	PQ
Stoppering Test	PQ

Limit of damaging Stopper Force

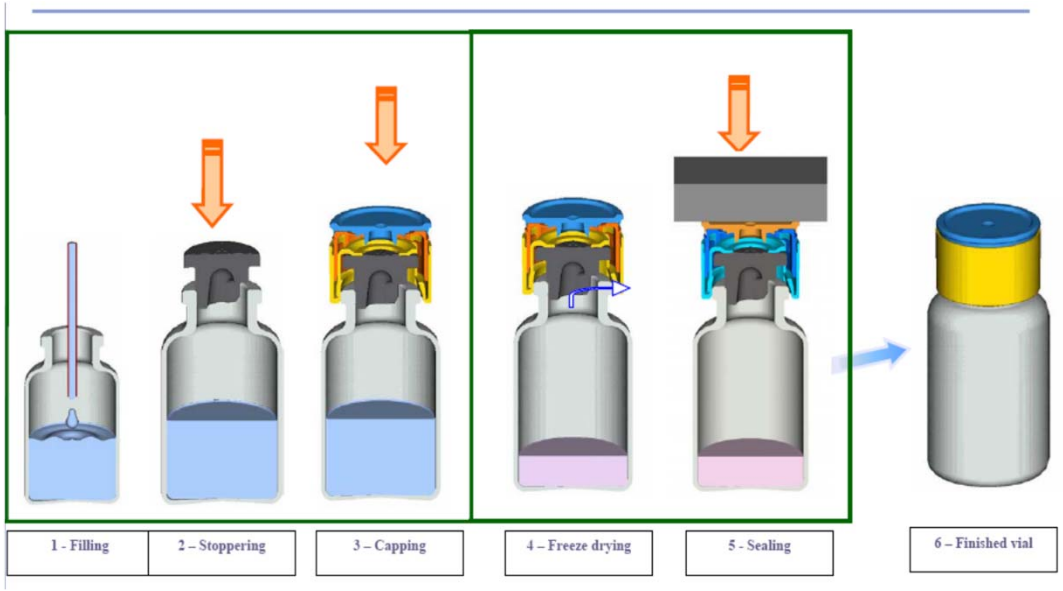


Stoppering Force vs. Displacement



- Stoppering process is a very complex function, Force depends on vertical stoppering position
- Current processes are usually over-stoppered to maintain adequate stoppering force at any stopper
- Dedicated Stoppering Process with full tracking allows ideal stoppering conditions
- 20N represent a good stoppering value for 20mm Systems

Shelf System – Example for special requirements - Lyoseal

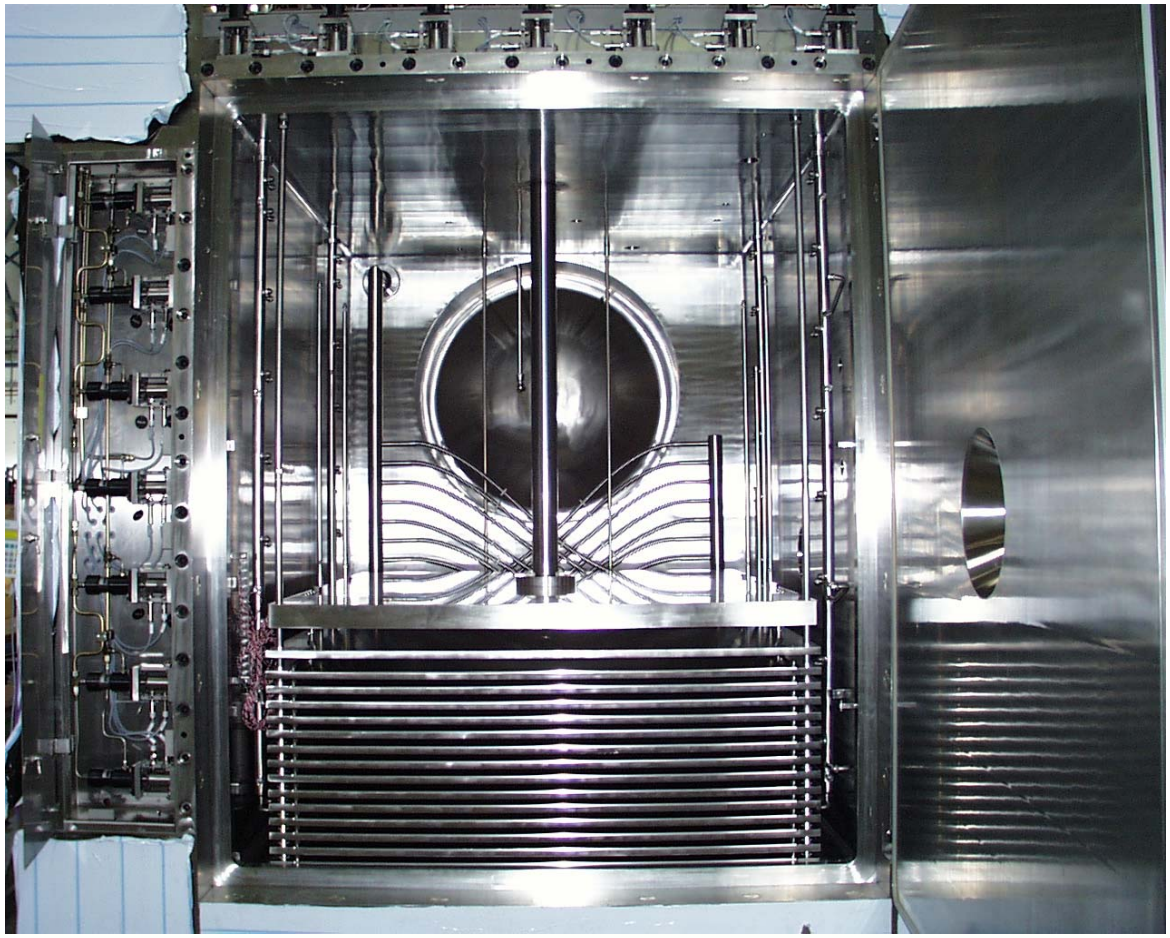


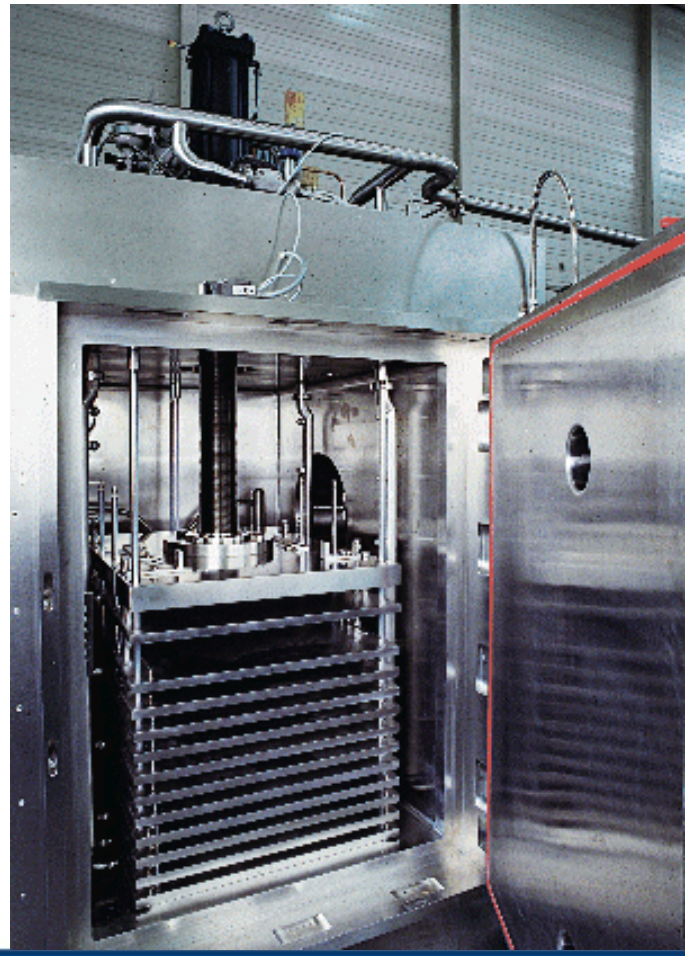
vial type require high stoppering force!

