Freeze Drying Fundamentals, New Technologies, and Automatic Vial Loading

Christopher Fee, 7 Nov 2019 SoCal PDA

IMA LIFE
Aseptic Processing & Freeze Drying Solutions

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  - Vacuum System
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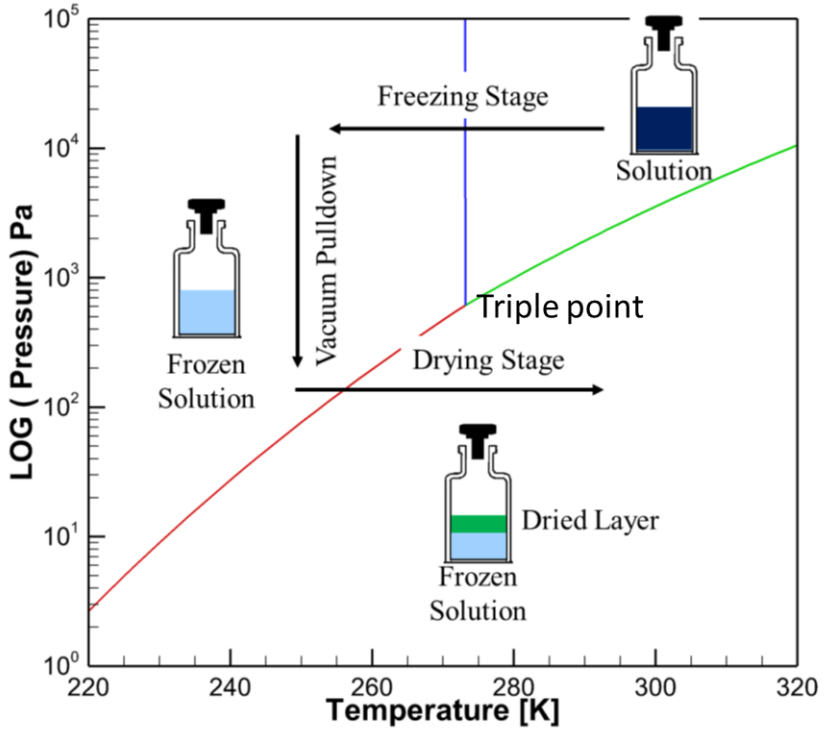
  - PAT tools
  - Mass Spec
  - Computational Fluid Dynamics
  - Lyo 4.0 and Data Analytics
  - Wireless Temperature sensors
  - Continuous Freeze Drying
- Automatic Vial Loading/Unloading Systems

WHAT IS FREEZE DRYING

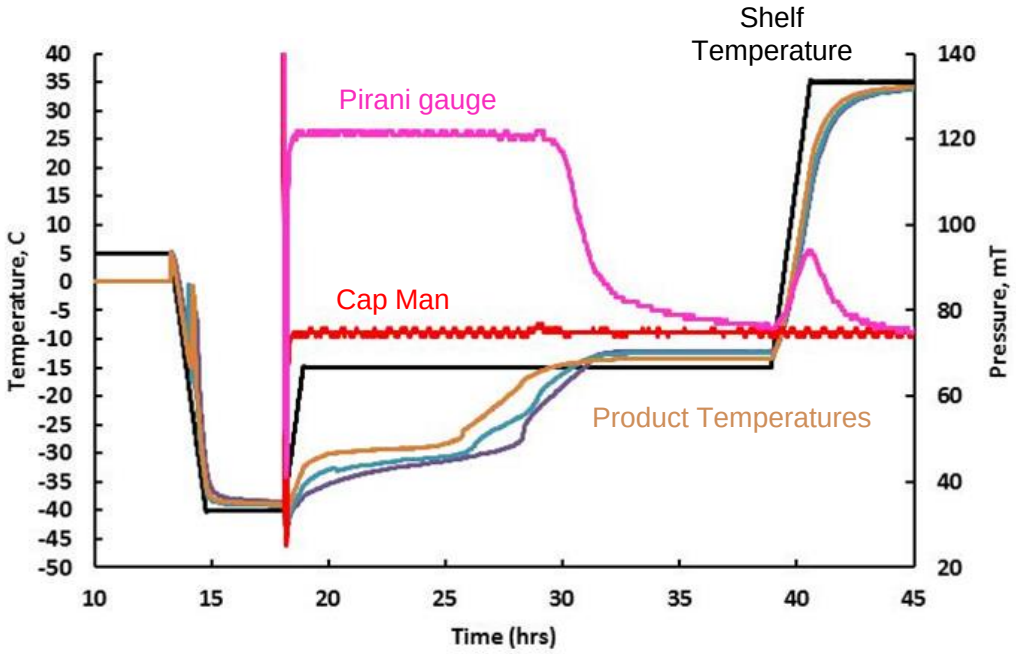


Phase diagram for H_2O

- Process to remove solvents from a solution while preserving the active drug substance
- Improve stability and maintain drug product potency
- 3 main stages: Freezing, Primary Drying and Secondary Drying
- Extremely energy intensive process: overall efficiency only between 3-5%

