Process Design

Derive design from process requirements

PDA Europe
Development of a Freeze Drying Process

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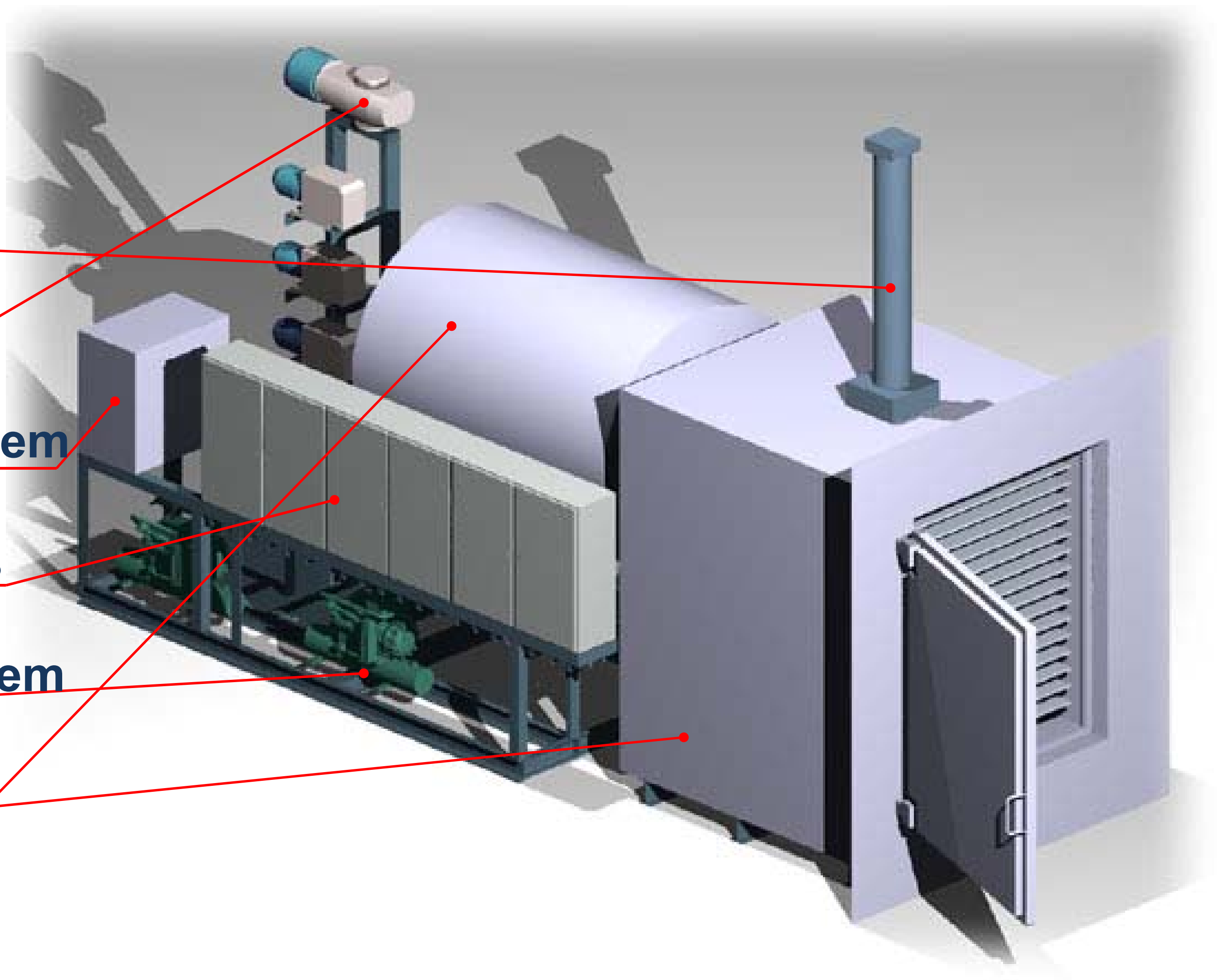
General Concept of a Freeze Dryer



Lyo-Process steps

- Loading
- Freezing & Evacuation
- Primary Drying / Sublimation
- Secondary Drying / Desorption
- Stoppering
- Unloading

