Auxiliary Systems of a Lyophilizer

Design & Engineering

PDA Europe
Development of a Freeze Drying Process

Georg Frinke
Bayer

Georg Frinke - *Process Engineer*

Volunteer for PDA

Overview – Auxiliary systems with direct GMP-relevance

- Aeration System
- Sensor Equipment / PAT-Methods
- Process Control System (PLS) / HMI (SCADA)

Aeration System

General Design Requirements

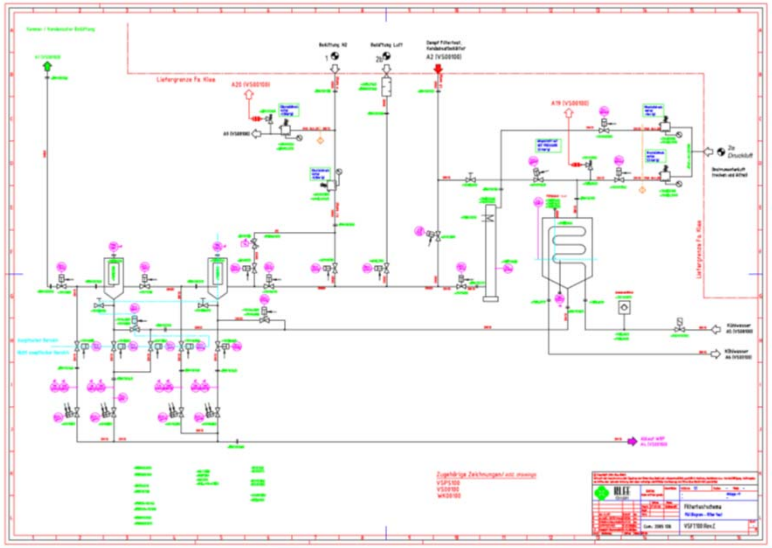
- Consists of:
  - Filter units (redundant) with inline intrusion test
    - Test water preparation
    - Filter drying equipment
    - Pressure & temperature sensors in filter housing
    - Designed to maintain validated test conditions
  - Vacuum control devices (part of vacuum system)
  - Equipment for sterilisation

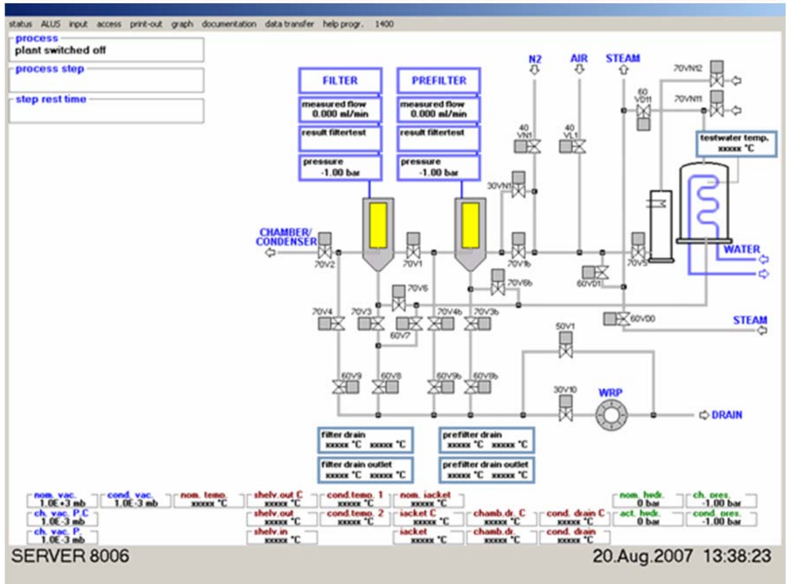
- Pressure / Vacuum regulation
- Providing sterile air/nitrogen into the vessel system
- Aeration during Turn-Around Processes **(“20min”)**

Filter Test

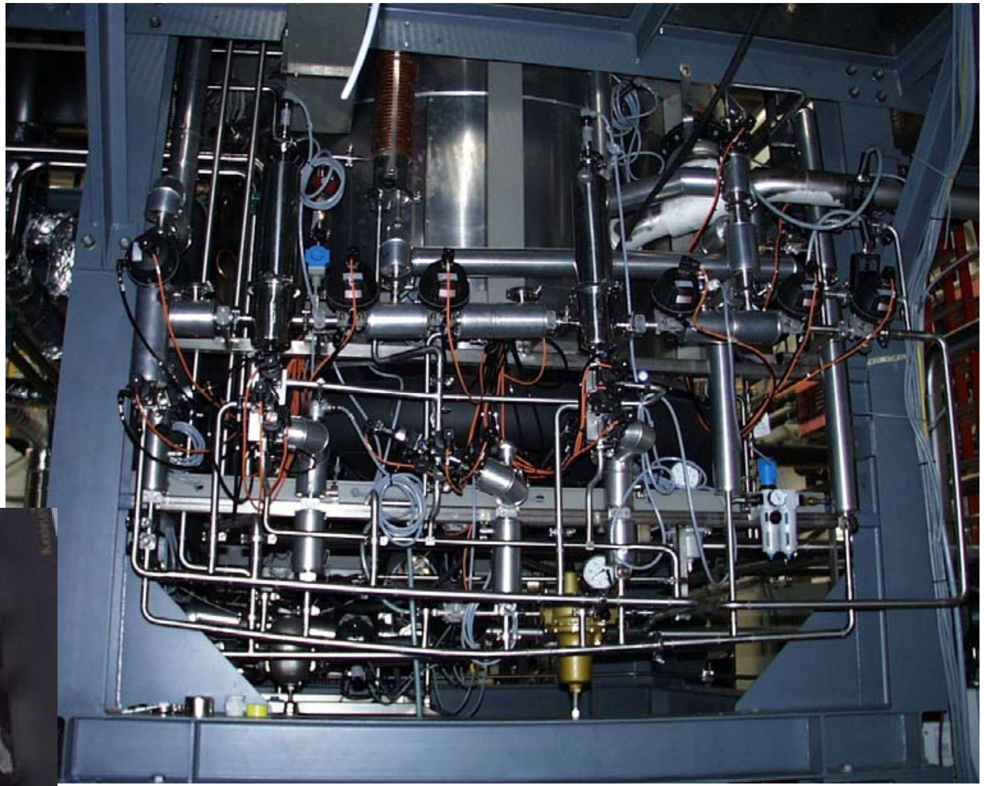
State of the Art

- Automated integrity tests of filters by the Freeze Dryer control system with internal test water generator
- Compatibility to all well-known cartridge suppliers by variable Testparameters
- Filtertest results are part of the automatically generated Batch documentation
- Indication, record & control of test water conditions at storage tank and filter housings