IMA PHARMA

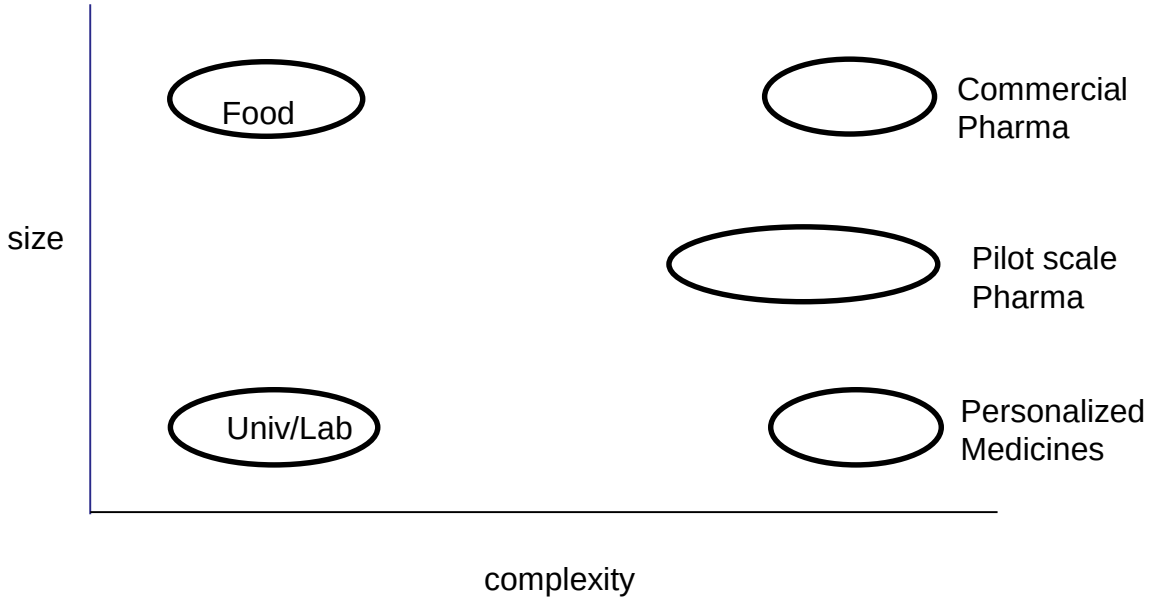
TYPICAL FREEZE DRYING RECIPE



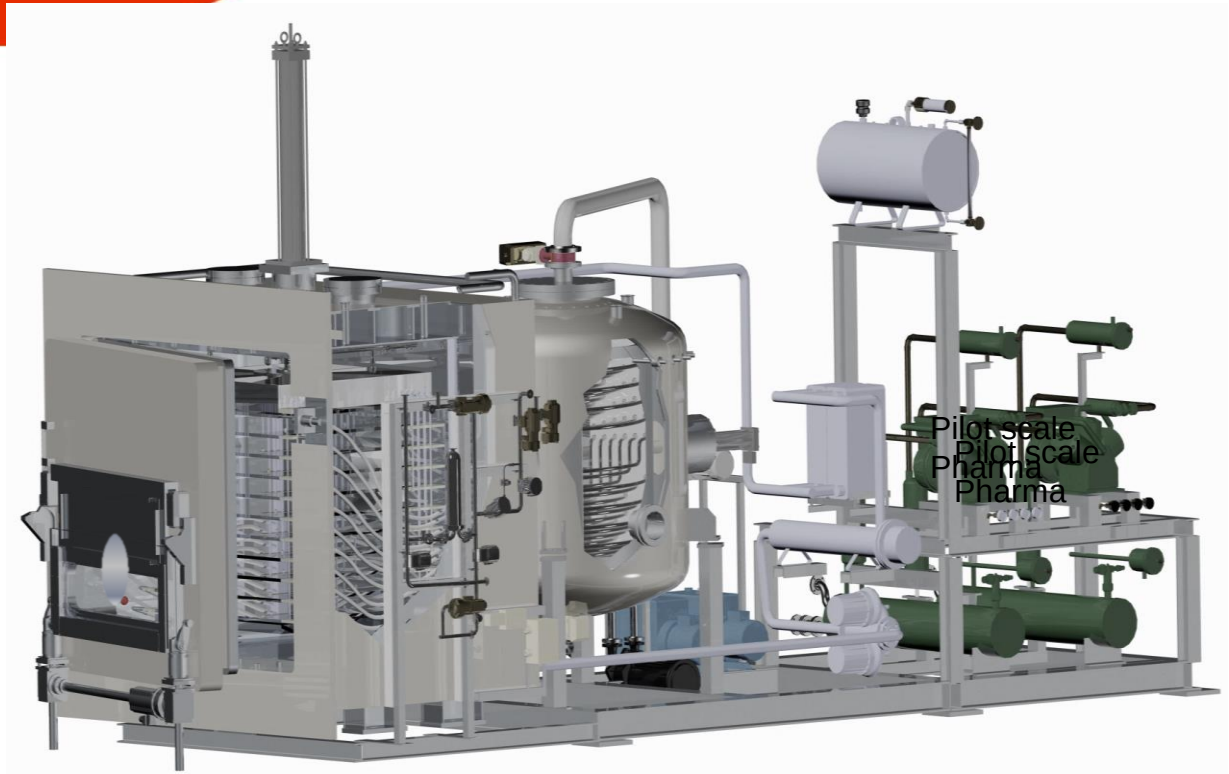
A typical freeze drying cycle, showing freezing, primary and secondary drying