=> Process Requirements determine Design (URS)

Loading – Main Design Requirements

- **Loading speed must correlate with filler speed**
- **Class A environment**
- **Pusher design should consider open vial**
- **Row-by-row to be preferred 100% position tracking**
- **Shelf package capacity must fit batch size**
- **Shelves to be temperature controlled**
- **Shelf interface**
- **Chamber to be pressure controlled**

Systems/Requirements to be considered:

- Cooling performance & heat transfer system accuracy & performance
- Controlled nucleation device
- Temperature distribution at temperature plateau
- Shelf package capacity must fit batch size
- Evacuation performance

Systems/Requirements to be considered:

- Cooling/heating performance & heat transfer system accuracy
- Main valve size
- Condenser performance & capacity
- Evacuation performance & vacuum control accuracy
- Devices for product temperature measurement & end point detection

Systems/Requirements to be considered:

- Heat transfer system accuracy
- Shelf temperature distribution
- Vacuum control accuracy
- Devices for desorption rate measurement

Stoppering – Main Design Requirements

Systems/Requirements to be considered:

- Pressure control accuracy
- Shelf temperature distribution
- Shelf evenness
- Maximum stoppering force
- Stoppering force homogeneity
- Devices for desorption rate measurement

Unloading – Main Design Requirements

- Unloading speed must correlate with Capper speed
- EU Annex 1 (Grade C with grade A air supply)
- Shelf interface
- Chamber to be pressure controlled

Requirement overview (URS => PRS)

	Loading System			Shelf System					Chamber		Condenser				Cooling System	Heat Transfer System		Vacuum system		Process control			Unloading System	
	Performance	Class A environment	Positioning Tracking	Capacity	Shelf interface (Loading/Unloading)	Temperature Distribution	Surface Evenennes	Force distribution	Pressure Control	Stoppering Force	Main Valve Size	Performance	Capacity	Operating temperature	Performance	Performance	Control Accuracy	Performance	Control accuracy	Product temperature	End Point detection PD	Desorption Rate measurement	Performance	Class C environment, (A- Air supply)
Loading	X	X	X	X	X				X								X							
Freezing				X		X			X						X	X	X			X				
Sublimation				X		X					X	X	X	X	X	X	X	X	X	X	X			
Desorption				X		X								X			X		X			X		
Stoppering				X		X	X	X	X	X														
Unloading				X	X				X														X	X

Aspects of “True-PAT”

- Process Homogeneity of Equipment
- Process Progress replaces Time as abscissa
- PAT implies Transfer & Upscale (“Right first time”)

Reasons for Process Inhomogeneity

- Manufacturing tolerances of vial format in connection with filling accuracy of whole filling system
- Variations of heat conductivity depending on vial surface at bottom
- Variations in Freezing
- Different environmental conditions of Freeze Dryer (FD) chamber (indefinite conditions at machine area / Edge effect etc.)
- Variation of vial quality due to supplier (long term)
- Variation of product composition (long term)

Conclusion:

- True PAT is available for all Lyo-Phases
- Not Every Process Device is compliant with True PAT, but still provides a valuable Development Tool for robust & reproducible cycles
- Time Based Cycles are Taylor-Made for the specific Lyo, Each Lyo has its unique optimum cycle (Ice temperature during sublimation varies with Lyo Design)
- The Variation in Progress vs. Time within the PAT-Process must be considered

Conclusions regarding Upscale & Transfer

- Freeze Drying must be considered as a “multi-process” taking place in each vial in a variation range
- Pilot and Production Plant require same equipment
  - Capacitance pressure transmitters
  - Same Thermo sensors (PT100/Thermocouples)
  - Same industrial standard
- Process model can be supported by use of archived process data
- Compatibility of Pilot FD to archived cycle data might require “historical” Sensor equipment e.g.
  - Pirani pressure gauge
  - Thermocouples AND PT100
- Reduction of design depending influences e.g.
  - Adjustable process parameters (high & low equipment performance)
  - Adjustable flow characteristics
  - Reduction of edge effect by temperature controlled walls
- Increase of Upscale Ratio allows reduction of required test material and general R&D-efforts

