楚天 TRUKING

Pharmaceutical Advanced Development and Case Analysis

- High-end preparation Freeze-Dry case Analysis

CONTENTS

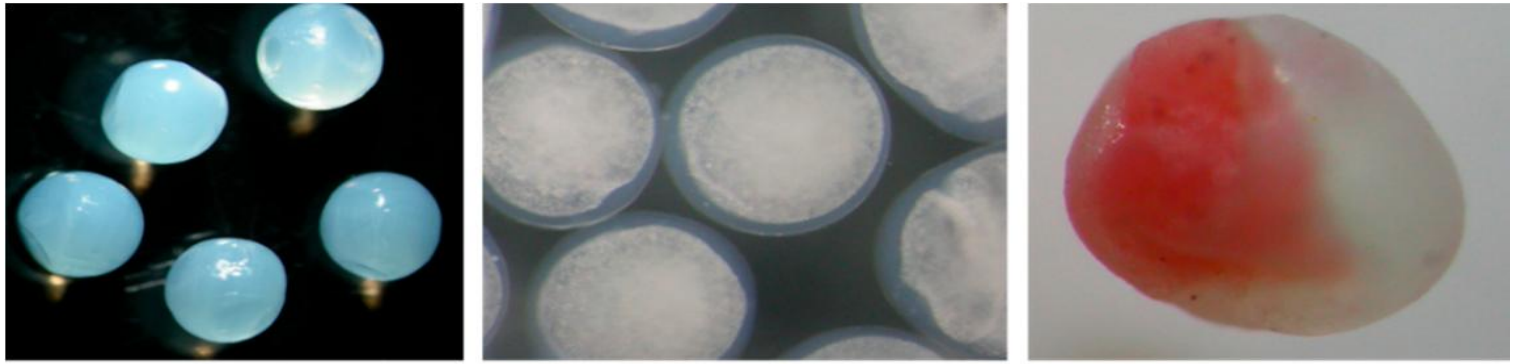
Part-1 Advanced formulations and development

Current Demands and focus of research in the field of drug carrier focused on:

- Improve the bioavailability of the drug,
- Prolong the time of drug action,
- Achieve targeted positioning in the drug, and
- Reduce the focus of poisonous side effects

Microparticles, Microspheres, and Microcapsules for Advanced Drug Delivery

- Widely used constituents of multiparticulate drug delivery systems
- Microparticles are generally in the 1–1000 m size range
- **Microparticles** may be characterized as either a homogenous or heterogenous structure depending on the formulation and processing
- **Microspheres** can be characterized as matrix systems in which the drug is homogeneously dispersed, either dissolved or homogenously suspended
- **Microcapsules** are heterogenous particles where a membrane shell is surrounding the core forming a reservoir



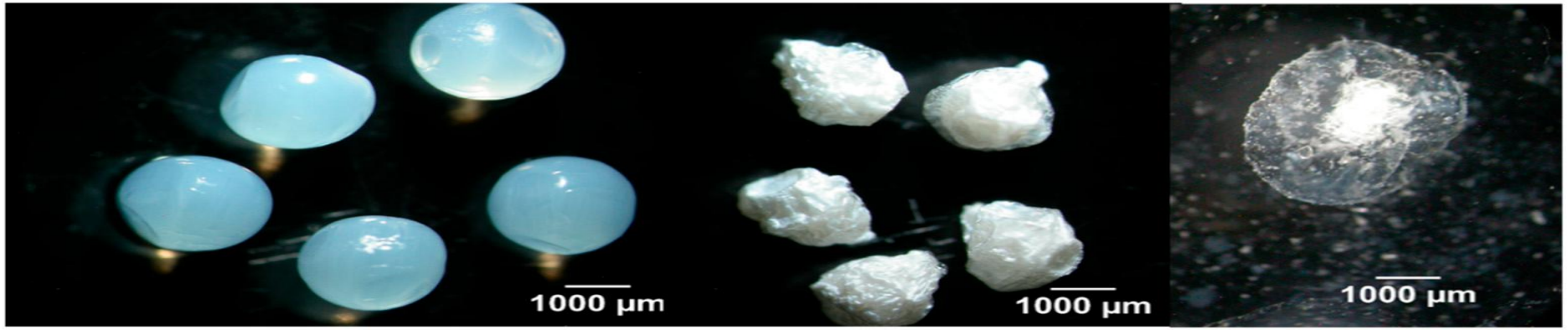
(a) (b) (c)

(**a**) microspheres, (**b**) microcapsules (C) Microparticle

Processes of particle formation

Most important methods for micro-encapsulations are:

- Air Suspension Method
- Spray Drying
- Coacervation
- **Freeze Drying:** Freeze-drying is successfully used in the microencapsulation of protein APIs. Lyoprotectants or cryoprotectants (trehalose, dextran) can stabilize API molecules during the process by replacing water, forming a glassy matrix, reducing molecular mobility by establishing hydrogen or van der Waals bonds between the molecules



(a) (b) (c)

Figure: Calcium alginate microparticles: (**a**) initial (prepared using a Büchi B-390 Microencapsulator), (**b**) freeze-dried, and (**c**) reconstituted in a pH 6.8 phosphate buer (60 min).

MICROSPHERE

Advantages

- The microspheres have the ability to bind & release the high concentration of the drug
- Due to the smaller size & spherical shape they could be injected into the body.
- The microsphere morphology allows the controllable variability in the drug release & degradation.
- The microspheres provide a constant & prolonged therapeutic effect.
- The microspheres reduces the dosing frequency & thereby improves the patient compliance.
- The better utilization of drug will improve the bioavailability & reduce the incidence or intensity of the adverse effects
- They have Improved protein & peptide drug delivery system
- Simple method of preparation. It enhance biological half-life

Disadvantages

- The controlled release formulations generally contain the higher drug load & thus any loss of the integrity of the release characteristics of the dosage form may lead to the potential toxicity
- From the variety of factors like food & the rate of transit through the gut the release rate of the controlled release dosage form may vary
- The dosage forms of this kind should not be chewed & crushed.
- From one dose to another there is differences in the release rate.