FREEZE DRYER CHARACTERISTICS

Freeze dryers are characterized by both size and sophistication



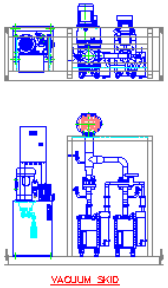
MACHINE FEATURES

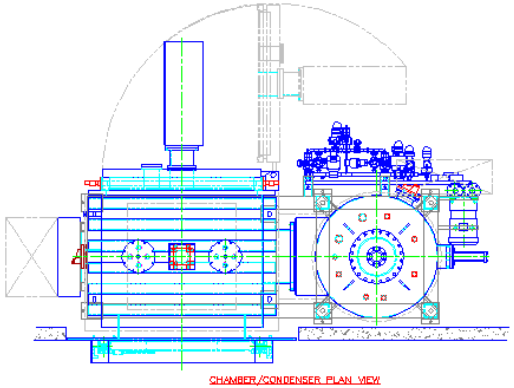


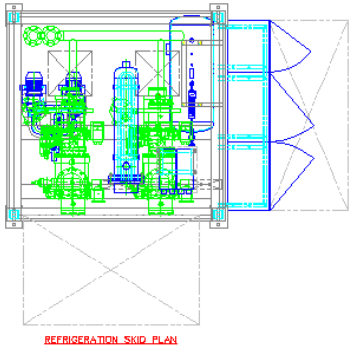
Pilot scale
Pharma

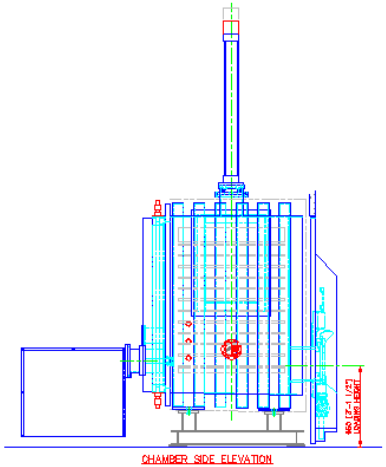
PRODUCT CHAMBER

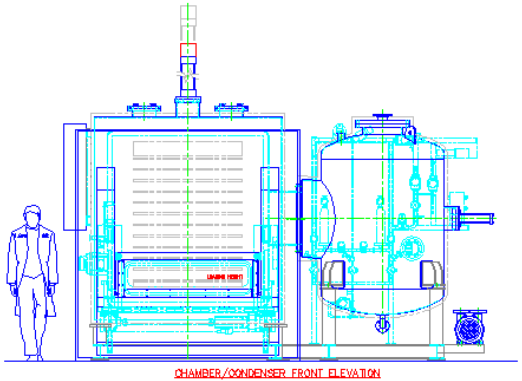
EXTERNAL CONDENSER

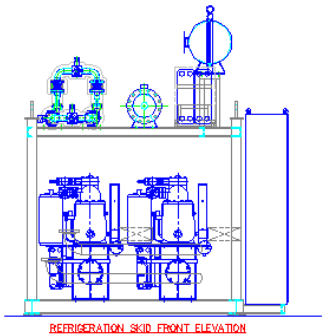




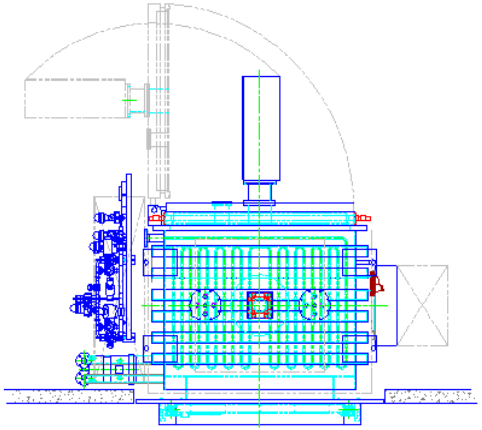




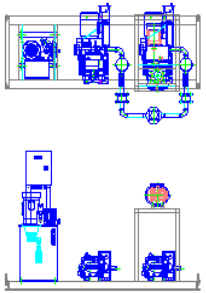




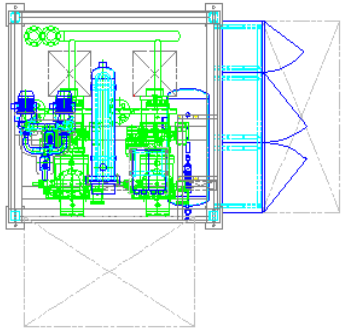
INTEGRAL CONDENSER



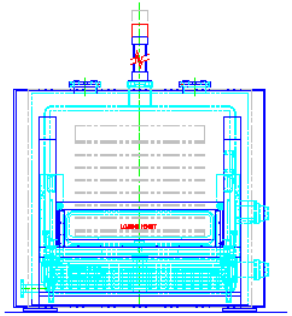
CHAMBER/CONDENSER SKID PLAN



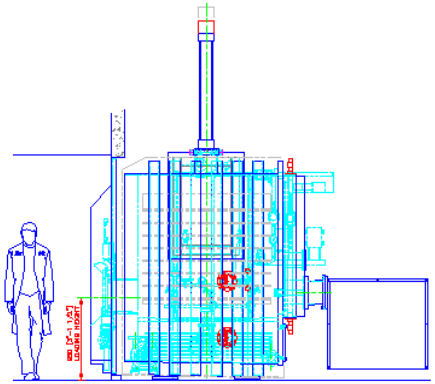
VACUUM SKID FRONT ELEVATION



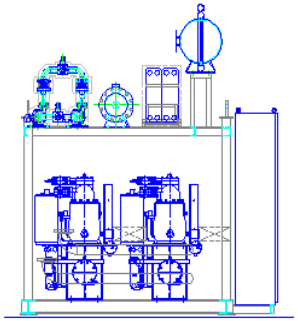
REFRIGERATION SKID PLAN



CHAMBER/CONDENSER SKID FRONT ELEVATION

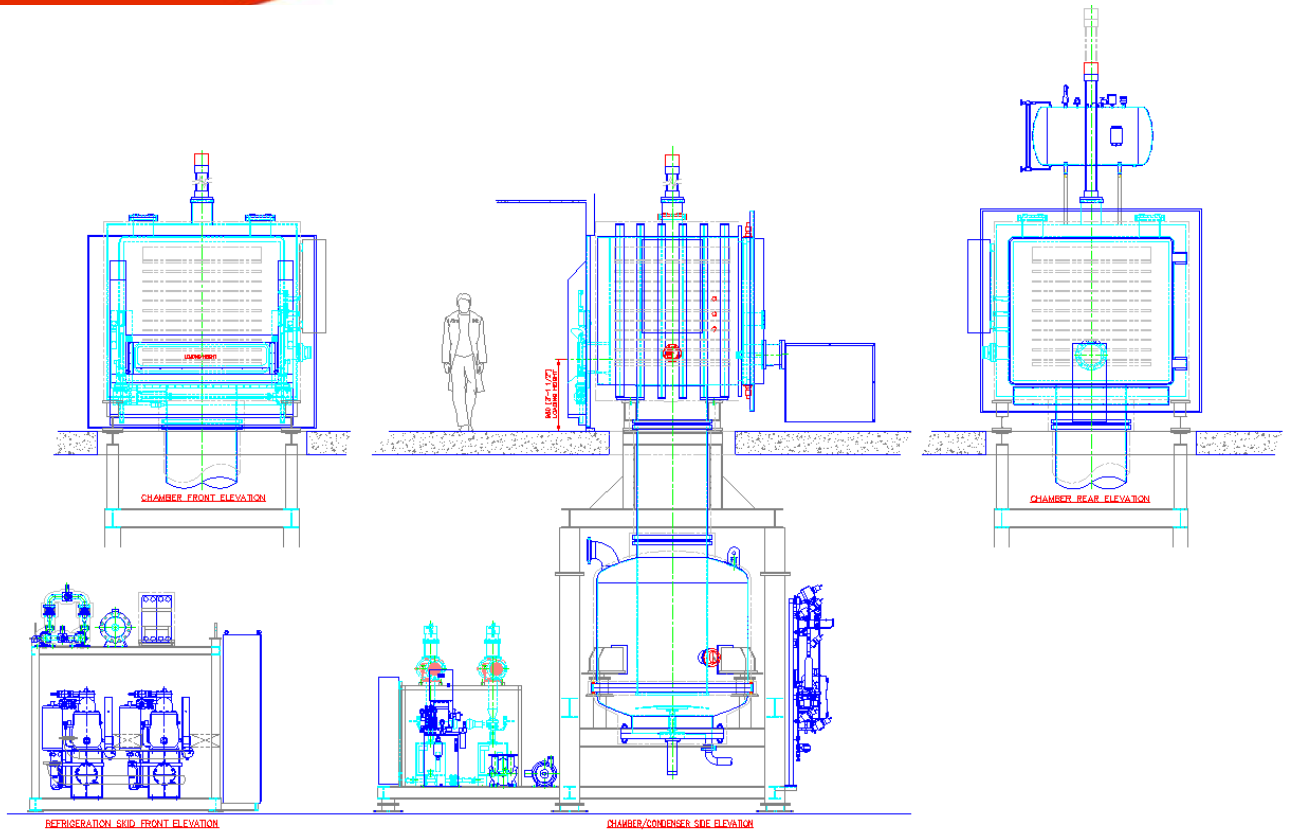


CHAMBER/CONDENSER SKID SIDE ELEVATION



REFRIGERATION SKID FRONT ELEVATION

2-STORY ELEVATION VIEWS



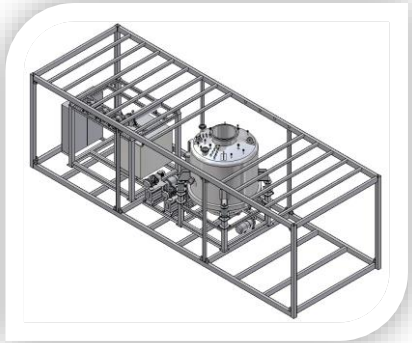
TWO-STORY BASIC CONFIGURATION

Above the Chamber:
- Hydraulic ram & expansion tank
- (HVAC)

Process Floor:
- Lyophilizing chamber
- (Isolator & Loading System)