Parameter	QPhase
Hydraulic Force	DQ
Shelf evenness	IQ

Chamber System

Chamber-Condenser System with shelf package





Vessel System

- Integer system hull for the process
- Pressure and vacuum resistant vessel
- Supports the shelf system
- Aseptic design

Parameter	QPhase
Pressure Code Certificates	IQ
Mechanical calculation	DQ

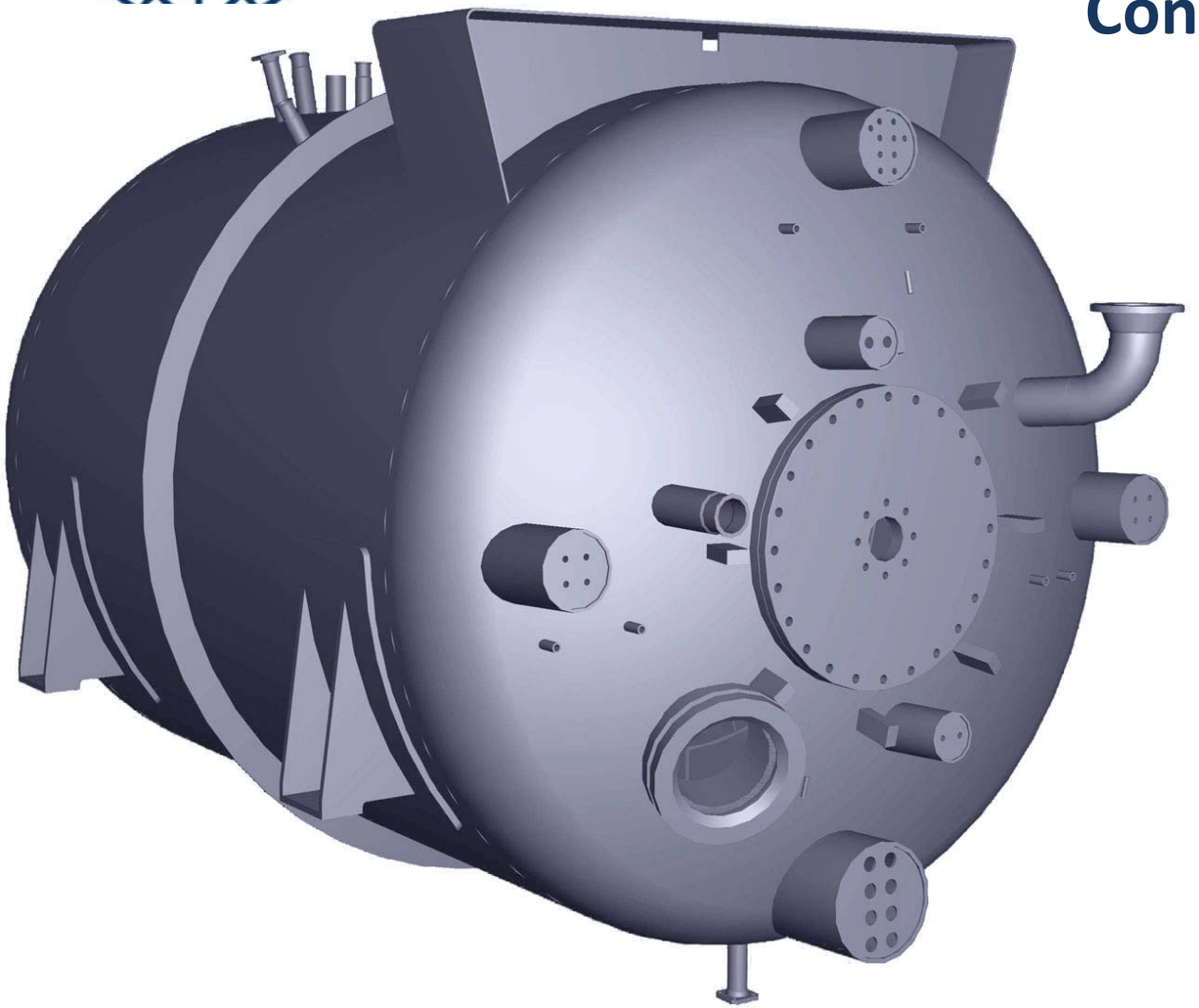
Ice Condenser System

Condenser

- The Ice condenser operates as ice trap by removing the vapor due to condensation
- Condenser coils refrigerant cooled or indirect by silicone oil

<u>Indirect cooling („Fluid condenser“)</u>

- Plate heat exchanger (refrigerant)
- Heater (electrical)
- Circulation pumps (redundant)

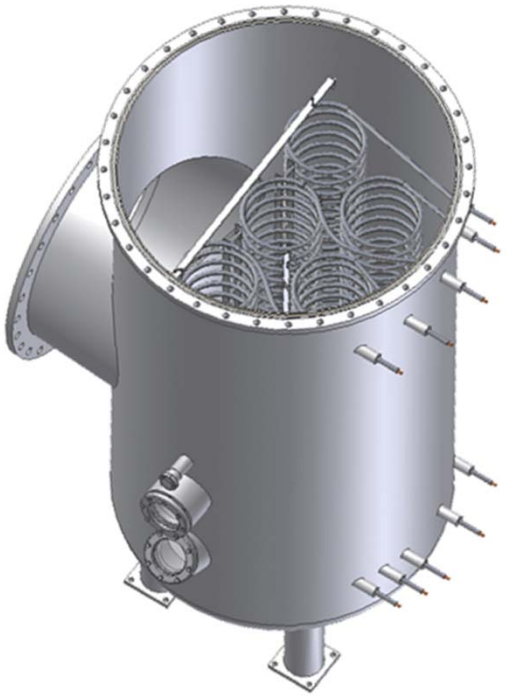


Condenser

- Removal of water vapor by deposition at the coils
- Must be sufficient to remove the high deposition enthalpy

Design concept – Ice Condenser

- Condenser Temperature below -80°C with R404-based compressors
- Condenser Temperature below -90°C (LN_2-based)
- Condensation on coil pipes
- Flexible Arrangement (behind, beside or below the chamber)
- Placement of Temperature sensors at exhaust and intermediately
- Position of bull eyes placed for observation of ice build up



Parameter	QPhase
Sensor & Bulleye Position	DQ/IQ
Condenser Temperature	OQ

Design concept – Ice distribution

Ice Condenser Requirements

Condenser Performance is based mostly on the robustness vs. Heat load by resublimation at low temperatures under low vacuum

⇒ ***A condenser should be designed to perform nominal averaged sublimation rate at 100µbar, -50°C surface temperature and constant shelf temperature***

⇒ ***A common ration of ice condenser surface with shelf system area is at 0,9 or higher to supply sufficient heat transfer performance***

⇒ ***Capacity should be designed based on 25mm Ice Layer***

Vessel System – Condenser Performance

$$\dot{m}_{max,Sublimation} = \dot{m}_{aver,Sublimation}\ x\ 1,8$$

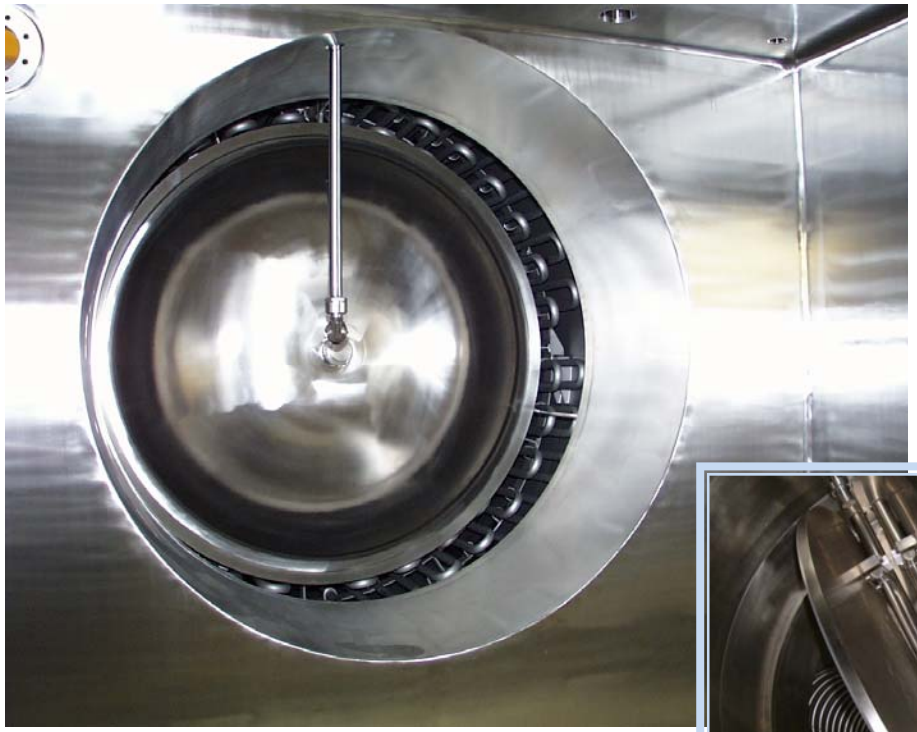
$$\dot{m}_{aver,Sublimation} = \frac{m_{sublimation}}{\Delta t_{Primary\ Drying}}$$