Part-2 Freeze Drying Process Technology Research and development sharing

- Stability - retention ratio after reconstitution during freeze drying
- Stability of the storage process

Low temperature protection mechanism

- Freeze-drying of medicines is a multi-step process, which will produce a variety of stresses to denature the medicines, such as low temperature stress, freezing stress and drying stress. The freezing stress can be divided into the formation of dendritic ice crystals, the increase of ion concentration, the change of pH value and the phase separation.
- In order to protect the activity of drugs, protective agents for active substances are usually added to the drug formulation. It needs to have four characteristics: high glass transition temperature, poor water absorption, low crystallization rate and no reducing group

Protein common protective agent

Commonly used protector has the following types of substances:

- Sugar / polyol: sucrose, trehalose, mannitol, lactose, glucose, maltose, etc .;
- Polymer: HES, PVP, PEG, glucan, albumin, etc.
- Anhydrous solvent: ethylene glycol, glycerol, DMSO, DMF, etc.
- Surfactant: TWEEN 80, etc .;
- Amino acid: L-serine, sodium glutamic acid, alanine, glycine, sarcosine, etc.
- Salt and amines: phosphate, acetate, citrate, etc

Prescription lyophilization characteristics: process parameter determination

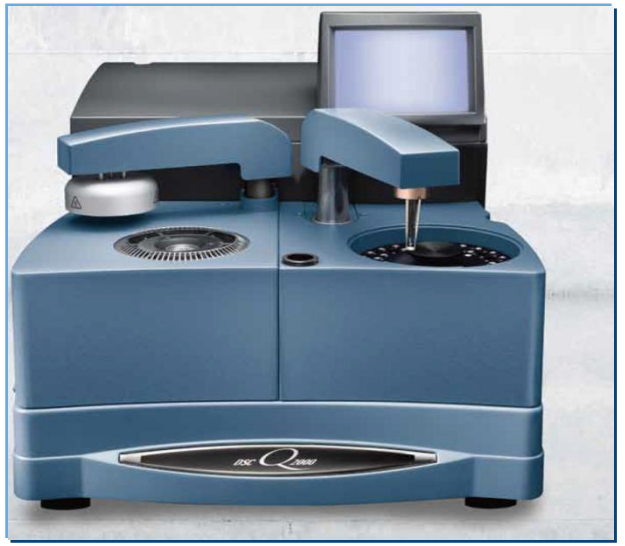
- Detection of collapse temperature (Tc)
- Glass-state transition (TG) temperature measurement
- Experimental data and report

Truking Science and Technology Freeze Laboratory

Application of lyophilized microscope:

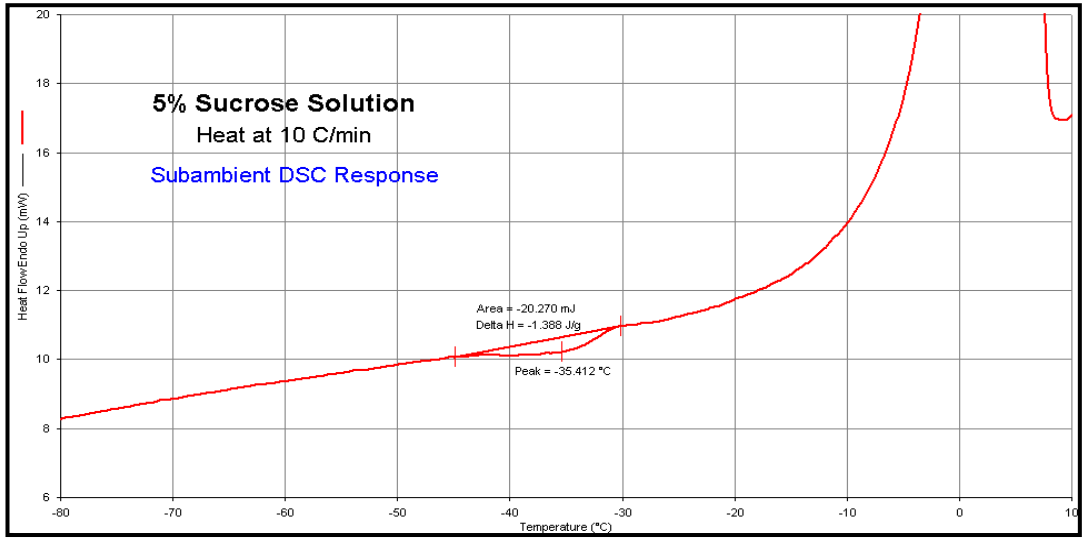
During sublimation, it can directly observe the collapse temperature Tc to ensure successful sublimation.

Truking Science and Technology Freeze Laboratory



Differential Scanning Calorimetry application:

- DSC uses complex phase transition in frozen solution into heat capacity and dynamics, which is beneficial to optimize formulation and process parameters.
- Accurately analyze the physical state and structure of the frozen solution, select more reliable process temperature
- It is possible to measure the change of the structure over time and temperature, which will optimize the freeze-drying temperature to optimize the dry cycle.
- It can measure the effects of additives and concentrations on drying rates, and improve the development of new dosage forms or dosage forms.



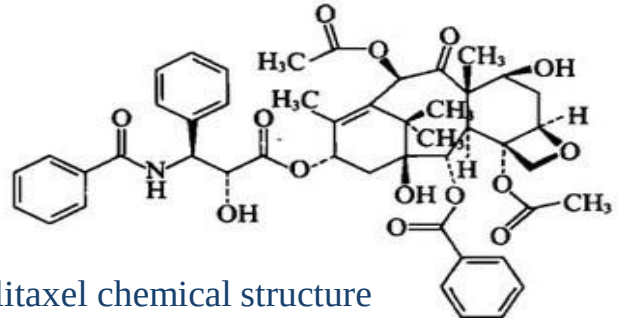
Heat capacity step change peak

Taking paclitaxel as an example:

Paclitaxel, also known as taxol, is the best natural anti-cancer compound that has been discovered so far. As a diterpene alkaloid compound with anti-cancer activity, paclitaxel has a novel and complex chemical structure, a wide range of Significant biological activity, new and unique mechanism of action, and scarce natural resources have made it extremely popular among botanists, chemists, pharmacologists, and molecular biologists, making it a worldwide focus in the second half of the 20th century. Anti-cancer star and research focus.

- Sample information: The sample is a liposome suspension with a particle size of 150-160nm, containing paclitaxel and trehalose.
- Customer demand: the average particle size of the product after freeze-drying does not exceed 15nm, D90<400nm, PDI does not increase significantly, moisture content after freeze-drying <2.5%, freeze-drying cycle <6 days
- Loading method: use a 50ml vial with a volume of 20ml
- The key parameters of the product are measured by DSC and freeze-drying microscope: glass state brick changing temperature, eutectic point temperature and collapse temperature.