Machinery Level:
- Chamber support frame

- CIP/SIP devices
- Condenser
- Refrigeration
- Electrical Panel



- Condenser
- Refrigeration
- Vacuum Pumps
- CIP/SIP Devices
- Electrical Panel

HEAT TRANSFER FLUIDS

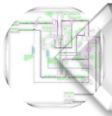
Numerous heat transfer fluids used depending on performance requirements and regulatory requirements: Typically it is Silicone Oil.

- 5 cSt
- 3 cSt
- 1.6 cSt
- SafeTherm HX™

Expansion tank fitted to account for thermal expansion and contraction of the fluid

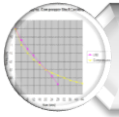
In the event the fluid selected has a flash point <126 °C, a nitrogen purge is installed

REFRIGERATION SYSTEMS



Reciprocating

Screw Compressor



LN2

RECIPROCATING COMPRESSOR

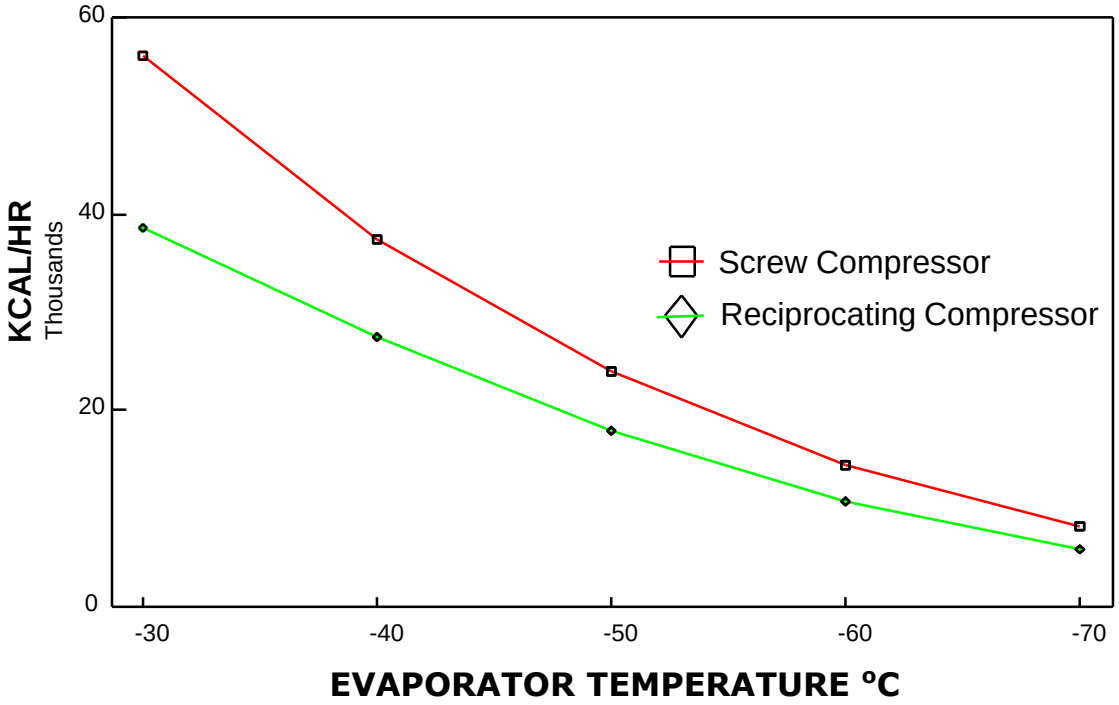
- Two stage, internally compounded, semi hermetic design
- Available in sizes from 5hp to 30 hp
- Full monitoring of suction pressure, interstage pressure, discharge pressure, discharge temperatures, oil pressure, oil temperature, etc.
- Full interlock for safe operation including suction pressure pump down at idle conditions, suction cooling during high temperature operation