Real installations



Sartorius procedure

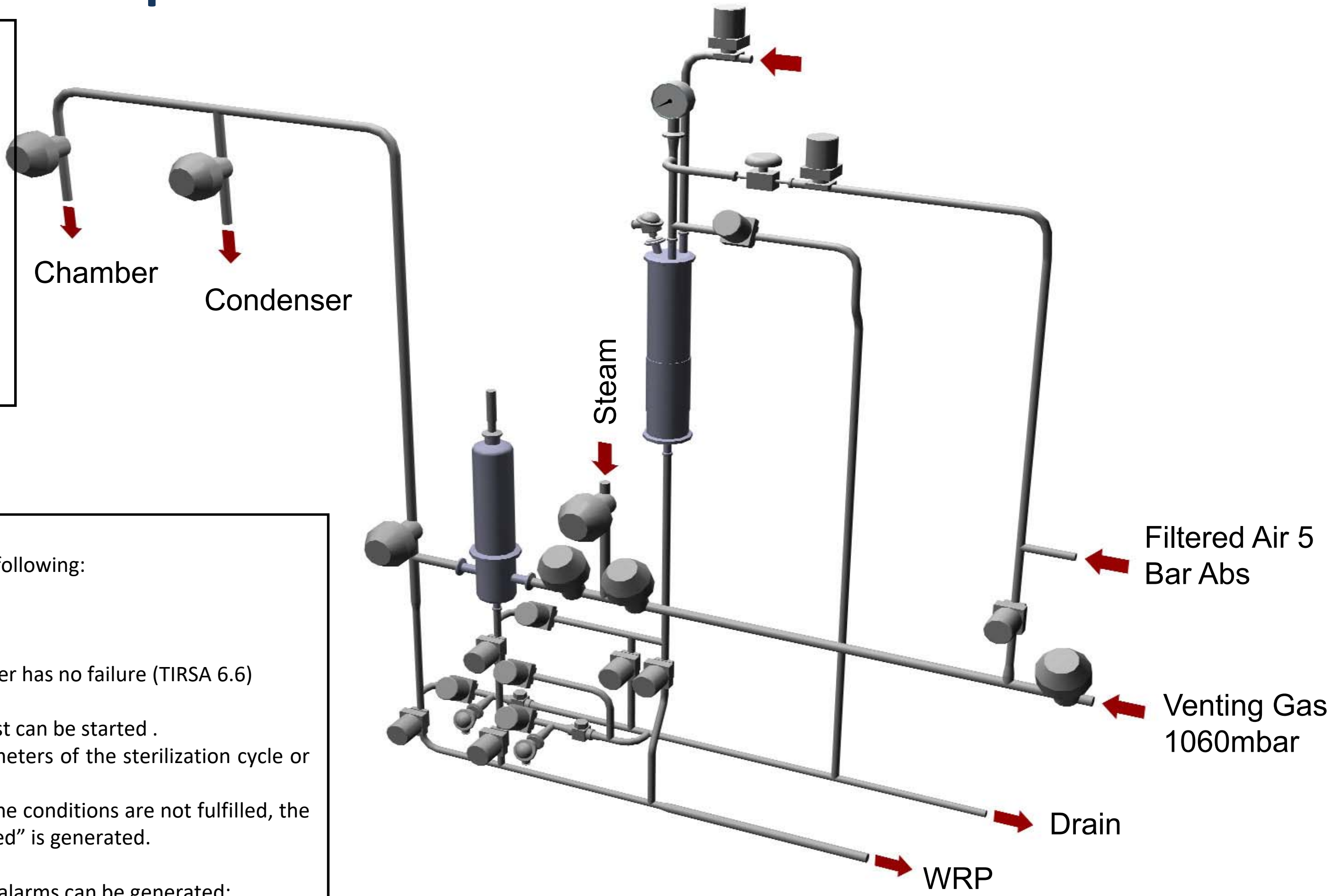
Integrity Test

Integrity test is effected automatically.

General Information

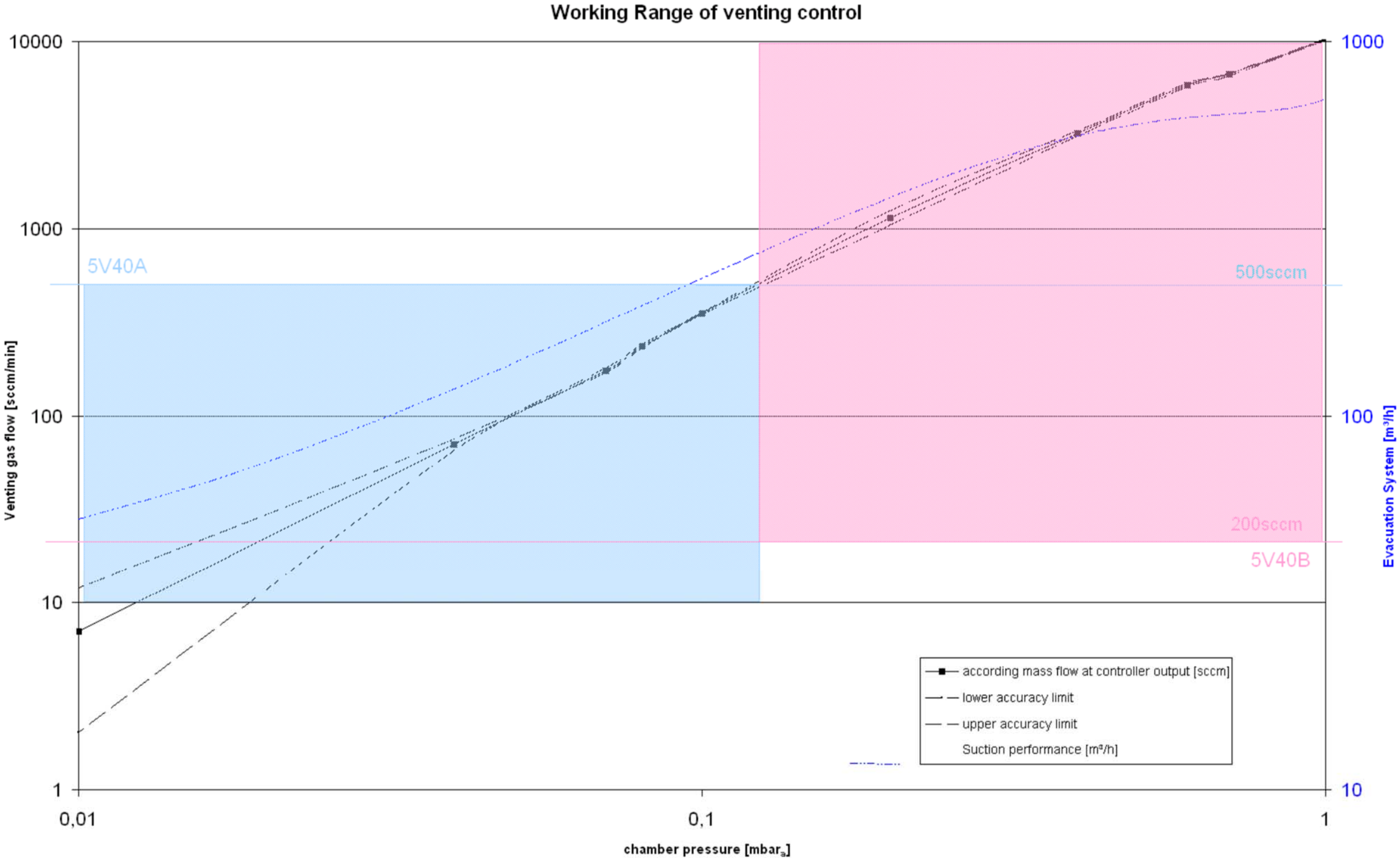
The integrity of the venting filter is tested using the Water Intrusion Test method (WIT).