Collapse Temperature	Eutectic point Temperature	Glass Transition Temperature
-21.4℃	-28.83℃	-28℃



Paclitaxel chemical structure

20210316 Apply to freeze drying test:

According to the freeze-drying Recipe, start the freeze-drying machine

Lyophilization Recipe

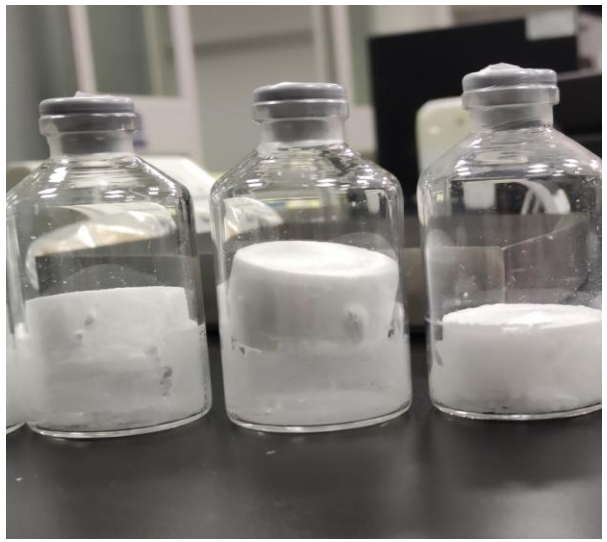
STEP TYPE	TEMPRATURE	VACUUM	SET TIME
Freezing	-10℃	/	5min
Freezing	-10℃	/	30min
Freezing	-40℃	/	5min
Freezing	-40℃	/	4H
Evacuation		5Pa	
Drying	-15℃	5Pa	6H
Drying	-15℃	5Pa	44H
Drying	25℃	5Pa	3H
Drying	25℃	5Pa	9H

IN CONCLUSION:

- The sample was completely lyophilized and the moisture content was 0.93%, and the lyophilization cycle was 69 hours. The product bottle has a powder, crystalline, but not uniform.
- The average particle size of the product was 17 nm after lyophilization, and D90 was 380 nm, and PDI was not significantly amplified.

20210319 Apply to freeze dry the test:

In view of the fact that the average particle size of the product after the last freeze-drying is greater than the customer's demand, this experiment adopts the super-cooling + quick-freezing mode to extend the super-cooling retention time and make the product crystal more delicate. In the sublimation drying stage, step sublimation drying is used to solve the problem of product flying. Powder and product spiking phenomenon.



Lyophilization Recipe

STEP TYPE	TEMPRATURE	VACUUM	SET TIME
Freezing	-15℃	/	5 min
Freezing	-15℃	/	1H
Freezing	-50℃	/	5min
Freezing	-50℃	/	4H
Evacuation		5Pa	
Drying	-15℃	5Pa	8H
Drying	-15℃	5Pa	36H
Drying	5℃	5Pa	2H
Drying	5℃	5Pa	5H
Drying	25℃	5Pa	2H
Drying	25℃	5Pa	6H

IN CONCLUSION:

- The sample was completely freeze-dried, with a moisture content of 1.63%, and a freeze-drying period of 66 hours. The product is easy to take off the bottle, and the crystal is fine and uniform
- After freeze-drying, the average particle size of the product is 13nm, D90 is 380nm, and PDI is not significantly enlarged

Liposomes are suspensions, low temperature protection agents, and pre-free cooling rates have an important impact on their stability.

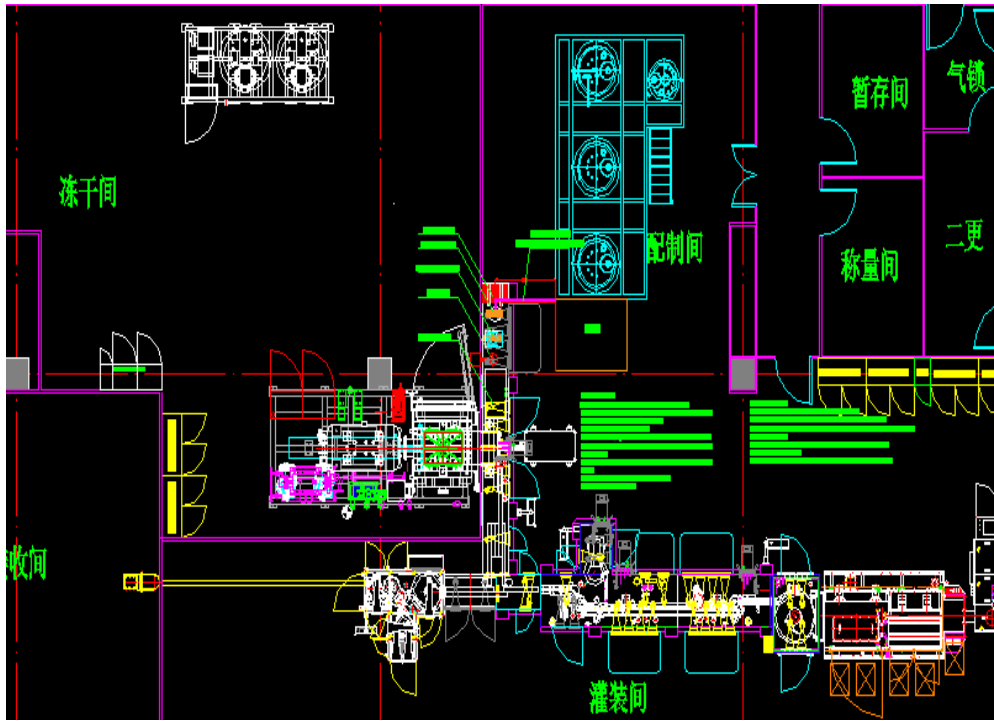
Part-3 Case Analysis

- Microspheres and liposome freeze-dried equipment case sharing

Case 1

Realization of water needle process description :

Microsphere suspended materials-microsphere collection-transfer barrel (fixed volume and quantitative of microspheres and water for injection)-filling buffer tank (quantity of freeze-dried protective agent and water for injection)-filling and docking



Realize freeze-dried formulations:

Vial Unscrambler → Vial Washing Machine (Ultrasonic) → Three Water Three dry air wash → Depyrogenation Tunnel (Preheating > High Temperature Sterilization Drying > Cooling) → Vial Filling → Half Stoppering → Lyophilization → Full Stoppering → Capping machine