SCREW COMPRESSOR

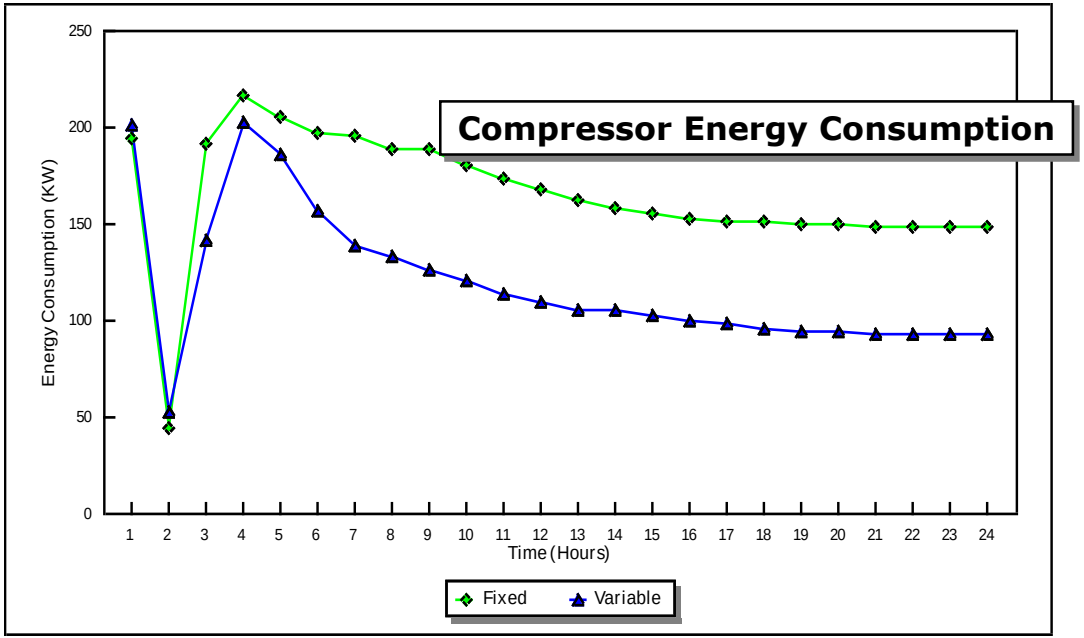
- Two stage, internally compounded, semi hermetic design
- Available in 30hp to 50 hp sizes
- Full monitoring of suction pressure, interstage pressure, discharge pressure, discharge temperatures, oil pressure, oil temperature, etc.
- Full interlock for safe operation including suction pressure pump down at idle conditions, suction cooling during high temperature operation

REFRIGERATION CAPACITY COMPARISON

Compressor Comparative Performance Chart



EFFECT OF VARIABLE SPEED MOTOR



LIQUID NITROGEN COOLING

Application

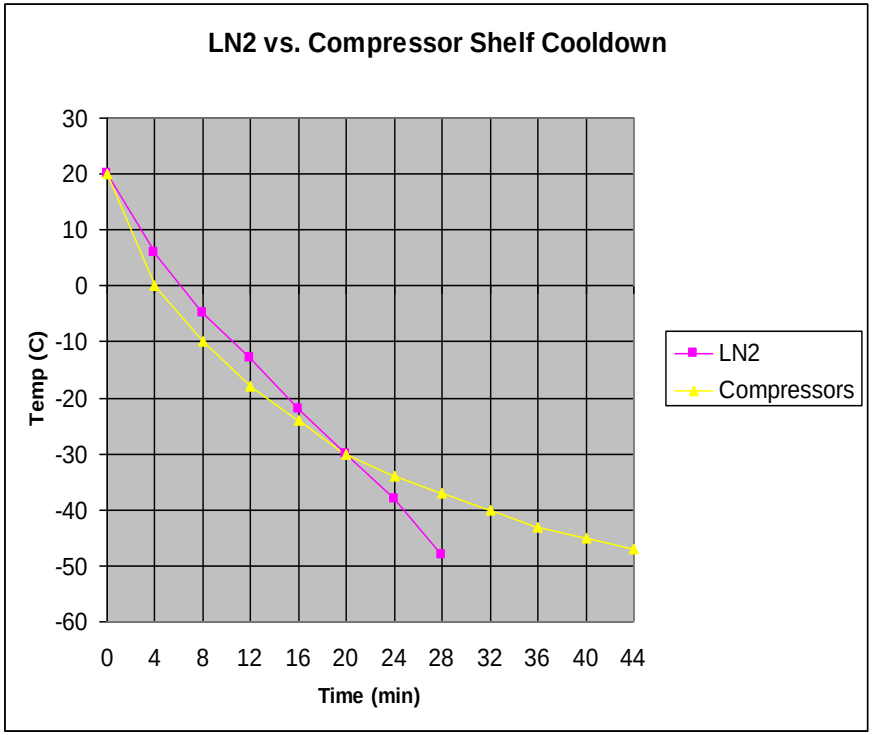
Shelf Cooling:
- Via heat exchangers utilizing silicone oil, or SafeTherm HX heat transfer fluid

Condenser Cooling:
- Direct injection of cold gas into coil assembly

Liquid Nitrogen offers performance advantages over conventional compression refrigeration

- Increased cooling performance
- Linear cooling vs. compressor decreasing capacity with temperature
- Less equipment space required
- Increased reliability, only two valves as operational components
- Low maintenance
- Environmentally friendly, zero GWP and ODP
- Low noise