Process Parameter	Performance Value
Required Sublimation Performance	500kg
Sublimation Time:	24h
=> Average Sublimation speed	20,8kg/h
=> Maximum Sublimation speed	37,5kg/h

Parameter	QPhase
Condenser load assessment	DQ
Condenser Performance run	OQ

Main Valve

Design concepts



$$p \cdot V = m \cdot R \cdot T$$

$$V = \frac{m \cdot R \cdot T}{p} = \frac{37{,}5\,\frac{kg}{h} \cdot 462\,\frac{kJ}{kg \cdot K} \cdot 293K}{10Pa} = 508.000\,\frac{m^3}{h}$$

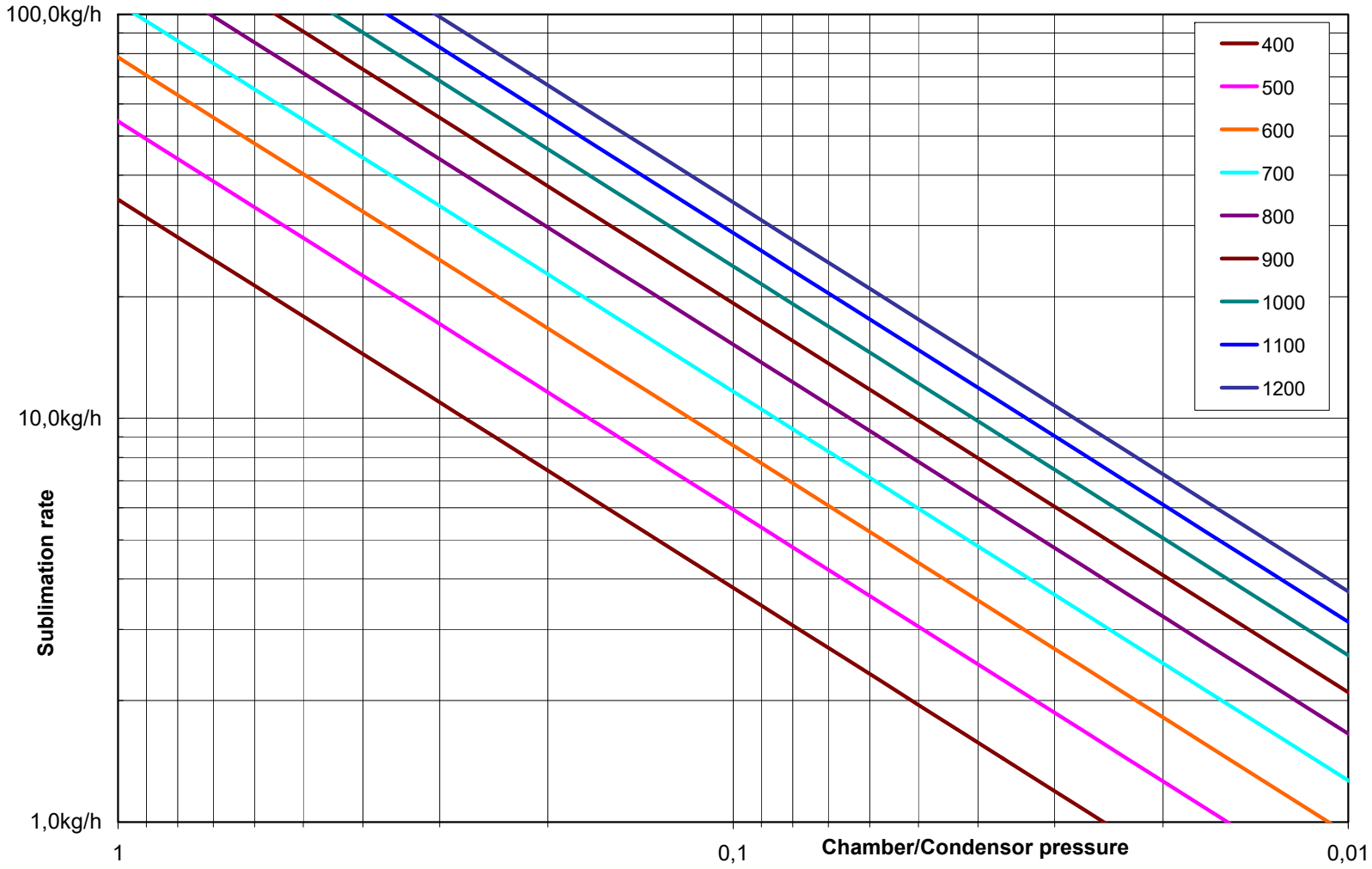
p = 0,1mbar = 10Pa

m = 42kg/h

R = 462 kJ/kg K

T = 20°C = 293K

Sublimation limit vs chamber pressure of valve diam.



- Optimized size
- Stability at -1bar$_g$ / -60°C and +1,5bar$_g$ / +121°C
- Design for Clean-In-Place and Sterilization-In-Place
- Planar fit into sterile room walls
- Integer bellow to cover hydraulic piston
- Customized door concepts depending on loading / unloading situation
- Connections for sensors and media pipes

Parameter	QPhase
Design to be checked	DQ / IQ

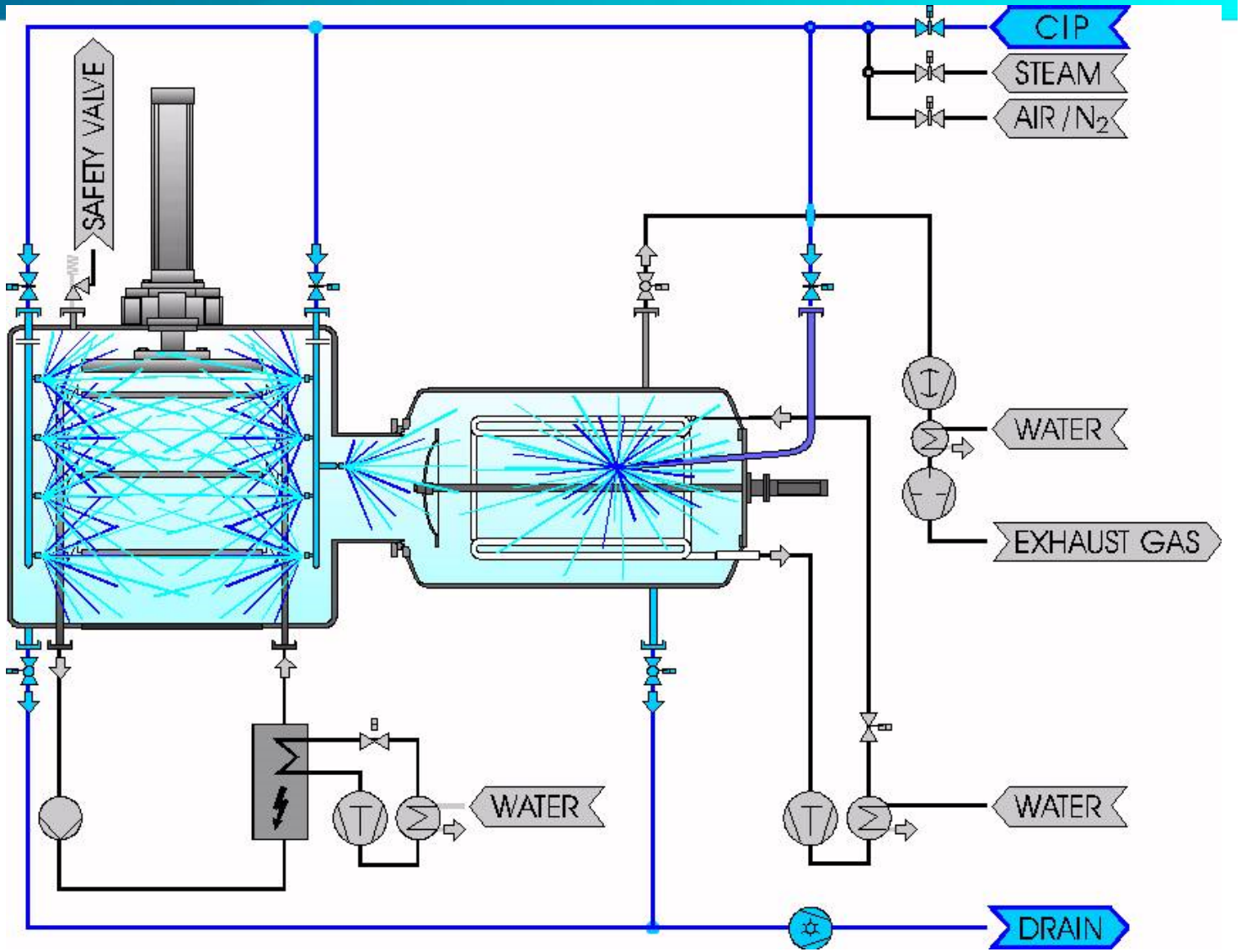
CIP- & SIP-System

For aseptic operation, the vessel system must fulfill additional requirements due to the following processes:

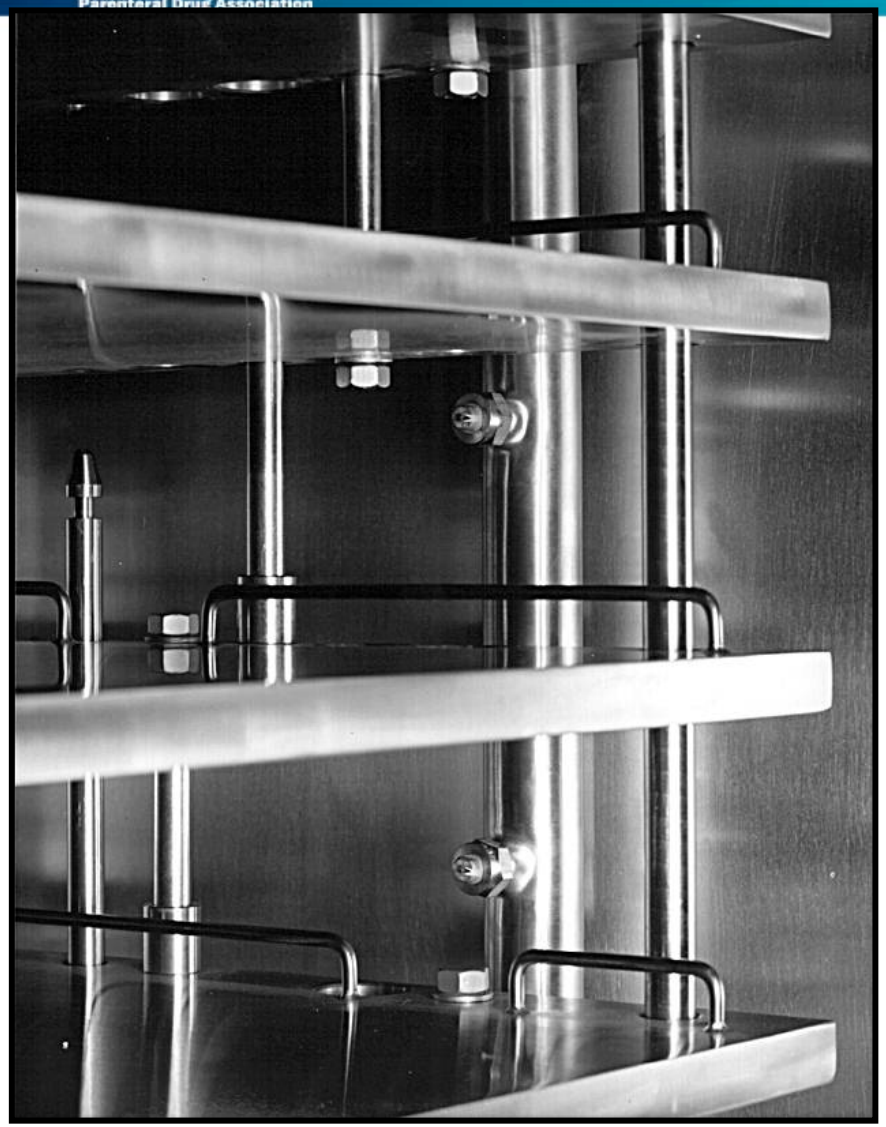
- CIP
- SIP
- Leak Test

CIP-Design

- Pressure controlled CIP-Pump
- Pipe-System with valves and nozzles
- Conductivity sensor at the drain