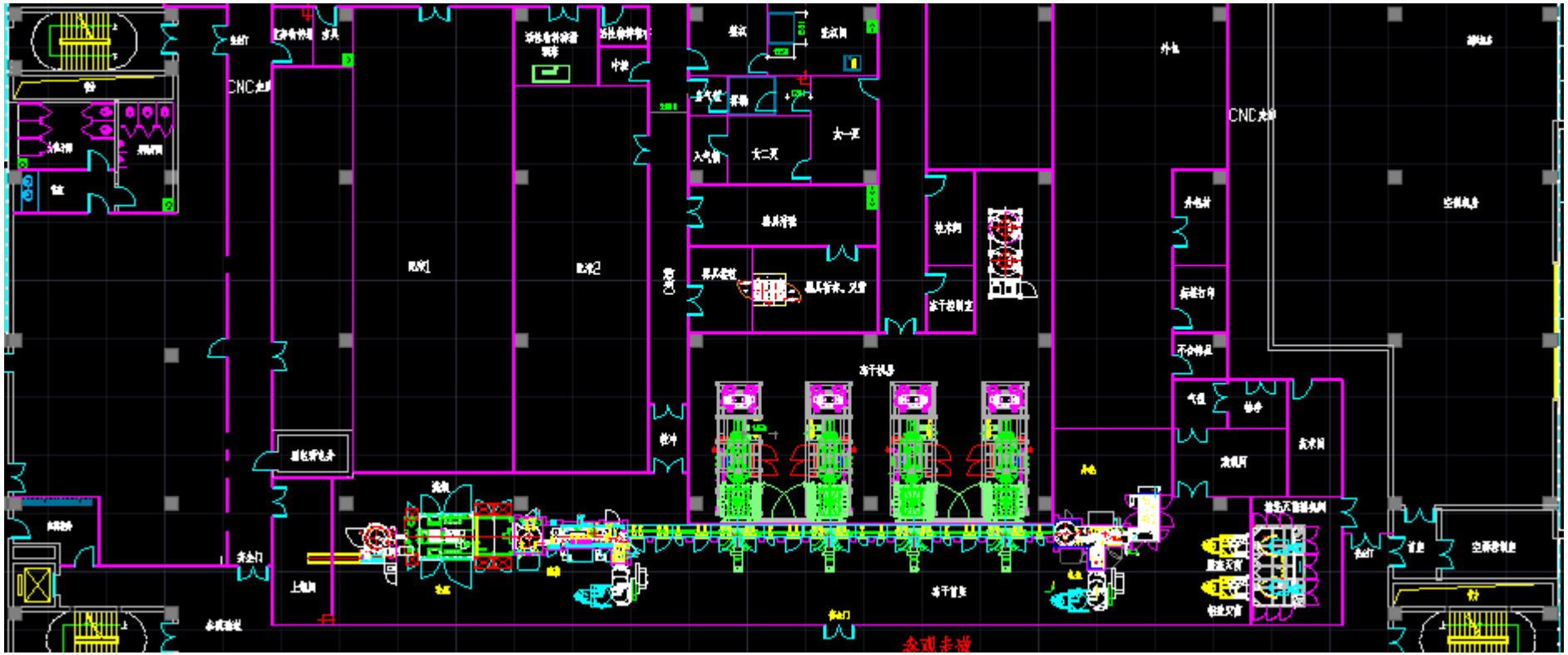
Realization of powder(API) injection process description:

Suspended microspheres—microsphere collection—transport barrel (fixed volume and quantitative of microspheres and freeze-dried protective agent)—plating—automatically enter the freeze dryer—automatically exit the freeze dryer—transport barrel (microsphere collection, crushing, mixing)-Filling docking.

Case 2

Lyophilization of liposome preparations:

Vial Unscrambler→ Vial Washing Machine (Ultrasonic) → Three Water Three dry air wash → Depyrogenation Tunnel (Preheating > High Temperature Sterilization Drying > Cooling) → Vial Filling → Half Stoppering → Lyophilization → Full Stoppering → Capping machine → External Washing



Part -4 PAT Tools and latest configuration for Lyophilizer

Truking Technology & Germany Romaco Joint manufacturing

Process Analytical Technology

Process Analysis Technology PAT introduced in pharmaceutical engineering, its purpose is to monitor the quality element of each process during the analysis of the pharmaceutical process to determine whether to perform, reduce or avoid the management cost of market risk, and the resulting product is not sampled but qualified.

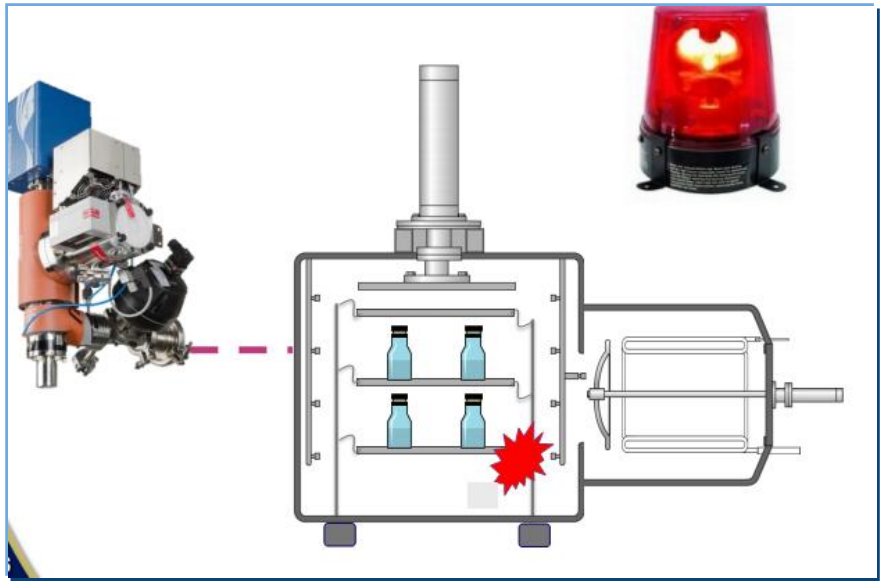
PAT technology = qualified product.