INCREASED COOLING CAPACITY

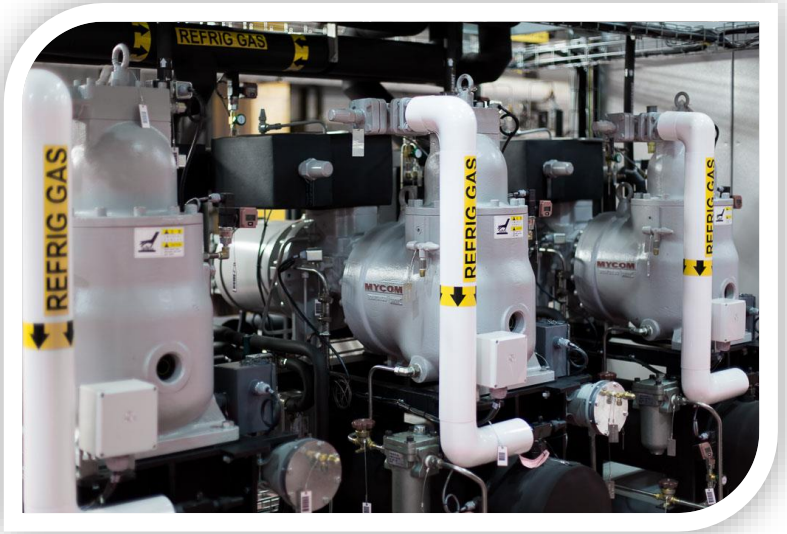


- Can increase cooling rate without large capital cost
- Graph shows cooling rate of same freeze dryer with LN2 versus 4 x 50hp screw compressors

REDUCED FOOTPRINT

Liquid Nitrogen systems have a much smaller footprint than mechanical refrigeration systems.

- *<u>Example</u>:*
  Compressor skid for Lyomax 30
- *LN2 system for Lyomax 30*



Dim in-[mm]	Length	Width
Compressor Skid	168″ [4267]	96″ [2240]
Veriseq® Skid	48″ [1220]	48″ [1220]

VACUUM SYSTEMS

Oil Sealed Vacuum Pumps

- Reliable technology
- Combined with a booster pump for increased pumping speed
- When equipped with two pumps, both ran during initial evacuation, only one runs after reaching set point

Dry Vacuum Pumps

- Screw or claw pump technology
- Combined with a booster pump for achieving ultimate pressure
- Ideally suited for non-aqueous solvents as there is no oil dilution risk
- Ideally suited for high potent product as there is no contaminated oil
- No risk of back-streaming
- Equipped with nitrogen purge for post operation drying

New and Advanced Technologies in Lyophilization

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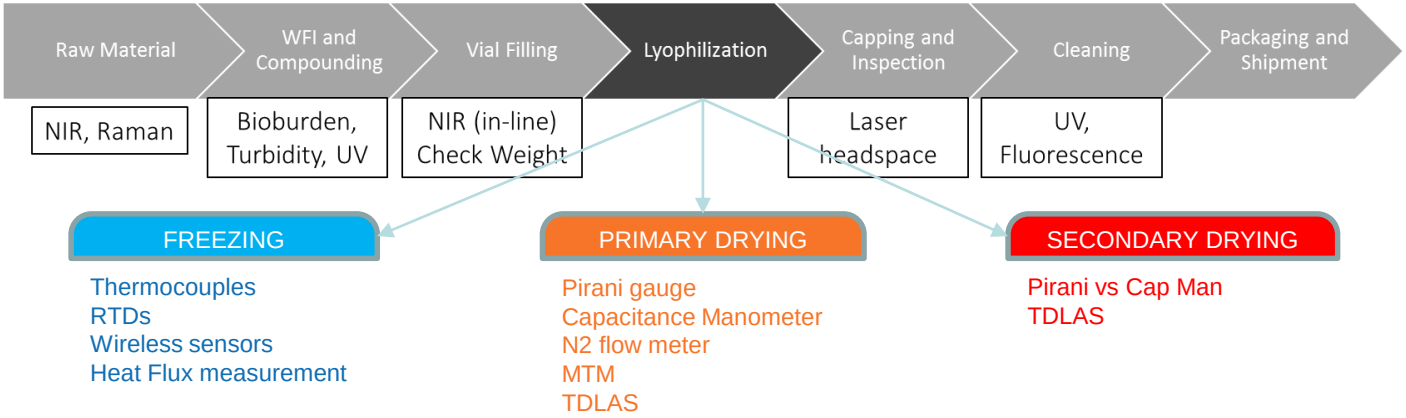
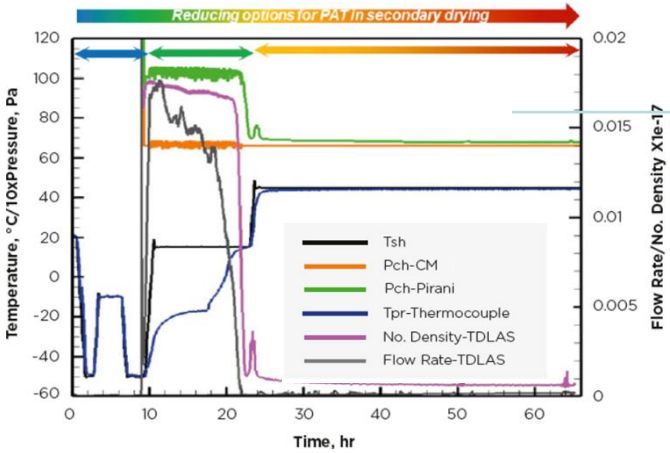
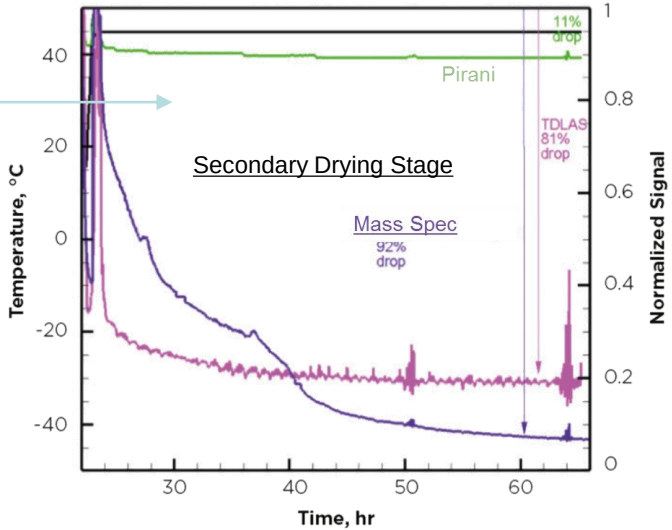
PAT Tools in Aseptic Process Monitoring