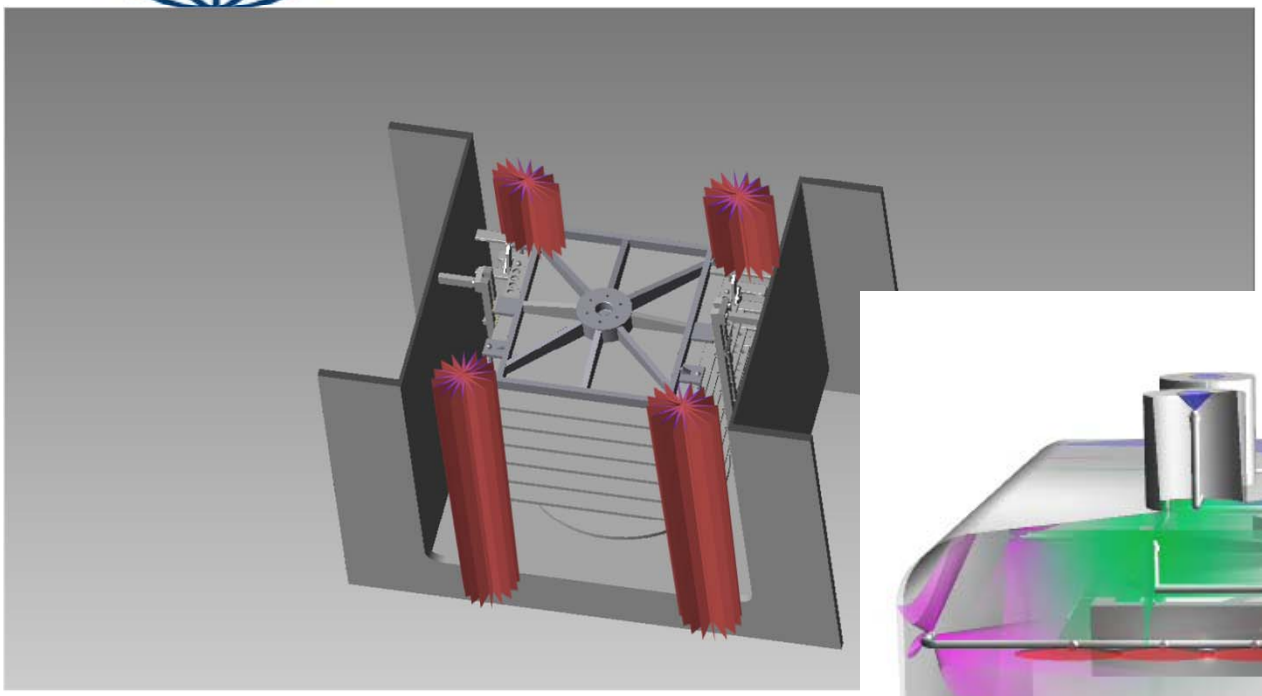
CIP-Design

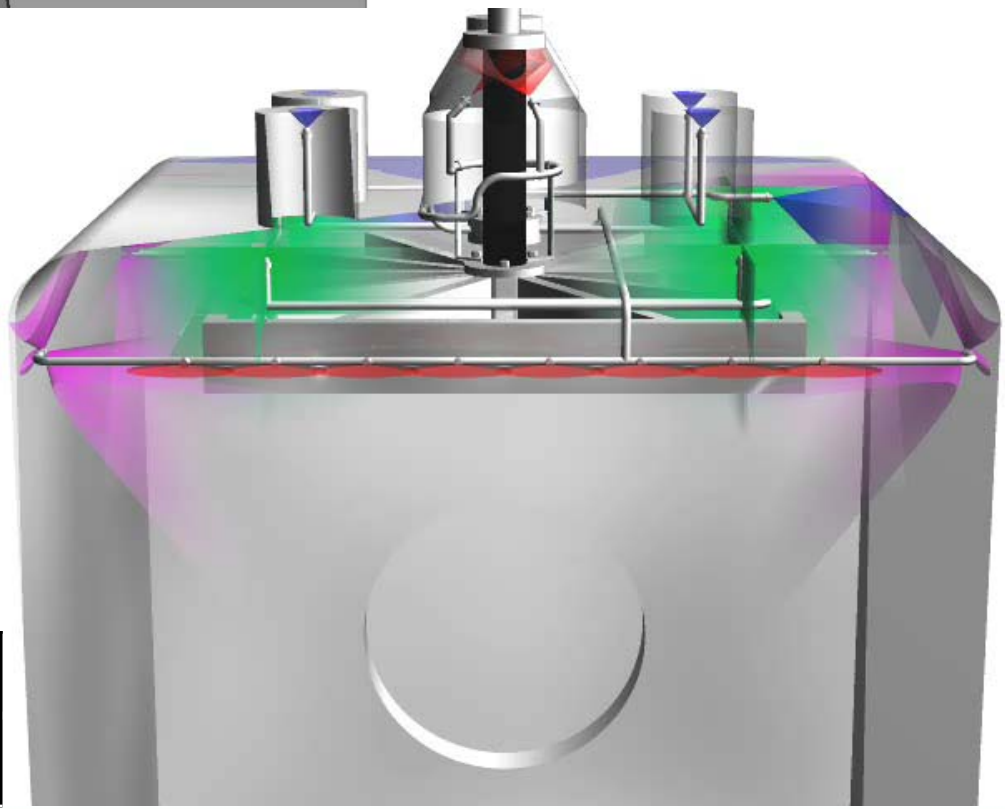


Avoid dynamic nozzles

Parameter	QPhase
Design to be checked	DQ / IQ

Simulation of nozzle system





Parameter	QPhase
Spray Shadow assessment	DQ / IQ

Requirements for Riboflavin test

- 100% cleaning efficacy is current standard
- Minimum amount of nozzles
- Only static nozzles to be used
- Conductivity sensor allows monitoring of cleaning progress online
- Sufficient drain flow capacity to avoid backwater

Parameter	QPhase
Spray Shadow test	OQ
Riboflavin test	OQ

Qualification of CIP-Systems

Only 100%-Riboflavin success provides a risk free cleaning validation in future

Prepare that during project to avoid discussions with supplier:

- **Spray Shadow assessment & test**
- **Standard procedure for Riboflavin test to be supplied with FAT**
- **Step times of the CIP-recipe should be parametrizable to support future modification of CIP-recipe**

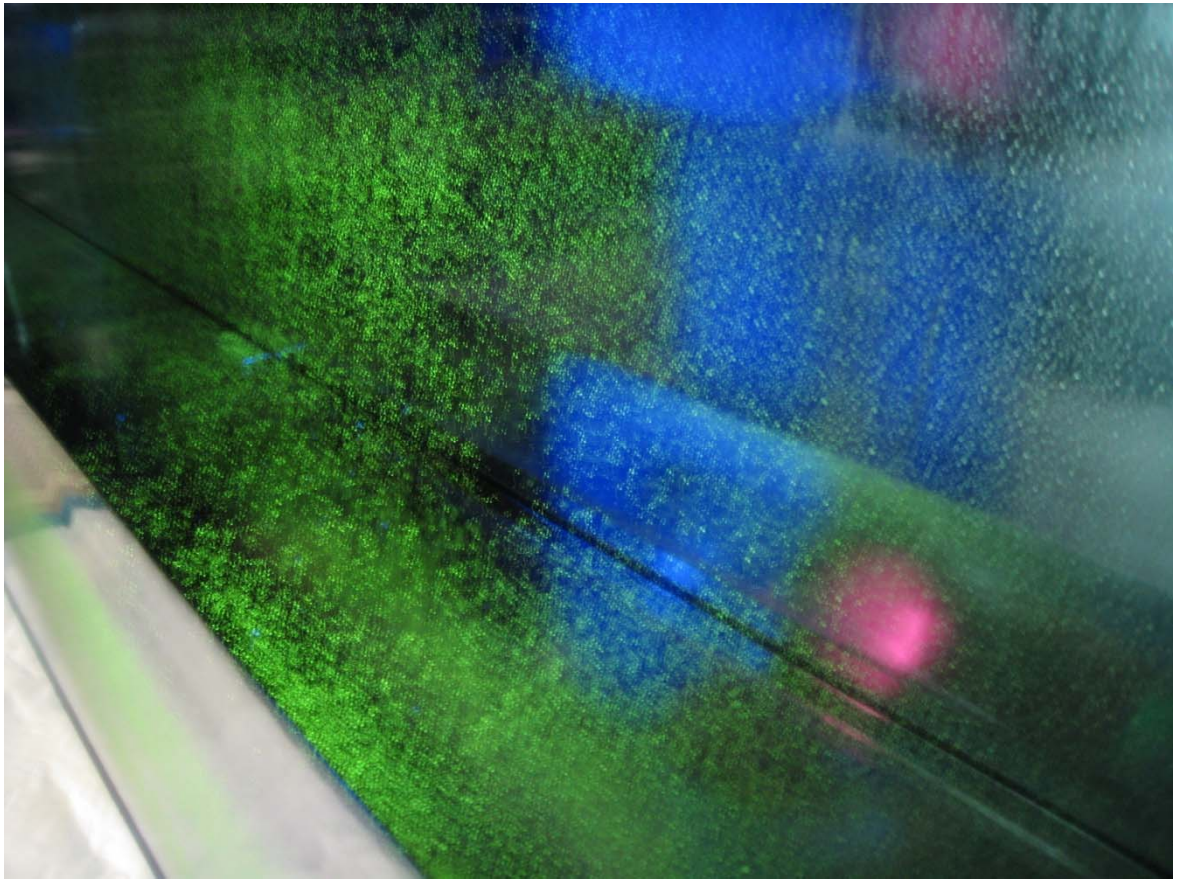
Examples for a Riboflavin prepared chamber

Spray Shadow Test

- Nozzle operates short at each position
- The spray structure from the preparation must be completely destroyed
- Recipe is quick, but not optimized for full cleaning
- Some Riboflavin may remain

Riboflavinetest

- No remaining Riboflavin should be visible
- A common recipe takes 2...3,5h

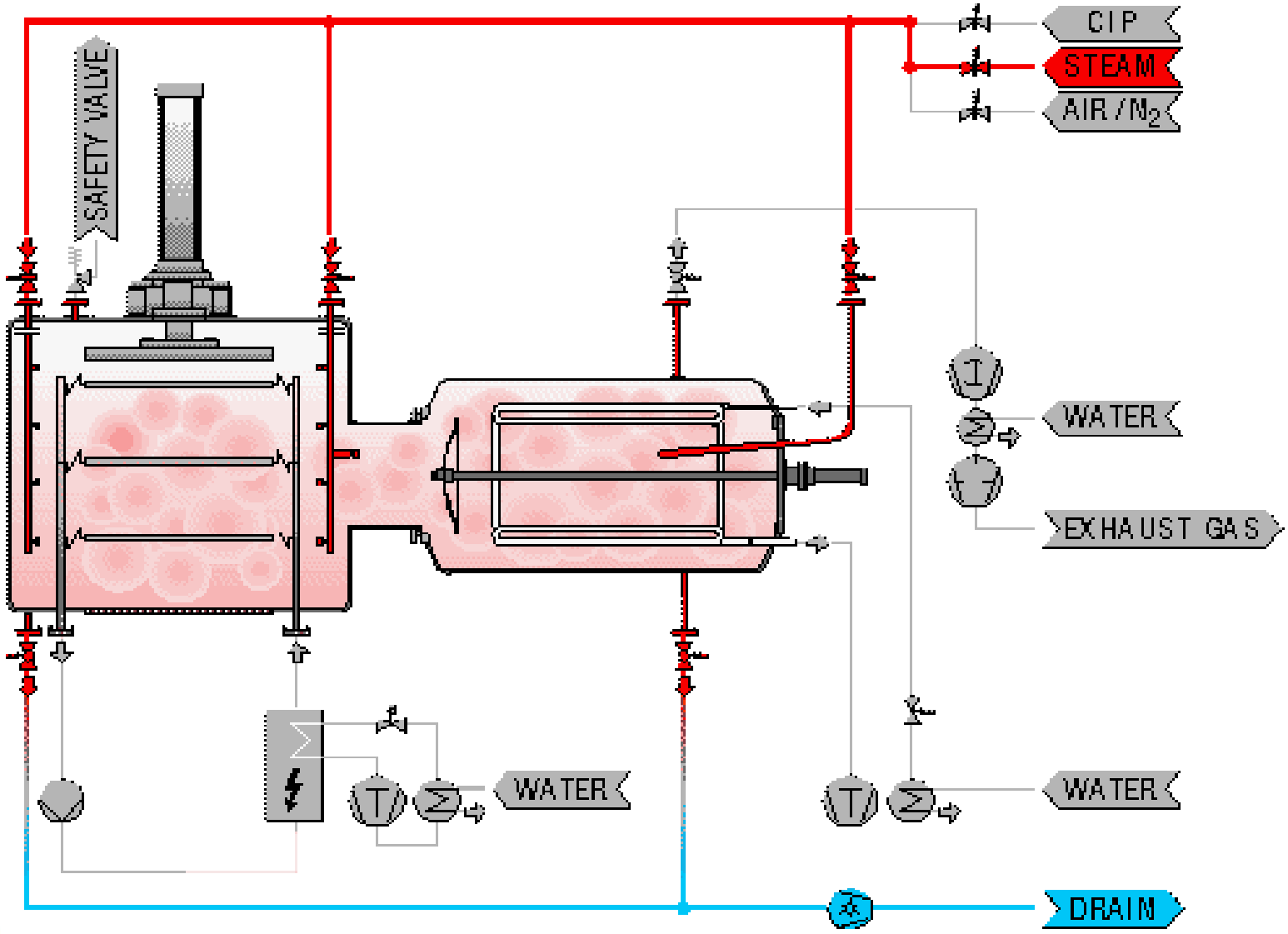


Acceptance criteria:

- Only ZERO remaining riboflavine is acceptable
- The result has to be achieved with cold water only
- Turning nozzles are not allowed within the whole Vessel-System
- The water pressure at the supply pipe to the nozzles must be quite constant – and logged in the GAMP-Recorder
- Water Tailback at drain during washing is not acceptable
- Duration of 2h for Door-Locking and Riboflavine Test shall not be exceeded

SIP-Design

- Steam inlet valves
- Steam traps
- Recooling installation for the chamber wall
- Pressure Sensors
- Temperature Probes



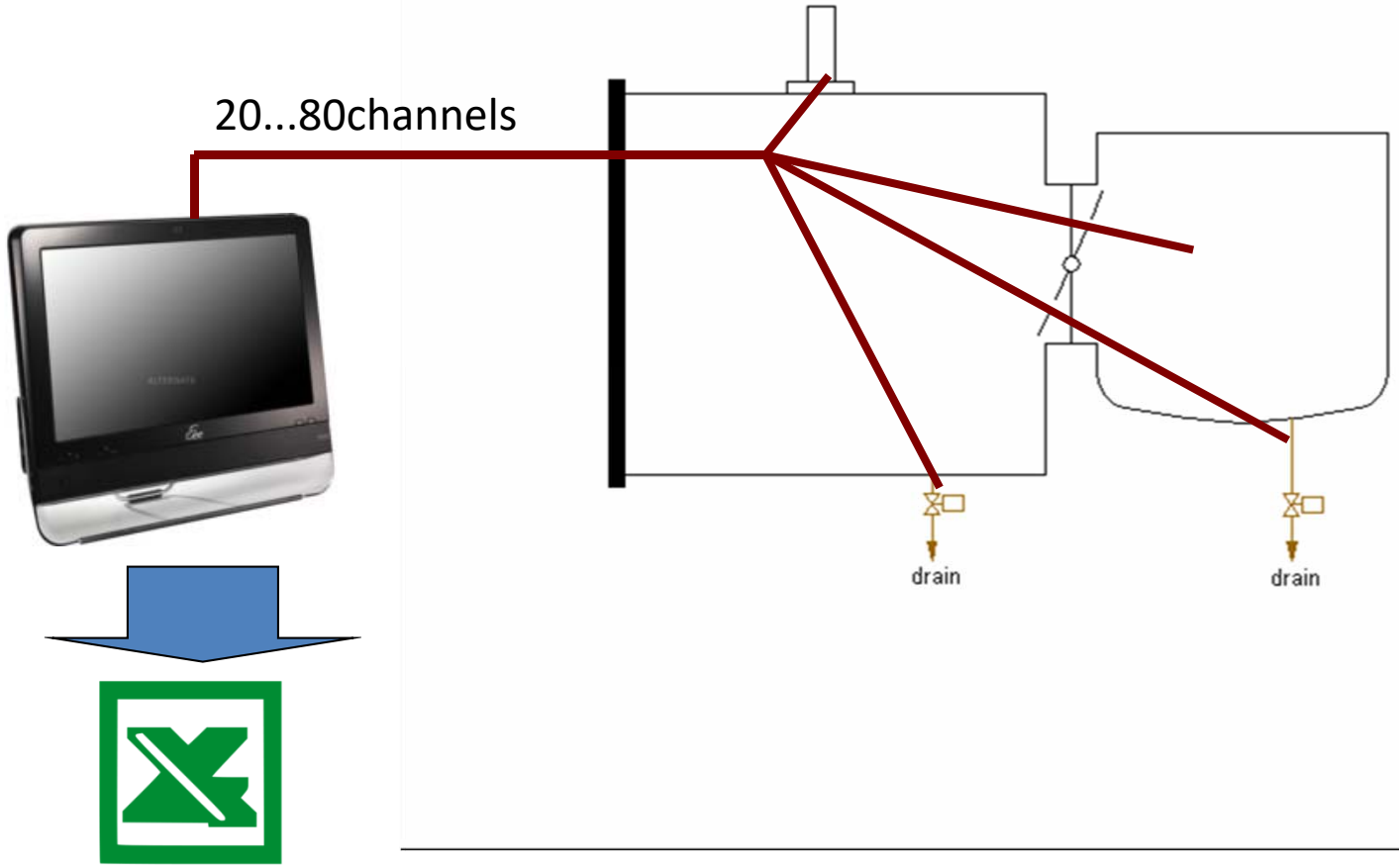
SIP-Qualification

- Steam is the most famous, well-known and proven sterilization procedure for freeze-dryers
- Vaporized Hydrogene Peroxide also allows good sterilization results, its validation is more complex *(will not be discussed here)*
-

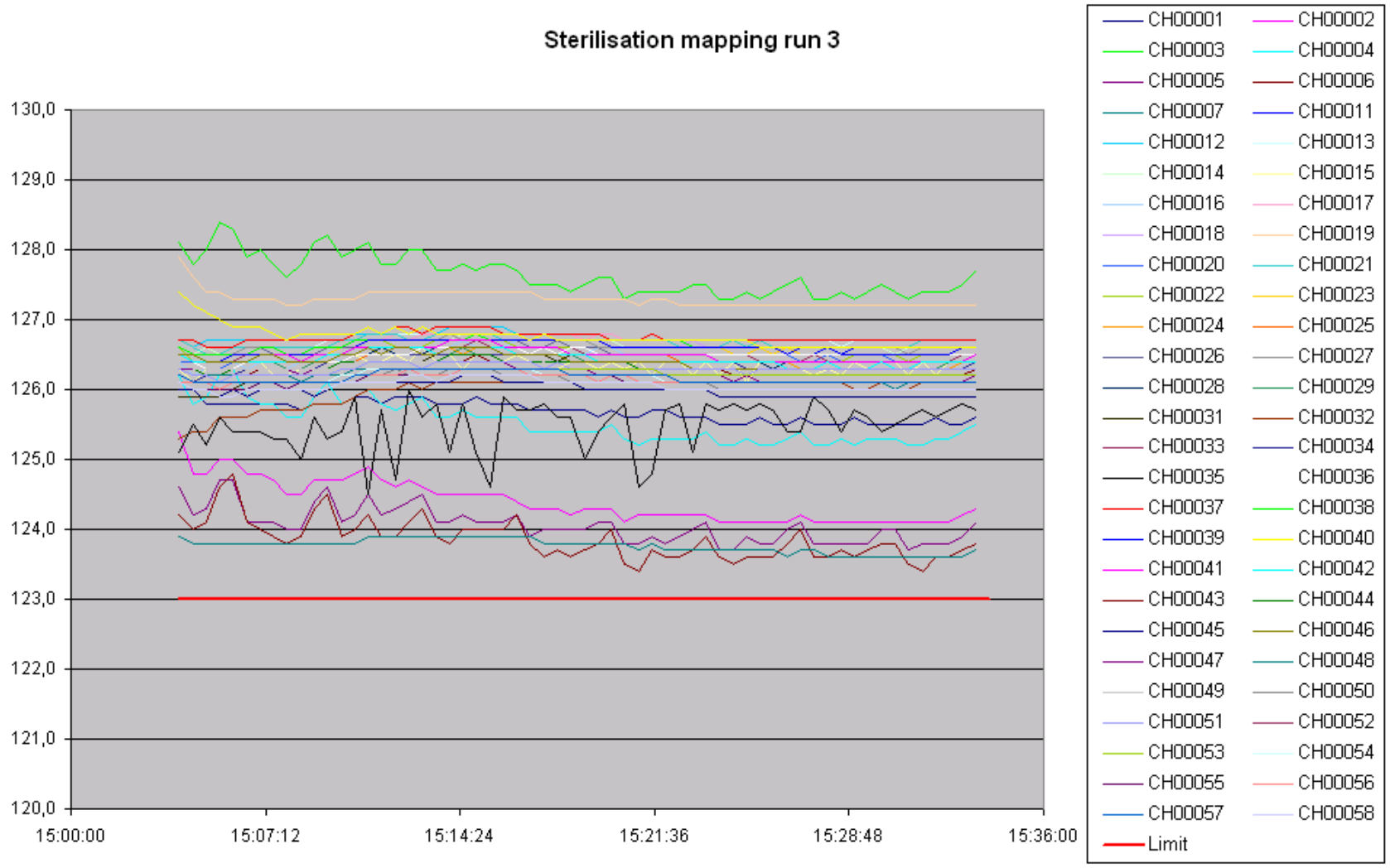
Critical areas at Steam sterilization

- The temperature “behind” the drains, outside of aseptic area are automatically observed by the control system
- Proper function of the steam traps are normally validated once during qualification phase by thermo-mapping
- Once the safe temperature at all places is proven, the critical places do not need to be observed at all places – re-qualification must be performed annually