The filter housing is filled with water on the upstream side up to the top of filter cartridge. The remaining volume of air is compressed to a pressure of 3500 mbar abs.. After a stabilization time the water intrusion rate is determined by measuring the pressure drop in the filter within a defined testing time. After the test, the water needs to be eliminated and the filter must be dried.



Start of Integrity Test
The preconditions to start the integrity test are following:
- All operating media are present.
No other sub process is running.
Freeze-drying process is not running.
Temperature measurement point in the container has no failure (TIRSA 6.6)
Filter pressure gauge has no failure (PIRSA 6.4)
If all this conditions are fulfilled, the integrity test can be started .
This program can be selected in the start parameters of the sterilization cycle or can be started manually.
When the operator clicks the start button and the conditions are not fulfilled, the failure message “Integrity test process not started” is generated.
Integrity Test Alarms
During the cycle following integrity test specific alarms can be generated:
Integrity test process not started
Test pressure not built up
Test pressure too high
Test pressure drop too high

Flow Controller – vacuum system



Sensors

Use of sensor types

- Pressure control
  - Venting during Turn-Around-Cycles (CIP, SIP, Filtertests)
  - CIP-Inlet Line to maintain reproducible nozzle spray behaviour
  - Sterilization control
- Vacuum control
  - Freeze Drying Cycle
  - All evacuation processes
- Temperature
  - Silicone oil circuit control
  - Product (preferably wireless)
  - CIP-Water (upstream to nozzles)
  - All drains to monitor sterilization efficacy
  - Filter System to monitor test water conditions

Use of sensor types

- Conductivity Sensors
  - Measure purity of WFI at final rinse
- Flow Sensors
  - CIP-Inlet Line
- Limit Switches
  - Safety installation to secure all actuated mech parts againts malfunction
    - Doors and loading doors
    - Shelf system components
  - Binary positioning indicators of valves

Parameter	QPhase
Calibration of each GMP-relevant sensor	IQ / OQ

Pressure sensors – available technologies:

Standard pressure transducer:

Range: -1...4bar$_g$
Accuracy: ±20mbar
Resolution: 10mbar
Output: 4...20mA

Vacuum sensors – available technologies:

Capacitance Sensor

Range: 0,1...1.000µbar$_a$
Accuracy: ±0,25% of reading (<1.000µbar)
Resolution: 0,1µbar
Output: Digital (Profibus)
Temperature corrected by permanent heating up to 150°C

Vacuum sensors – available technologies:

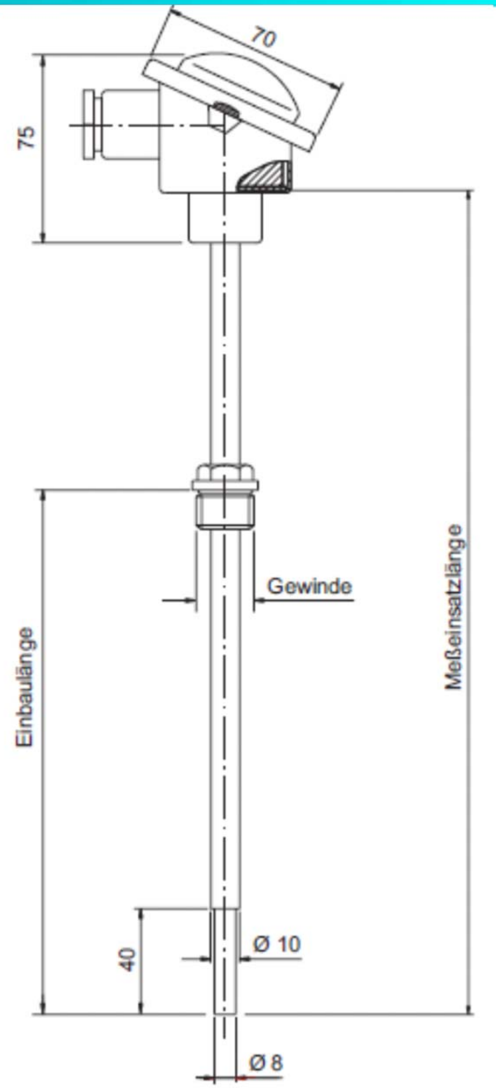
Pirani Sensor

Range: 1...1.000.000μbar$_a$
Accuracy: ±15% of reading (<10.000μbar)
Resolution: 0,1μbar
Output: 0...10V

Temperature sensors – available technologies:

Thermoresistive sensor (RTD)

Range: -200...400°C
Accuracy: ±0,5°C
Resolution: 0,1°C



Temperature sensors – available technologies:

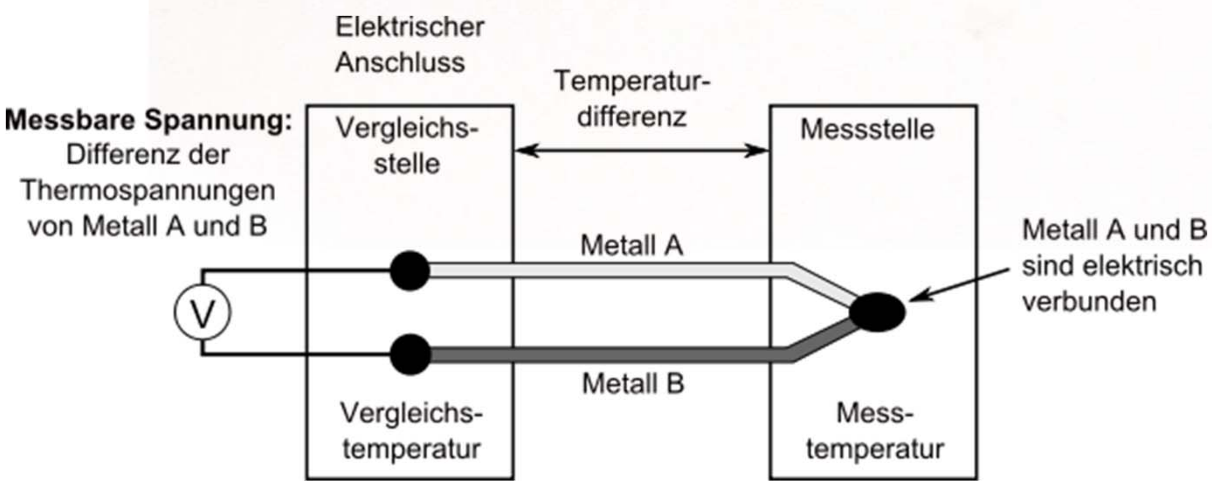
Wireless thermoresistive sensor (PT100)

Range: -200...400°C
Accuracy: ±1°C
Resolution: 0,1°C

Temperature sensors – available technologies:

Thermocouple element

Range: -100...+150°C
Accuracy: N/A
Resolution: N/A



Temperature sensors – available technologies:

- Thermocouples come with smaller heat capacity
- RTDs come with better accuracy & repeatability

PAT-control

PAT & Development Tools (I)

Tool	Nucleation: Trigger	Nucleation: Feedback	Temp. Probes	BTD / MTD	Comp. Press. Meas.	Lyotrack / Cold Plasma	NIR Gas Analysis	MS Gas Analysis	TDLAS	DRM
1.) Pharma Compliance	Yes	?	Yes (if wireless)	Yes	Yes	(Yes)	Yes	?	Yes	Yes
2.) Process Feedback	Yes	?	No (only Samples)	(Yes)	Yes	Yes	Yes	Yes	Yes	(Yes)
3.) Process Control	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nucleation	Yes	Yes	No	No	No	No	No	No	No	No
Sublimation t_{crit}	No	No	Yes	Yes	No	No	No	No	Yes	No
Sublimation End	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Desorption	No	Yes	No	No	(Yes)	(Yes)	Yes	Yes	Yes	Yes
Costs	€	€€	€ (€€ if Wireless)	€	€	€€	€€€	€€€	€€€	€

PAT & Development Tools (II)

Tool		Micro Balance	Shelf Weighing	Condenser Weighing	Ice Layer Monitor	Dew Point Monitor
1.) Pharma Compliance		No	Yes	Yes	Yes	No
2.) Process Feedback		No	Yes	Yes	Yes	Yes
3.) Process Control		Yes	Yes	Yes	Yes	Yes
Nucleation		No	No	No	No	No
Subli-mation	t_{crit}	No	No	No	No	No
	End	Yes	Yes	Yes	Yes	Yes
Desorption		No	No	No	No	Yes
Costs		€	€€	€€	€	€€

Control System (PLC)

•Robust process control especially during dangerous failure situations (e.g. Power loss or SCADA Breakdown)