LIMITATIONS OF LYO PROCESS MONITORING





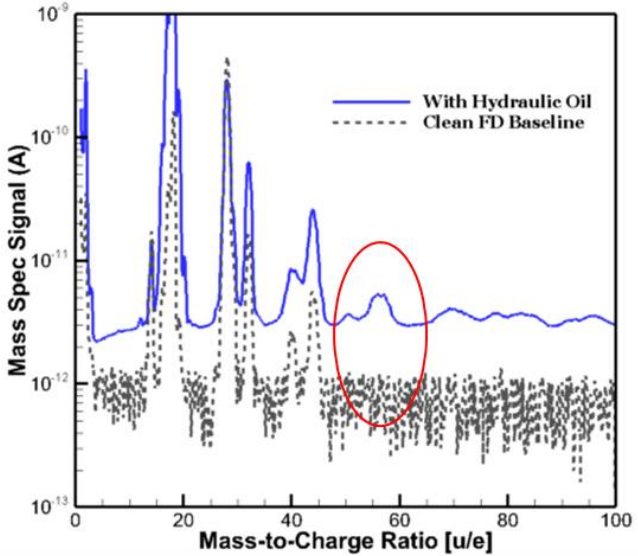
- PAT tools in secondary drying not able to provide enough resolution to monitor process
- No significant quantitative data available.

Mass Spectrometry → An additional PAT tool

MASS SPECTROMETRY FOR PROCESS MONITORING

- By focusing on obtaining real time scans using a residual gas analyzer, the composition of process gases inside the freeze drying chamber can be determined.
- The source of these gases, may be the product (such as water vapor), the process (such as nitrogen for pressure control) or equipment (such as contaminant leaks).

- **Only Mass Spec can differentiate these gases, and provide feedback for process control**.



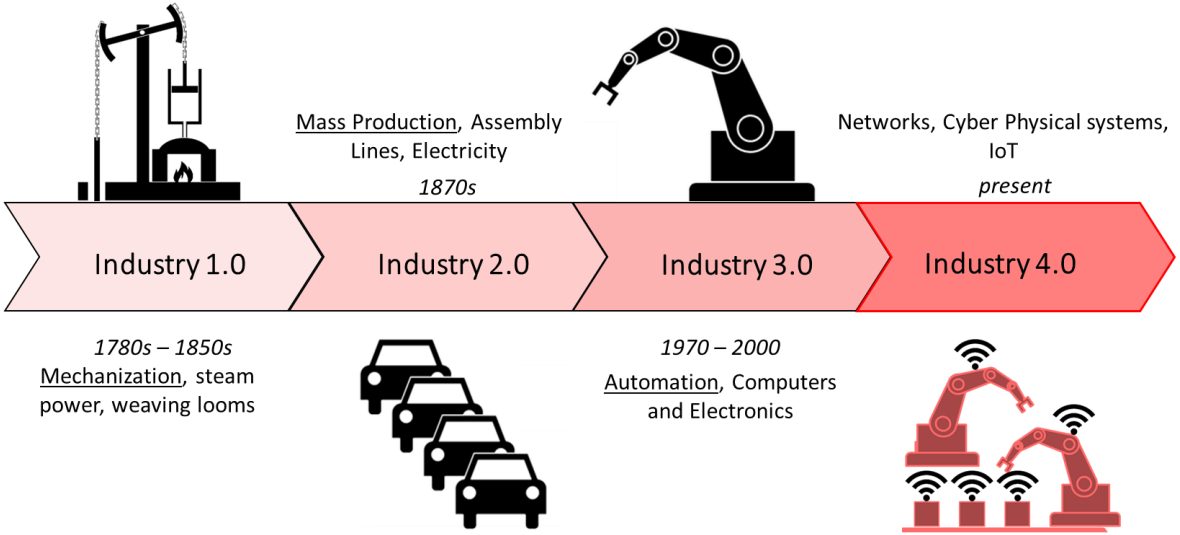
Detection of Unknown Oils

Use of Computational Fluid Dynamics in Freeze Drying

- Freeze dryer hardware and geometry affect the flow of vapor in the chamber and between the chamber and condenser.
- The design and configuration vary significantly at different scales. Production designs depend upon the available facility real estate and the required batch throughput.
- Optimal Sampling ports will depend upon the process and test conditions.
- A Physics based understanding of the process is crucial

The FD geometry matters, and CFD is essential for optimal Lyo design

PHARMA 4.0



Pharmaceutical industry: With the availability of multi-functional sensors & evolved process knowledge, implementation of continuous health monitoring of manufacturing process & equipment is feasible!

CURRENT FREEZE DRYER HEALTH MONITORING

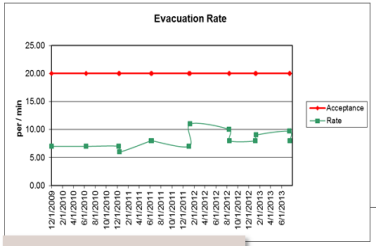
Preventive Maintenance

Reactionary Approach

Characteristics of Current Approaches

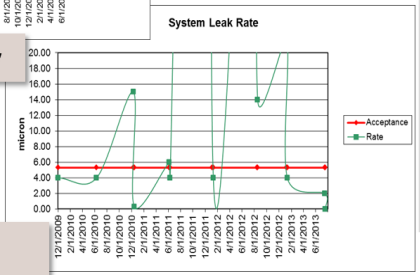
Increased Downtime

Frequent Scheduling Changes



Discrete Data only

Periodic Monitoring during scheduled PMs



No specific benchmarking

Maintenance & Equipment Usage Information

Maintenance Page 1

Device / Procedure	Units	Maint. Interval	Run Time	Time Since Last Maintenance		
Shelf fluid circulation pump 1	hours	4,320	40	Reset	40	Reset
Shelf fluid circulation pump 2	hours	4,320	3	Reset	3	Reset
Vacuum pump 1	hours	4,320	26	Reset	26	Reset
Vacuum pump 1 oil change	hours	4,320			26	Reset
Hydraulic pump	hours	4,320	4	Reset	4	Reset
Hydraulic pump filter	hours	4,320	4	Reset		
Liquid Ring Pump	hours	4,320	0	Reset	0	Reset
Sterile filter(s)	SIP cycles	10	0	Reset		
Calibration	days	182			91	Reset
Preventative maintenance	days	182			91	Reset