Qualification of Steam sterilization



Qualification of Steam sterilization

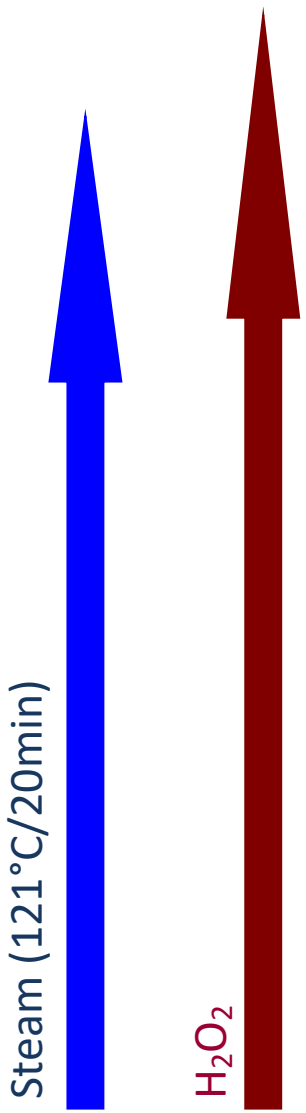


Requirements for Steam Sterilisation

- Initial evacuation into deep vacuum possible to skip purge cycles
- Rapid heating up capability (30mins)
- Homogeneous sterilization (*+3*/-0°C)
- Rapid system drying (no drips visible)
- Rapid system recooling (=> <45°C within two hours)
- Biological validation uses Geobacillus stearothermophilus as benchmark

Parameter	QPhase
Sterilisation Process	OQ / PQ

Microbial Resistance



Typically MORE difficult to eliminate

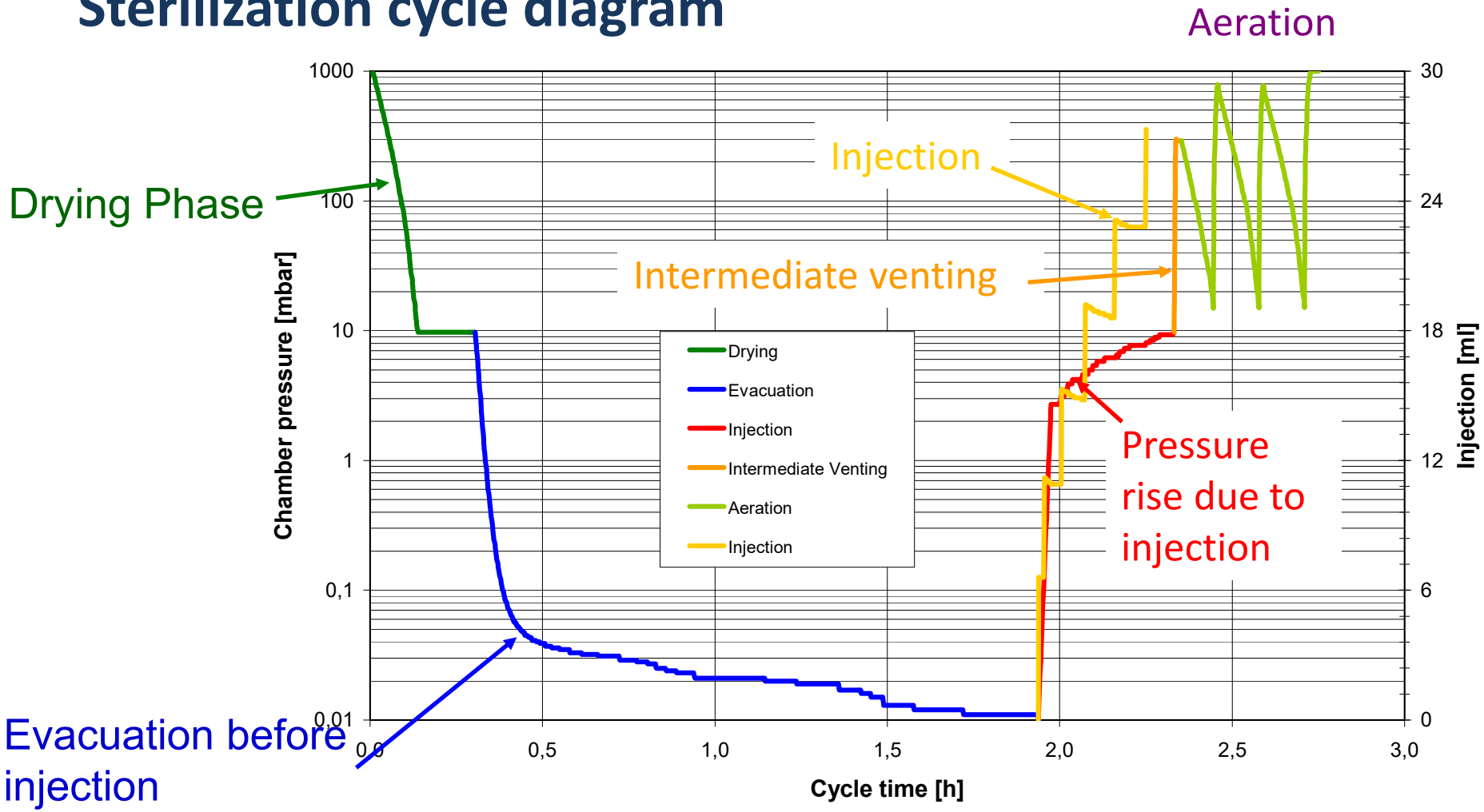
Creutzfeldt-Jakob Disease, CJD Bovine Spongiform Encephalopathy, BSE Scrapie	**PRIONS**	*Geobacillus stearothermophilus* *Bacillus subtilis* *Bacillus anthracis* (Anthrax) *Bacillus cereus* *Bacillis circulans* *Bacillus pumilus* *Clostridium difficile* *Clostridium botulinum* (Botulism) *Clostridium tetani* (Tetanus) *Clostridium sporogenes*
	Bacterial Spores	
Enterobius *Caenorhabditis elegans* *Syphacia* *Acscaris*	**Helminths**	
	Mycobacteria	*Mycobacterium tuberculosis* *Mycobacterium bovis* *Mycobacterium terrae* *Mycobacterium smegmatis* *Nocardia lactamdurans*
Parvoviridae (mouse and canine Parvovirus) *Picornaviridae* (Polio Type 1, Swine vesicular virus, Rhinovirus 14, Rhinovirus 16) *Reoviridae* (Avian Reovirus, Rotavirus) *Calciviridae* (Vesicular exanthema, Viral gastroenteritis) T7 bacteriophage	**Non-enveloped, non-lipid viruses (hydrophilic)**	
	Gram-negative vegetative bacteria	*Salmonella cholersesuis* *Escheria coli* *Yersinia pestis* (Plague) *Pseudomonas seruginosa* *Burkholdia cepacia* *Serratia marcesens* *Proteus vulgaris* *Klebsiella pneumoniae* *Actinobacter baumanii*
Molds *Aspergillus niger* (Black mold) *Aspergillus terrus* *Fusarium oxysporum* *Penicillium crysogenum* *Aspergillus fumigatis* *Trichophyton mentagrophytes* Yeasts *Candida albicans* *Candida parapsilosis* *Saccharomyces cerevisiae* *Rhodotorula glitinis*	**Fungi**	
	Large non-enveloped viruses	*Adenovirus* *Poxviridae* (Vaccinia) *Variola virus* (Smallpox)
MRSA *VRE* *Enterococcus faecium* *Enterococcus faecalis* *Staphylococcus aureus* *Propionibacterium acnes* *Lactobacillus casei* *Listeria monocytogenes* *Legionella pneumophilia*	**Gram-positive bacteria**	
	Enveloped lipid viruses (lipophilic)	*Orthomyxoviridae* (All influenza viruses) *Paramyxoviridae* (Newcastle, Mumps, Measles) *Herpesviridae* (Pseudorabies, Herpes simplex, Cytomegalovirus) *Rhaboviridae* (Vesicular stomatitis) *Togaviridae* (Rubella) *Flaviviridae* (Yellow fever, Dengue) Coronaviruses (SARS Urbani)