- **Defrosting**
- **Clean-in-Place (CIP)**
- **Sterilization-in-Place (SIP)**
- **Filter Test (FT) / Water-Intrusion-Test (WIT)**
- **Leak-Test (Vessel Integrity Testing)**

=> Process Requirements determine Design (URS)

- Complete discharge of condenser load

Desired business / commercial requirements:

- Process temperature below +60°C
- Defrosting time below 45min
- Waste water management
- Media free defrosting

- Fully automatic process control in batch recipe
- Removal of contamination by washing
- Robust and reproducible cleaning efficacy

Desired business / commercial requirements:

- Low consumption of steam
- Waste water management

Sterilization by steam condensation (121°C/20min)

- Fully automatic process control in batch recipe
- Robust and homogenious sterilization efficacy

Desired business / commercial requirements:

- Low consumption of cleaning water
- Waste water management

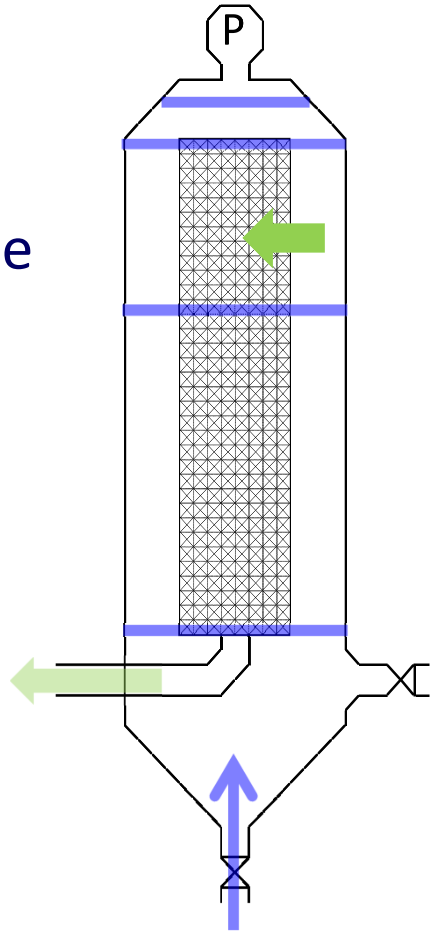
Test Procedures, Preparation Phase

Start of Intrusion Test: Water Inlet

Start of Intrusion Test: Isobaric Filling Phase

Start of Intrusion Test: Polytropic Filling Phase

Start of Intrusion Test: Stabilization Phase



⇒When stabilization time has elapsed

⇒all valves are closed

⇒The actual Water Intrusion Test begins

WIT/FT-Process – Parameter requirements

Formular of Flow

$$I = \frac{V_T}{p_0} \cdot \frac{\Delta p}{\Delta t} = \frac{[ml]}{[mbar]} \cdot \frac{[mbar]}{[min]} = \left[\frac{ml}{min} \right]$$

Comparison of "Different" Test Procedure specifications

	DIN 58356-2	Sartorius	PALL
V_T	Gas volume at reference pressure		
P_0	1.000mbar	1.000mbar	3.500mbar
Δp	Pressure Drop during Water Intrusion Test (normal: ~30mbar)		
Δt	Time of Water Intrusion Test (normal:10min)		
Intrusion Limit	------------------------	1,30ml/min	0,33ml/min
Temperature Jitter	±1°C	±1°C	±1°C
Reference Temperature	22 (±2)°C	20 (±2)°C	20 (±2)°C

- Fully automatic process control in batch recipe
- Test sequence according to specified conditions according to linked validation guide
- Steam-sterilizable
- Leak-testable

Desired business / commercial requirements:

- Inline test without filter dismounting
- Rapid dry precedure
- Parallel processing to leak test

To maintain vacuum integrity during freeze drying cycles, the system must be leak tight – at least theoretically