MKS In-line Process Monitoring System

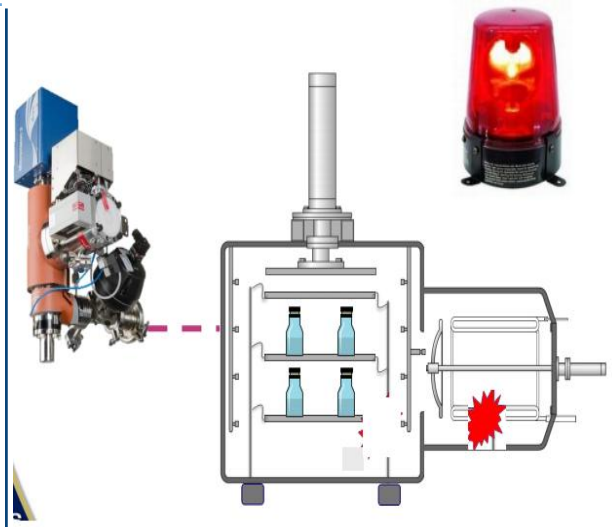
What we can find out by MKS In-line Process Monitoring System (Based on QMS technology)

- Unusual gas composition inside the chamber during Lyo cycle (silicone oil, Refrigeration gas etc)
- System Vacuum leak detection before start cycle
- Drying end point of the Lyo cycle verification

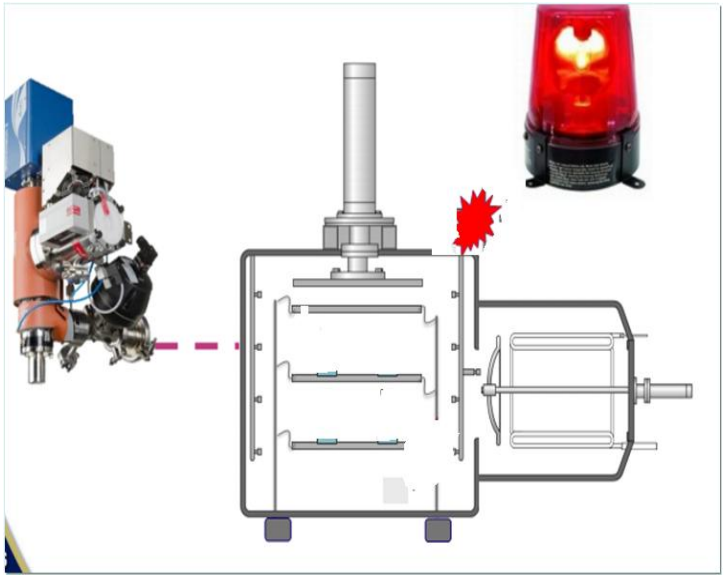
MKS In-line Process Monitoring System



Silicon Leak detection during Lyo production cycle



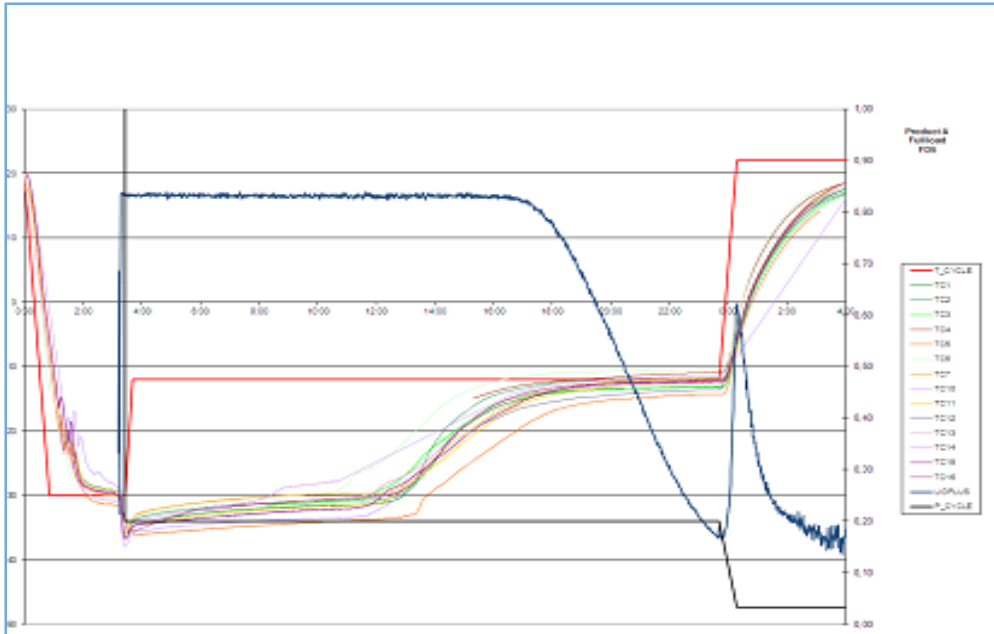
Refrigeration gas leak detection during Lyo production cycle