Typically LESS difficult to eliminate

Features of H_2O_2-Sterilization under vacuum

- Improved vapor distribution due to low pre-vacuum
- 90 times higher ratio of VHP/inertial gas
- Retrofit at existing Freeze Dryers
- Evaluation of pressure rise plot also allows:
  - Estimation of current VHP concentration
  - Detection of VHP saturation point
  - Detection of “cold spots”

Sterilization cycle diagram



Cycle time depends on

- Initial pressure for injection
- Performance of evacuation systems (WRP, Vacuum set)
- Dryness of the Freeze Dryer and the Sterilizer initially to sterilization process
- Flow resistance of pipe connection between vaporizer and chamber
- Number of required sterilization pulses

BI Mapping in the Antler

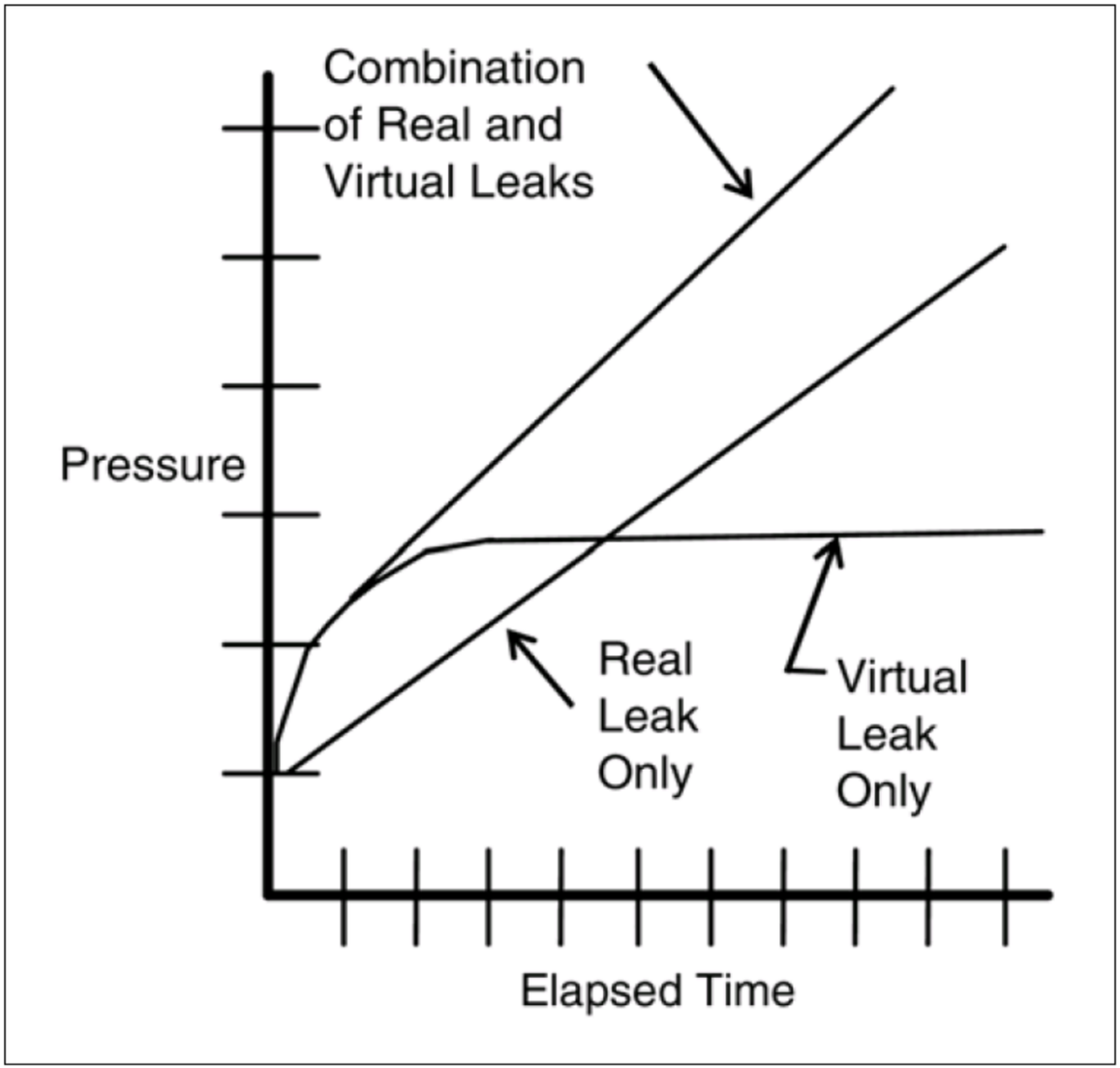
Leak Integrity Test

Leak “Design”

Diaphragm Valves	$1 \cdot 10^{-7}$ mbar x l / s	Up to 100
Safety Valves	$1 \cdot 10^{-2}$ mbar x l / s	2...4
Seals	$2 \cdot 10^{-4}$ mbar x l / s per meter	Up to 80m

Leak Evaluation

- Virtual Leaks must be excluded
- Robust results require long term measurement
- Long term average must be taken into concern for calculation



Requirements for successful leak test

- The leak rate must be below 0,02 mbar x l / s, a manual selection can be done, to expel “virtual leaks”
- State-of-the-art is a leak rate below 0,005 mbar x l / s
- A vacuum regulation time of >48h is recommended (weekend), test time should be > 12h (overnight)
- An automated test (1h + 1h) within Turn around process might show a higher value (trending recommended)

Parameter	QPhase
Leak test	OQ

The Vessel system is ready for operation

Questions?

Freeze Dryers are always customized and taylor-made installations according to customers requirements, conditions and preferences.

Each Lyo system is unique!

Production requires proven evidence of process-worthiness of the freeze dryer according to regulatory requirements

Taylor-made Systems require a taylor-made documentation also

Things which are not documented, did not take place!

=> A good documentation boosts quality (not only in Pharma Business)

General Design Requirements – Documentation

All aspects of the freeze dryer have to documented *as built* – at least the following:

- **Hardware build up:**
  - **Set of Layout Drawings with weight support points and media connections (x,y,z-coordinates)**
  - **Set of P&ID (Process & Instrumentation Diagram) (linked to each other) consisting the following informations (all tagged components, connections to other P&IDs, Slope with direction of pipes, untagged pipe devices like flanges, air breaks…)**
    - **Piping**
    - **Pneumatic / Hydraulic**
    - **Electric**
  - **Media Table (linked with layout drawings, P&ID and flange table)**
    - **All media (in & out; type, amount, connection, required temperature/pressure at interface)**
  - **Detail drawings of vessels and shelves (flange table)**
  - **Documentation about execution of stress tests of all pressure vessels according to local pressure code requirements**

General Design Requirements – Documentation

- Hardware build up (more):
  - List of components consisting of all tagged parts
    - Link to P&ID; function, Supplier/Manufacturer, Detail type code,
  - List of Pipes
  - FDA/EMEA compliant material certificates for all parts with process contact (linked with list of components)
  - List of all weldings (linked with P&ID)
  - Electrical hardware design specification (HDS)
  - Mechanical hardware design specification (MDS)

General Design Requirements – Documentation

- Process Performance / Software:
  - All performance criteria as specified in URS in SAT-protocols
  - To be executed and achieved according to GAMP5 (V-Model)
  - FS (Functional specification, describing all process steps
    - List of hardware interlocks
    - List of softcoded interlocks
    - List of Alarms
    - Process flow charts with complete specification of program branches, transition conditions, hold times etc. or alternatively a matrix of components and software control circuits describing the conditions of each component
  - SDS (Software Design specification, linked to subdocuments of FS)
    - Design overview
    - System architecture
    - System interface description
    - Detail description of software components
    - Detail Description of User Interface
- Spare part lists (linked to P&ID) consisting also non-tagged parts

General Design Requirements – Documentation

- Further Documents:
  - Spare part lists (linked to P&ID) consisting also non-tagged parts
  - CE-documentation
  - Documentation for use of refrigerants
  - Operation Manual
  - Local site engineering may require further documents (check at bidding phase!)
  - Maintenance Recommendation

Insist on each document!

Thank you for your attention!

Questions?

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Time for a Break