- **A common and all-over accepted limit is 0,02 mbar x l /s**

There is no regulatory standard specified for lyo vessels

- **The leak rate is indepent from the vessel volume and a direct gauge of the mass flow into the Lyo**

$$1\frac{\mu bar \cdot l}{s} = 4,1 \cdot 10^{-8}\frac{mol_{(20^\circ C)}}{s} = 1,2\frac{\mu g_{Air,(20^\circ C)}}{s}$$

- Fully automatic process control in batch recipe

Desired business / commercial requirements:

- Rapid evacution
- Parallel processing with filter test

	Vessel-System	CIP-System	SIP-System	Aeration & Filter System
CIP	X	X		
SIP	X	X	X	X
Leak test	X			X

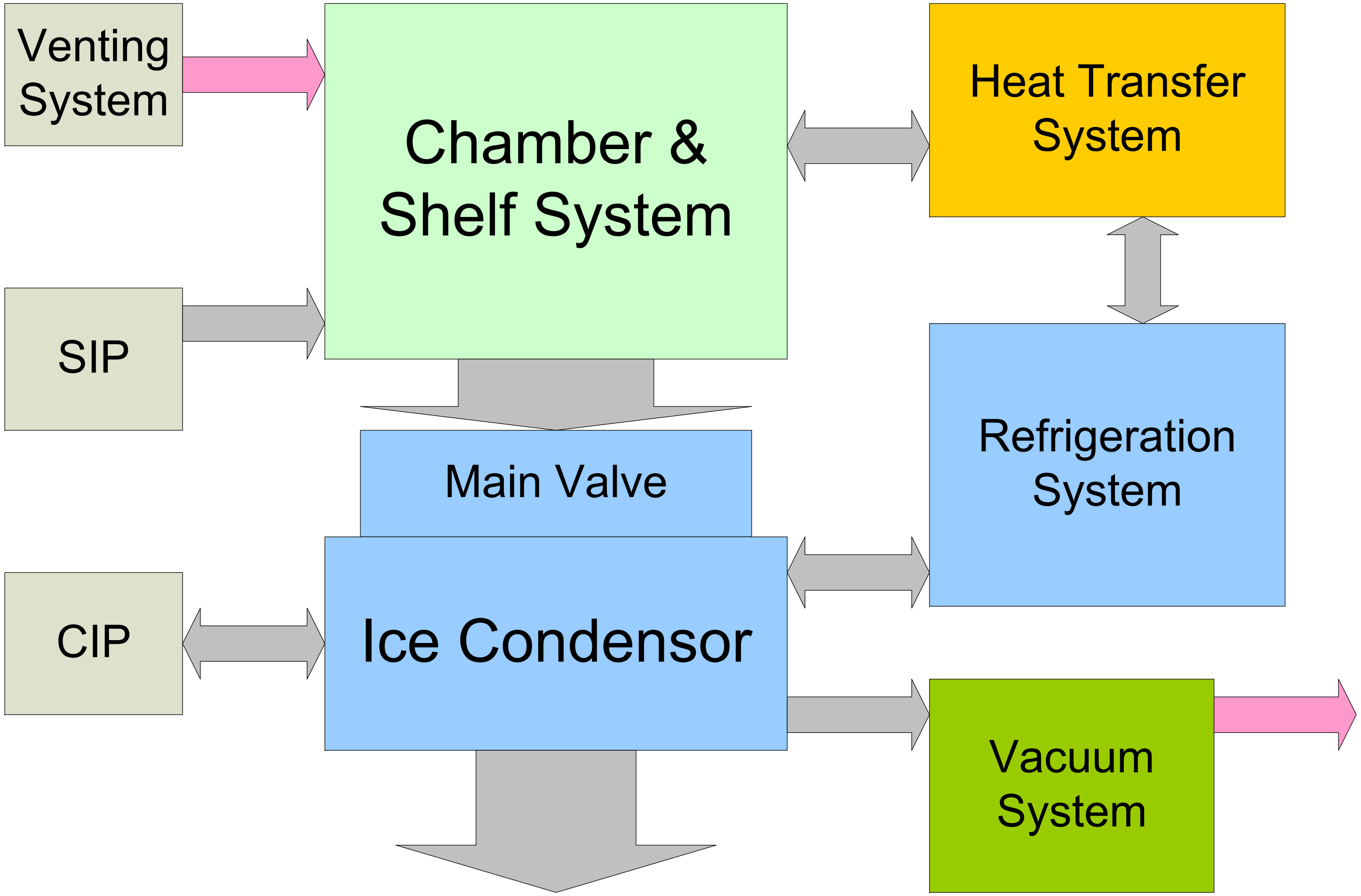
GMP-Requirement overview (URS => PRS)