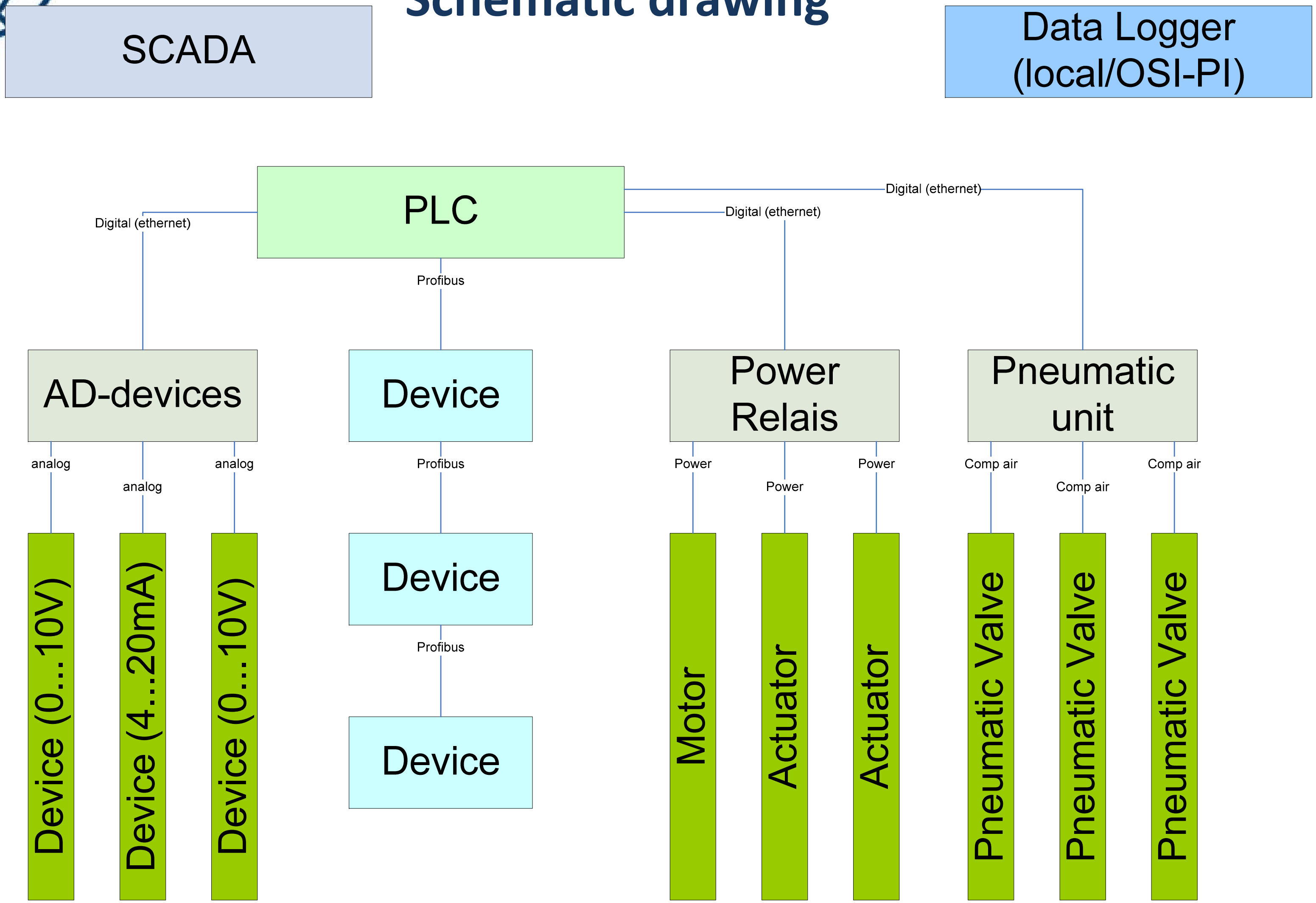
•Independent operation

•Data assembling for batch generation

•Central and in-time processing of all incoming and outgoing informations

•Reliable availability (99,9% enough?
Breakdown of plc => direct direct batch loss)

Schematic drawing



Overview – Control units

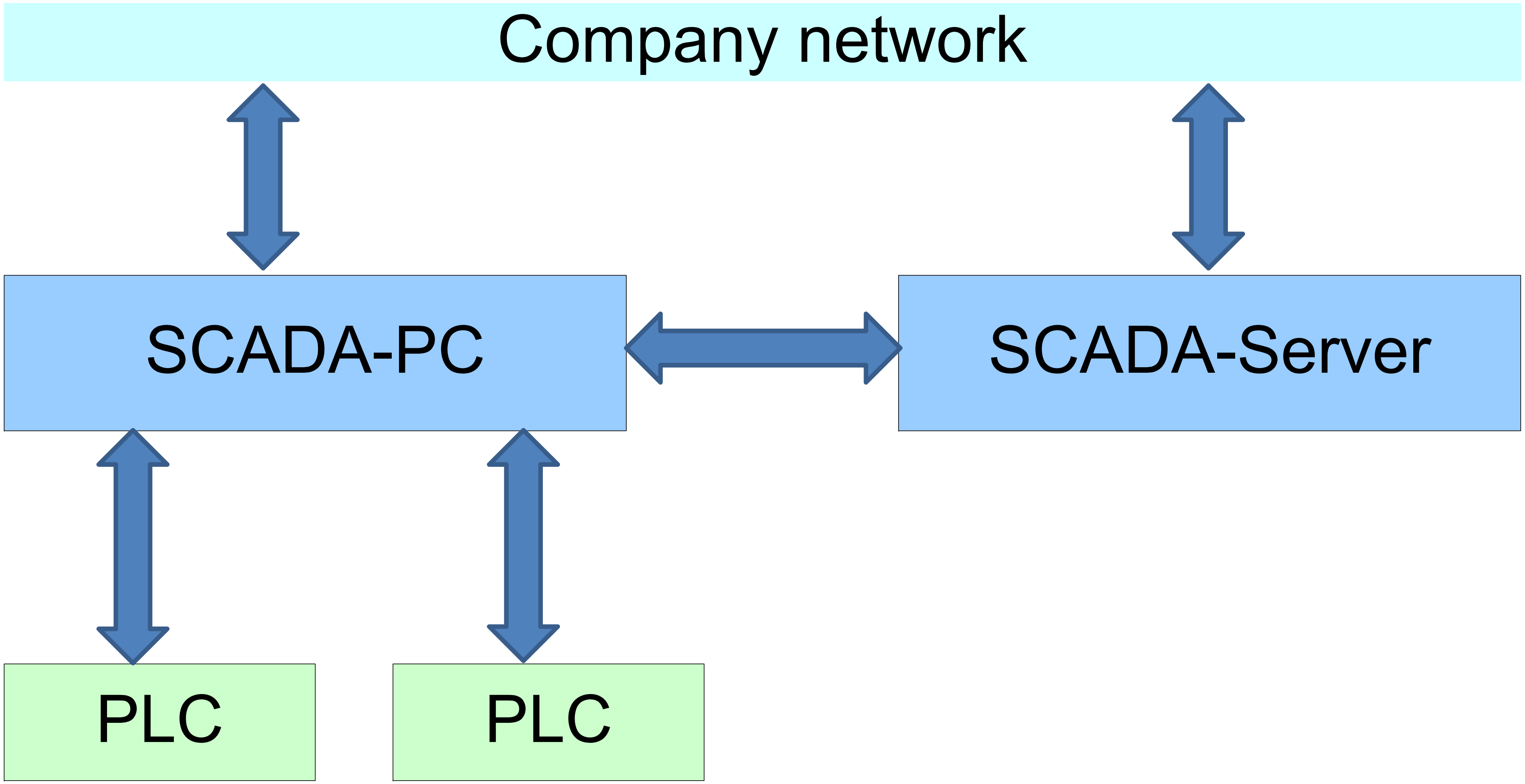
- PLC – Programmable Logic Control
- Europe vs. US ⇔ two completely different and independent worlds
  - Europe: Siemens is very common
  - US: Allen Bradley is very common
  - Further systems (as an also-ran) are available but not common for heav-duty
- Robust industrial standard, non-x86/x64-CPU based
- Very simple program-structure
- No recording functions, memory is restored when CPU is executed
- High-available redundant units are recommended
- An independent and dedicated power supply is current standard

SCADA

General Design Requirements – SCADA (Supervisory Control and Data Acquisition)

- User Interface for full control of process operation (HMI)
- Direct instructing unit to plc (e.g. recipe upload)
- Continuous data logging for process monitoring
- Generation of batch documentation
- Network based
- High hardware redundancy

Schematic drawing



Use industrial standard!