Pre-process System leak qualification

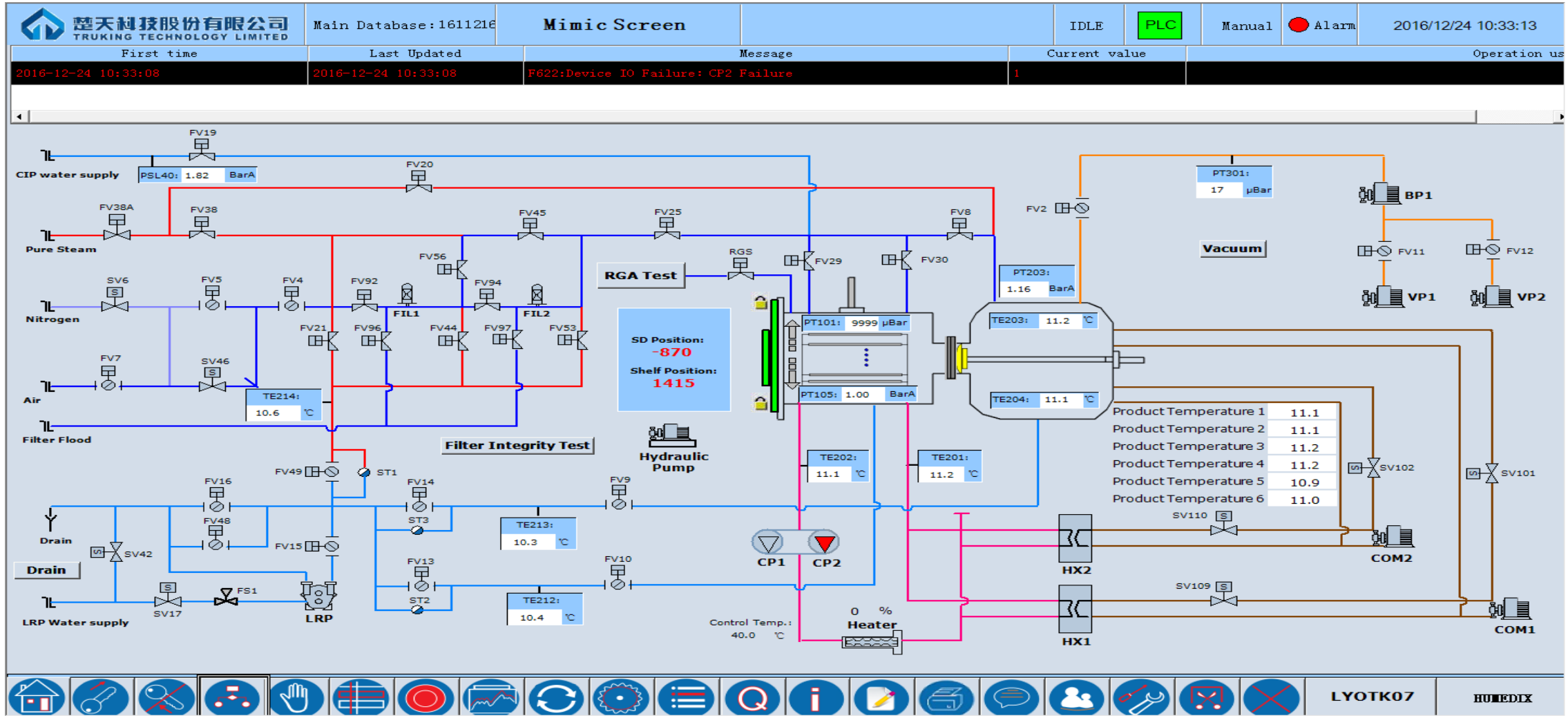
MKS In-line Process Monitoring System

Sensitive monitoring of the water concentration for optimizing the process and verification of the endpoint.

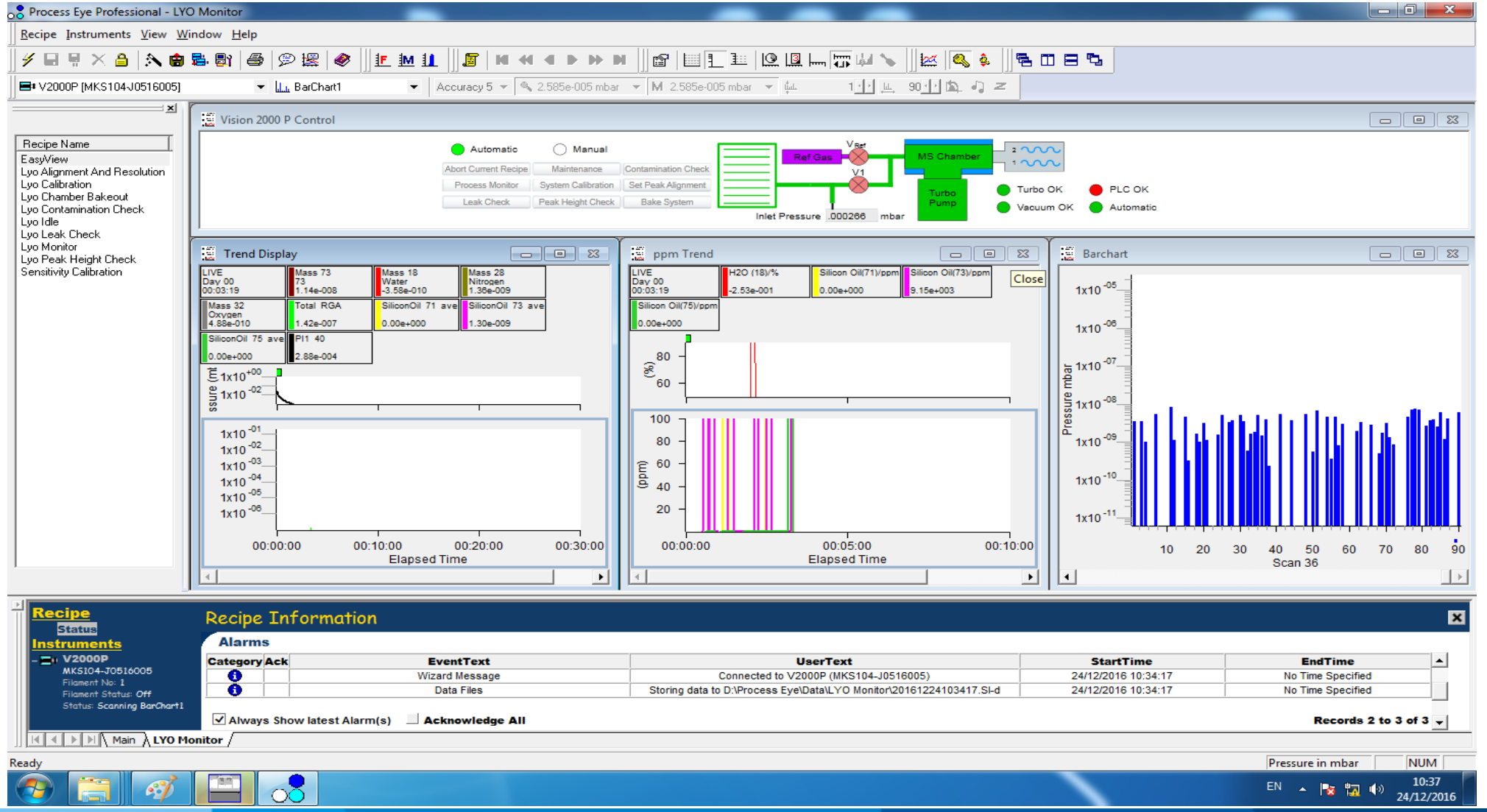


- Process endpoints are typically determined by pressure and temperature readings
- The QMS is providing more accurate data about the drying endpoint by monitoring of the water concentration
- Used to scale up processes from small to large batches