	Chamber	Condenser	CIP-System		SIP-System		Aeration & Filter System		Vacuum system	Process control
	Pressure Control	Pressure Control	Water pressure control	Water Temperature Control	Steam Pressure Control	Drain Temperature Monitoring	Filter Pressure Monitoring & Accuracy	Temperature Control	Vacuum Accuracy	Process protocol
Defrosting		X								X
CIP-Process	X		X	X						X
SIP-Process	X				X	X				X
FT-Process		X					X	X		X
LT-Process									X	X

Business-Requirement overview (URS => PRS)

	Vessel System	CIP-System		SIP-System	Cooling & Heat Transfer System	Aeration & Filter System				Vacuum system	Process control
	Process Parallelization	Waste Water Management	Performance	Performance	Rapid Vessel Cooling	Aeration Performance	Drying Performance	Temperature Control	Process Parallelization	Performance	Process Parallelization
Defrosting		X								X	
CIP-Process		X	X							X	
SIP-Process	X	X		X	X	X			X	X	X
FT-Process	X					X	X	X	X		X
LT-Process	X					X			X	X	X

Interconnection of Lyo-Subsystems



The specific Performance of the Lyophilizer depends mostly on

1. Installed Aggregates and Subsystems
2. Supplied Media
3. Design

- All Aspects of Cycle Optimization have been shown previously
- Performance restrictions at production sized Lyos must be considered
- There is no significant optimization potential at a well designed cycle at a well designed Lyo

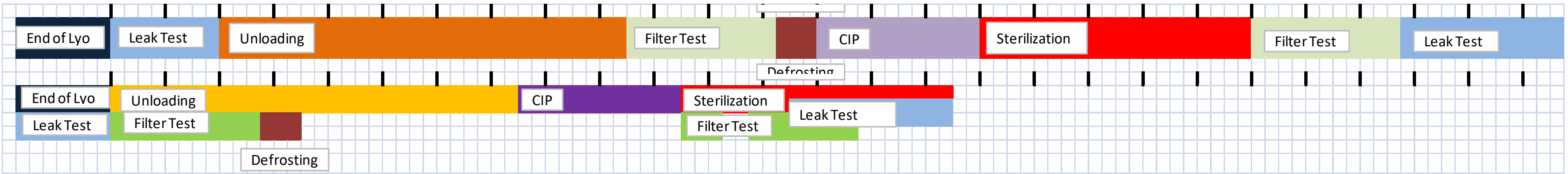
=> Further Potential comes with optimization of Turn-Around

Process Performance – Turn around cycle

1. Leak Test (previous to Stoppering)
2. Unloading
3. Filter Test
4. Defrosting
5. Cleaning (CIP)
6. Sterilization (SIP)
7. Filter Test
8. Leak Test