OK

Overview

- Common Systems are Windows / Linux based
- Process Data flow to recording units via SCADA should be avoided (direct transfer from plc to be preferred)
- GMP requires full accordance of SCADA software to 21 CFR 11

Thank you for your attention!

Questions?

Overview – Process supply system

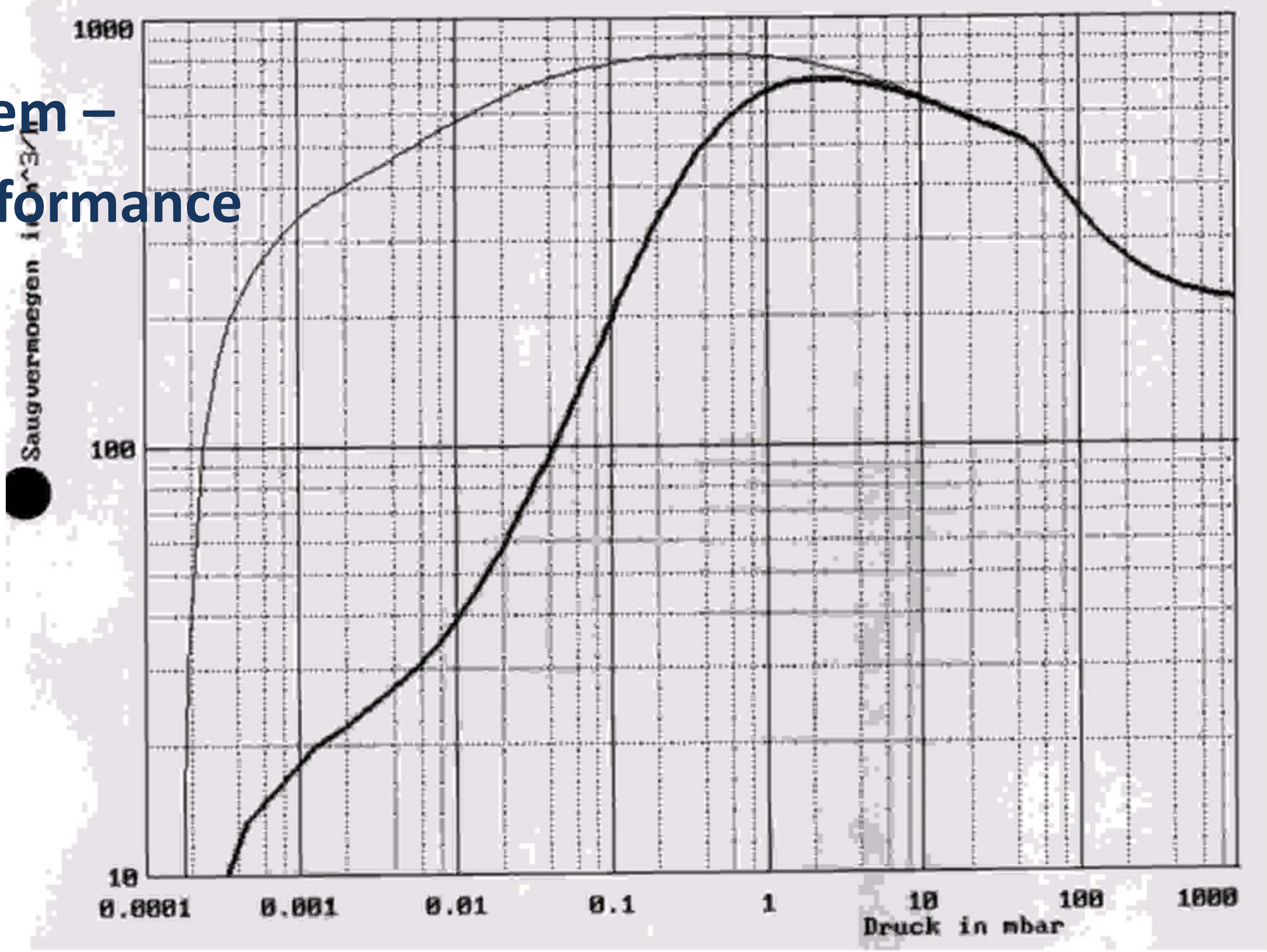
- Vacuum System
- Heat transfer System
- Refrigeration

Vacuum System

General Design Requirements

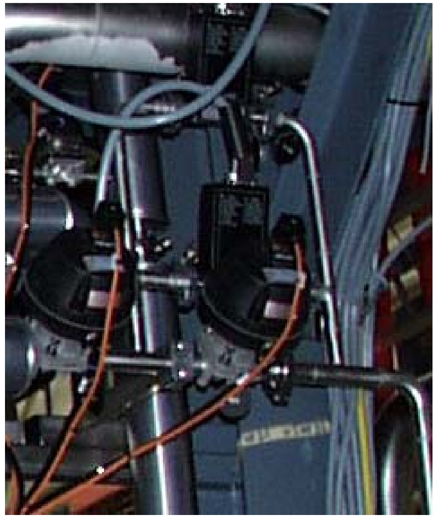
- Rapid evacuation from atmosphere to process vacuum (6 logs)
- Rapid evacuation from atmosphere to process vacuum (4 logs in 20min)
- Removal of steam and wet air after CIP/SIP (high air flow)
- Splash water may be pumped also (less than 20l/min)
- Preferably washable and sterilizable