No Information on System Health

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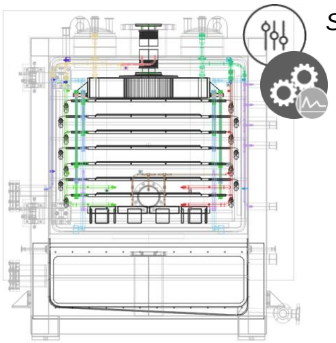
TYING IT ALL TOGETHER (LYO 4.0)

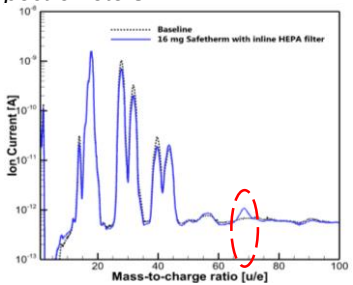


Sensors

Equipment

Process

✓ *Mass Spectrometers*



FREEZE DRYING

✓ *Computational Fluid Dynamics methods*

$$\nabla(\rho\vec{V}) = 0 \quad (1)$$

$$\nabla(\rho\overrightarrow{V\,V}) = -\nabla p + \nabla.(\tau) \quad (2)$$

$$\nabla\left(\vec{V}\left(\rho\left(e + \frac{1}{2}\vec{V}.\vec{V}\right) + p\right)\right) = \nabla.\left(\vec{q} + (\tau.\vec{V})\right) \quad (3)$$

$$e = h - \frac{p}{\rho} + \frac{\vec{V}.\vec{V}}{2} \quad (4)$$

Product

Post-Lyo Product CQAs monitoring using in-line or laboratory tools.

IMA PHARMA

Wireless Temperature probes

LIMITATIONS OF TRADITIONAL TECHNOLOGY:

Thermocouple: Single point, only at the bottom of the vial
PT100: takes average temp (not representative of real time process)
Both solutions are hardwired:

- Manual positioning is difficult (eg. center of Lyo shelf)
  - Extremely difficult with Auto Loading/Isolators

MARKET REQUIREMENTS

- *Wireless powered*
- *Battery-free*
- ***Less expensive solutions, suitable for lab***
- *Real time monitoring and* ***data management/visualization***
- ***Not limited to 16 sensors maximum***
- ***Not limited to single point of temperature detection*** *at the bottom*

IMA PHARMA

Continuous Freeze Drying

Traditional Freeze drying batch process = time consuming and energy intensive

- Drying rate is limited by poor heat transfer coefficient leading to long cycles.
- While the use of new process analytical technology has aided in-process understanding, most processes are run conservatively, making it inherently inefficient.

Thus, there is a need to re-think the heat and mass transfer for making the process more efficient.

Continuous Freeze Drying

Continuous Spray Freeze Drying process = high throughput and high cycle efficiency

The current development effort focuses on developing a robust yet gentle continuous aseptic process for spray freeze-drying.

LYnfinity can have a transcending impact on process efficiency related to Biologic drug substance storage, inhalation systems, antibiotics for bulk storage among others with direct powder dosing capabilities directly into product containment systems.

Continuous Freeze Drying

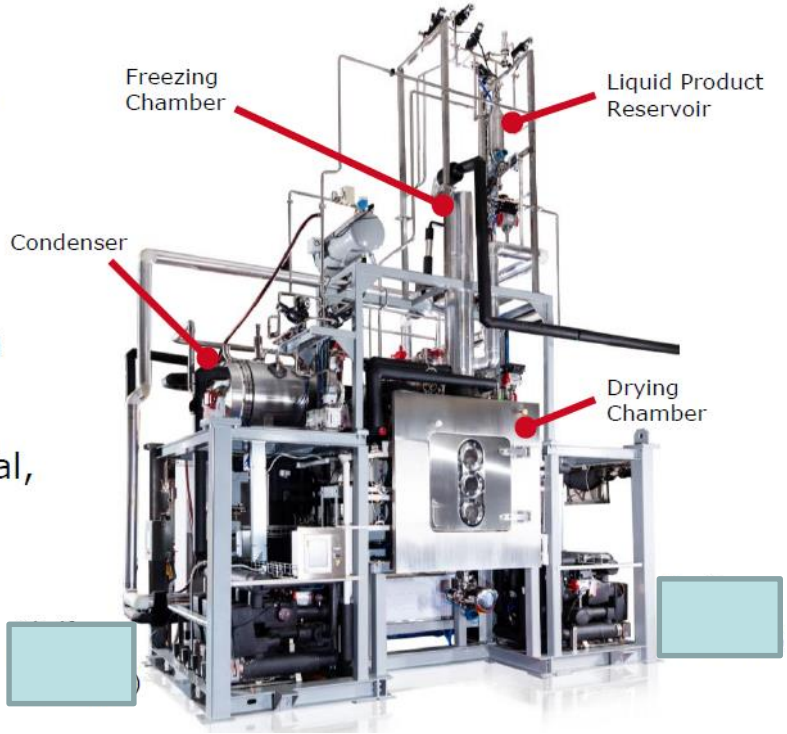
Continuous spray freeze drying that produces a dry powder in bulk form aseptically.

Technology

- Spray freezing in a freezing chamber.
- Continuous freeze drying of frozen particles in vibratory agitated drying chamber.

Resulting in dry powder ready for dosing into vial, syringe or inhaler.

Possibility to use CIP/SIP powder filler.



Continuous Freeze Drying

Benefits:

*Small freeze zone cooled by liquid nitrogen

•Split valve to allow simultaneous drying/product loading/discharge.

•Individual temperature control on each shelf.

•Split condenser for continuous condensing capability.

•Liquid nitrogen cooled condenser.

•A continuous process for greater throughput flexibility.

•Eliminates scale up and scale down challenges

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Automatic Vial Loading/Unloading

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THANK YOU FOR YOUR TIME!