=> 30h for such Turn Arounds are very common

Process Performance



=> 15h for such cycles are possible

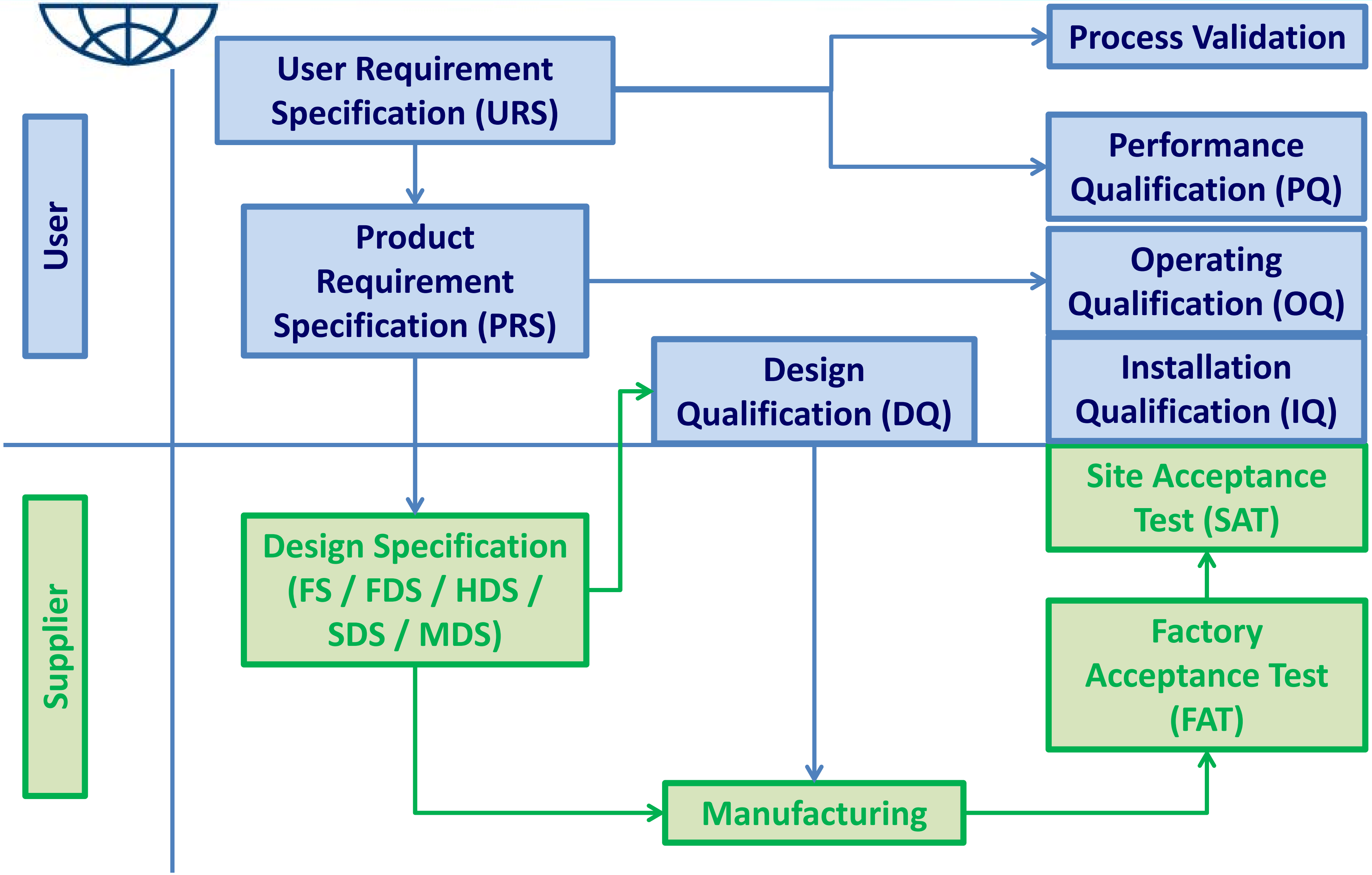
=> Further Cycle optimization potential comes by improvement of aggregates and media supply

=> 6h for Turn-Around after End of Unloading represents the limitation by current available Technologies
is it worth ?.???.??? € ???

Critical Media supply and aggregates vs. process

Process	Media	Aggregates
Leak test / Evacuation	N/A	Vacuum Skid
Leak test / Aeration	Pharmaceutical air	N/A
Filter Test / Drying	Pharmaceutical air	WRP
CIP / Door locking	N/A	WRP
CIP / Aeration	Pharmaceutical air	N/A
CIP / Cleaning	CIP-Water	N/A
CIP / Drying	Pharmaceutical air	WRP / Vacuum Skid
SIP / Heat Up	Steam	
SIP / Drying	Pharmaceutical air	WRP, Vacuum Skid
SIP / Recooling	N/A	Recooling system of vessels

Project Chart of a Lyo-Installation



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Thank you for your attention!

Any Questions?

Lunch Time