MKS In-line Process Monitoring System

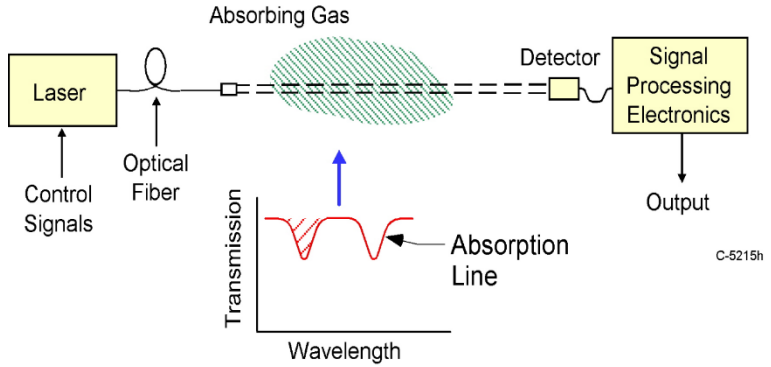


MKS In-line Process Monitoring System

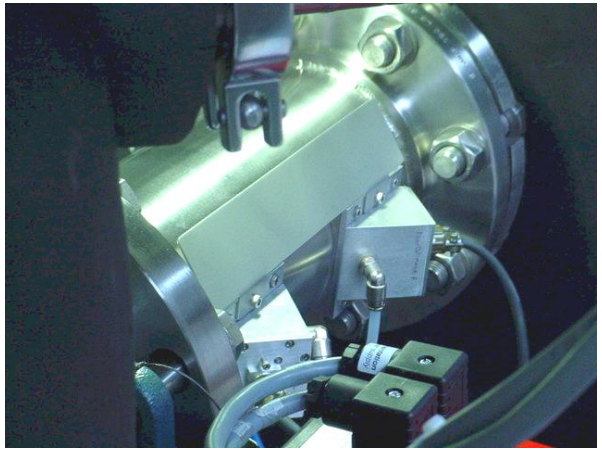


TDLAS-Tunable Diode Laser Absorption Spectroscopy

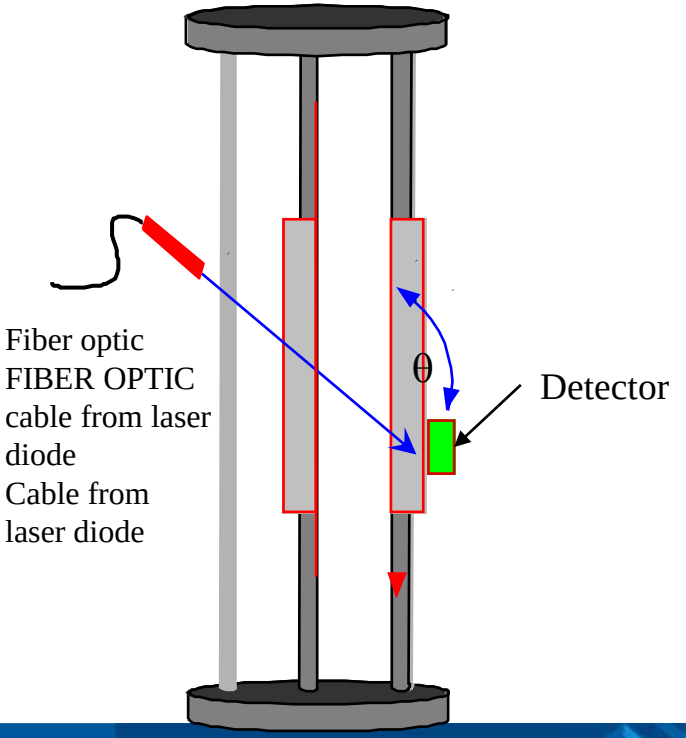
Through the combination of TDLAS measurements and a well-established heat and mass transfer model describing freeze drying, users can obtain information about Key Process Parameters (KPPs) affecting end product quality



The Physical Sciences Inc. (PSI) TDLAS based sensor, LyoFlux, measures water vapor concentration and gas flow velocity in the spool connecting a freeze-dryer chamber and condenser