Venting System – Vacuum Performance



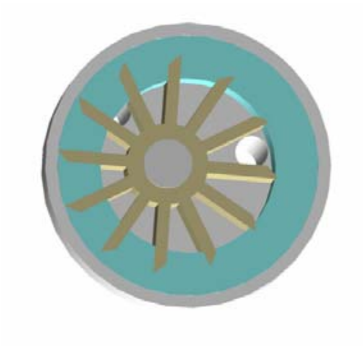
Vacuum System –
Flow Controller

- Pressure and Vacuum control

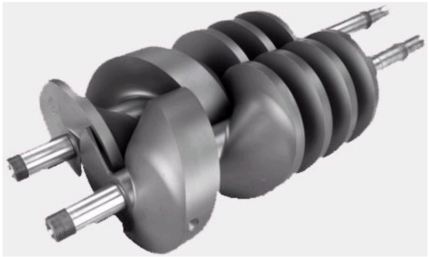


Overview off existing priciples

WRP

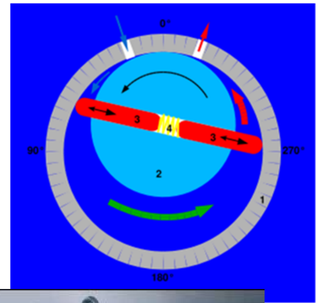


Screw



Roots

Rotary Vane



Overview off existing priciples

WRP	Screw	Roots	Rotary vane
• Minimum system pressure: <100mbara • Performance of 20...400m³/h available • Common evacuation time: 15...40min • Resistant against liquids and corrosive gases • Oilfree compression • High safety at compression of combustible gases • Simple concept, low maintenance • High cost specific performance • High power consumption • Conveyed medium and operating medium contact • Aggregate is far from being a „sterile" process member ***→ Pump is used at Turn-around cycles (Defrost, SIP, CIP) when Splash-water occurs and high air throughput is required***	• Minimum pressure: < 30µbara • Conveyed medium is carried through pump without contact to lubricants • Screw-Pumps can be cleaned inline • Inadequate minimum vacuum requires often an additional roots blower • Claw pumps come with high noise emmission • Screw pumps are not noisy • Due to high manufacturing requirements, all dry pumps are 60...100% more expensive • Their tolerance against water offers a high potential for aseptic processing with wet chambers and steam after cleaning & sterilization ***→ Screw is future technology, which can replace every other system***	• Roots Blower can not operate against atmosphere • Roots blower can be considered as "vacuum booster"	• Minimum vacuum: < 3 µbar • Minimum pressure sufficient for processes, performances decreases significantly below 100µbar • Robust design – long term proven • Low noise emission • Sensitive against water vapor, Liquids are forbidden • Conveyed medium and operating medium contact • Accumulation of toxic process residues in the lubricant • Frequent maintenance required

Heat Transfer System

General Design Requirements

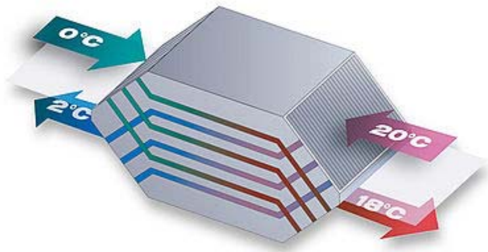
- Performant cooling (s. refrigeration) / heating rate supply ($\Delta\vartheta$ < 1,5K/min, unloaded) of the shelf system
- Operating range from -60…+60°C
- Adequate flow performance of the redundant pumps ($\Delta\vartheta$ < 1,5K)
- Robust Temperature Sensors at inlet & outlet

- Optional supply of indirect cooling for the ice condenser

$$\dot{V}_{Silicone\ oil} = \frac{\dot{m}_{Silicone\ oil}}{\rho_{(\vartheta),Silicone\ oil}}$$

$$\dot{Q} = \dot{m}\ x\ c_{p,silicone\ oil}\ x\ \Delta\vartheta_{in-out}$$

Components

Redundant Circulation pumps	Electrical Heating	Expansion Vessel	Plate Heat Exchanger
			

Shelf system is most important part of the silicone oil circuit

Refrigeration System

General Design Requirements

- **Performant cooling supply of the heat transfer system and direct cooling of the ice condenser ($\Delta\vartheta$ < 1,5K/min, unloaded)**
- **Redundant process performance**
- **Flexible arrangement of refrigeration units (each can take over every role)**
- **Integrated Failure detection system to avoid upcoming performance loss**

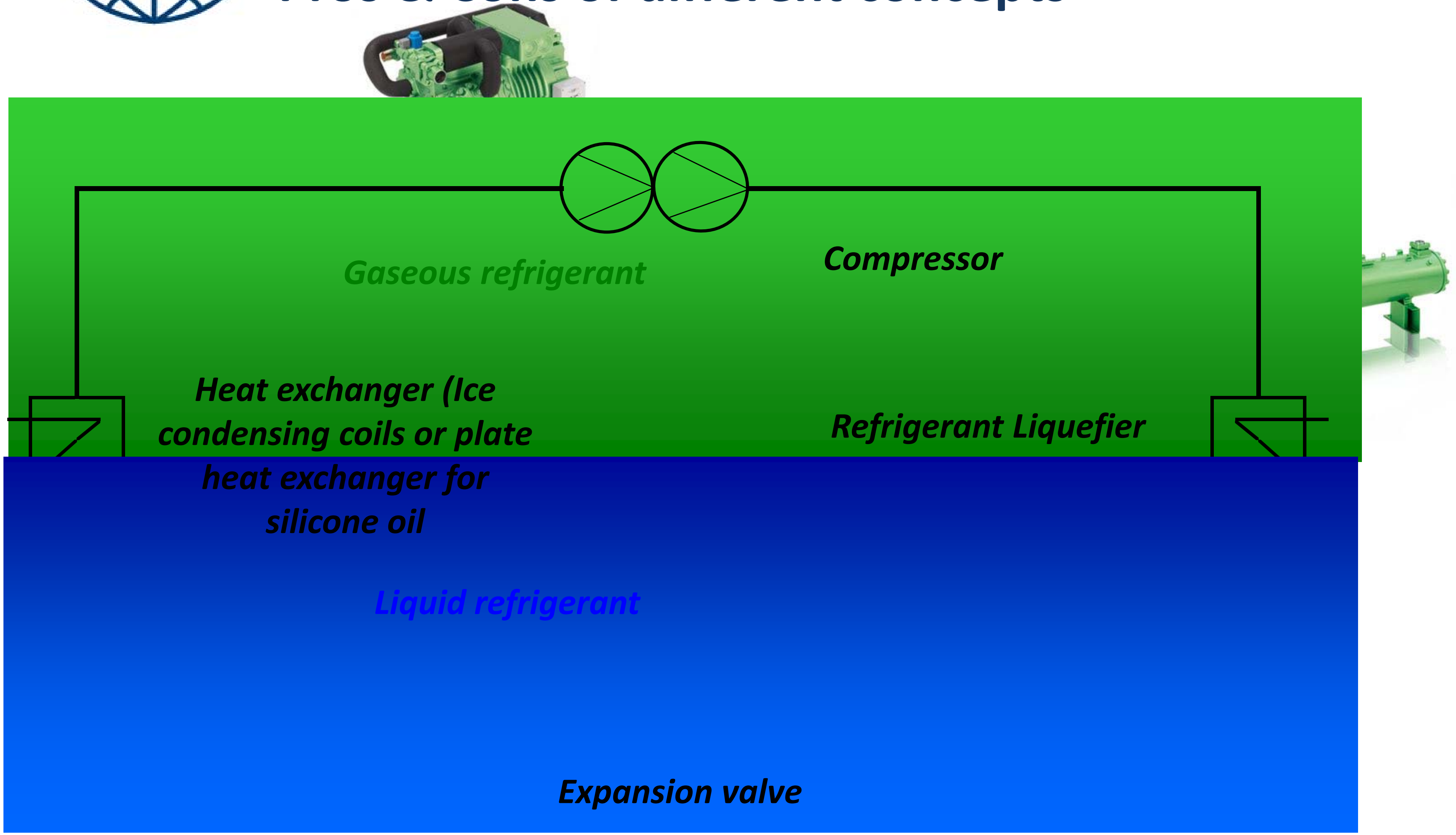
Pros & Cons of different concepts

	Liquid Nitrogen	Conventional refrigeration

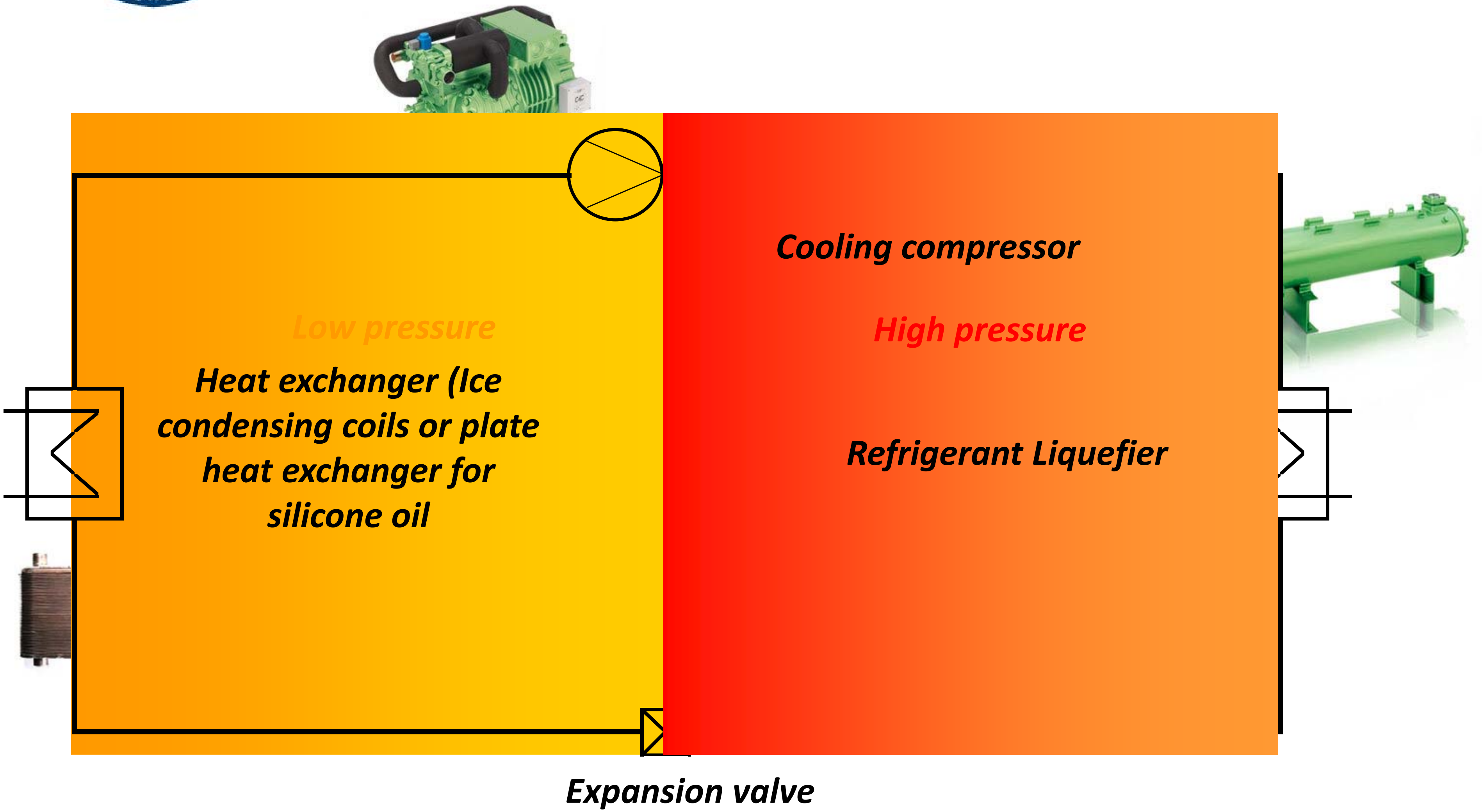
Advantages	• Reduced electrical power consumption
	• No cooling water circuit required
	• High cooling performance
	  • high cooling rates at shelves
	  • temperature controllable Ice Condenser
	• Drying of Products based on organic solvents
	• Very low noise emission
	• Low space requirements
	• Low Maintenance requirements
		• Independent Cooling supply
		• Safe operation without severe HSE / EHS / SHE risk

Disadvantages	• Economic LN_2 supply chain required • High investment costs for media supply system required • Additional Storage Tank required • Safety devices required – dangereous risk of oxygen depletion • Strong insulation required for safety reasons and better efficiency	• High electric power consumption • Cooling circuit required • Limited cooling performance below -50°C • High noise emission • High space requirements • Increased Maintenance requirements • Future ecologic Discussion expected due to use of refrigerants

Pros & Cons of different concepts



Pros & Cons of different concepts



Important EHS / SHE / HSE Regulatories for operation of industrial equipment out of GMP

- Pressure vessel directives
  - Pressure Equipment Directive 97/23/EC (PED)
  - ASME Boiler and Pressure Vessel Code (BPVC)
- Electrical directives (CE-Code)
- Directives for refrigeration equipment

Questions?

The material shown in this presentation does not represent the official opinion of Bayer or any linked subsidiary company

Bayer or any linked subsidiary company are not responsible for any content of this presentation

Thank you for your attention!