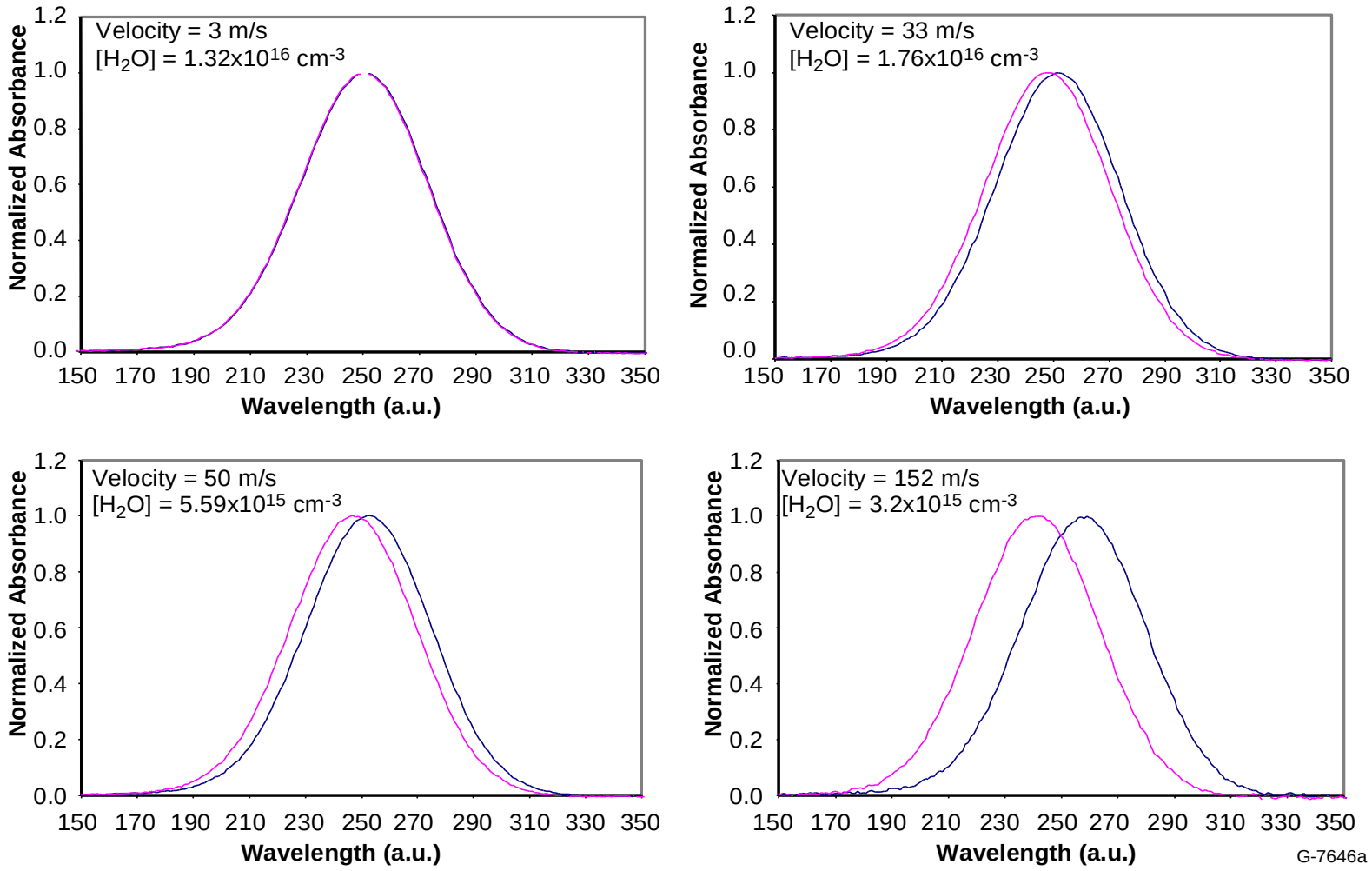


The near-IR spectrometer provides real-time measurements of water concentration and gas flow velocity that are used to determine the water mass flux (grams/second/cm2) in the spool



TDLAS-Tunable Diode Laser Absorption Spectroscopy

The application in the lyophilization process is: in the spool of the chamber and condenser, the vapor flow of a particular angle is measured, and the concentration and flow rate of the vapor can be calculated, so that the lyophilization process analysis and freezing Diffusion judgment.



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TDLAS-Tunable Diode Laser Absorption Spectroscopy

STEPS IN LYO:

- When the chamber is under vacuum, the sensor (speed) is zero at main valve closed position.
- Start / stop data record
- Start H20 mass flux points, calculate the total H2O removed at the beginning of a dry start
- Integrated in SCADA of Lyo system
- The data can be used for endpoint monitoring / automatic steps
- Automatic operation, no operator

Comparison with other PAT technology

- Thermocouple and RTD
- Pressure speed measurement (MTM)
- Relative component monitoring (mass spectrometer)

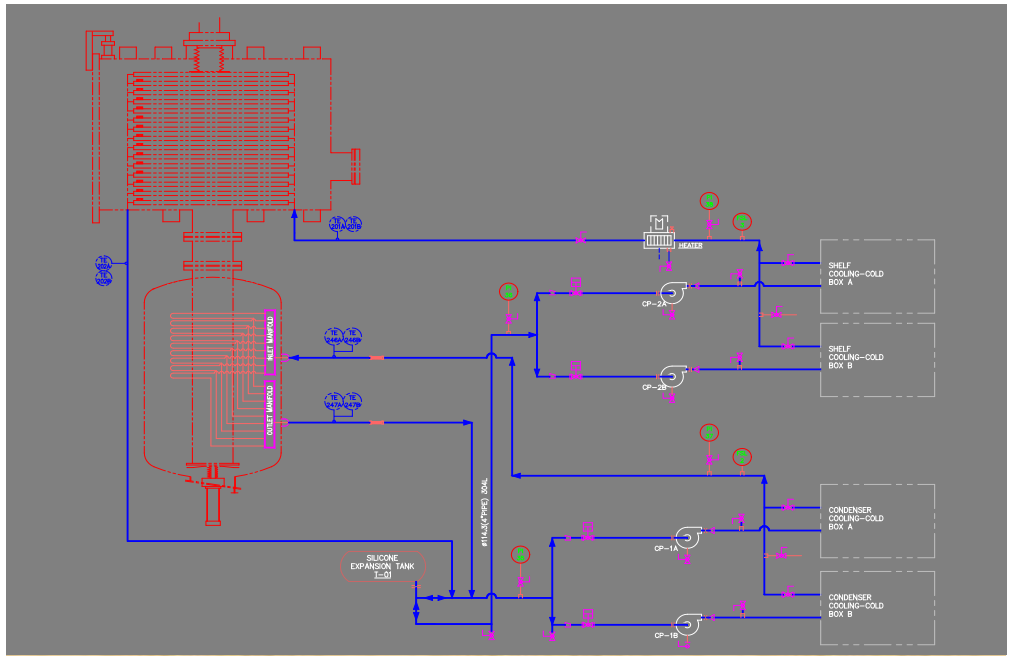
The above techniques can not directly measure mass flow, and can only be used as a terminal detection method.

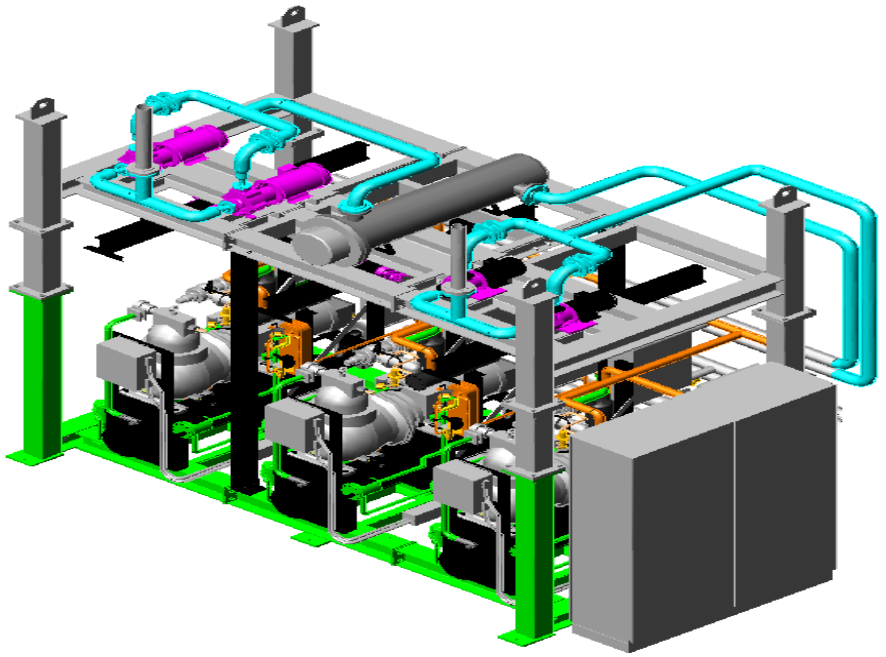
Dual cycle system

Length for lyophilization cycle:

Using low viscosity silicone oil to do a cooling machine dual cycle system:

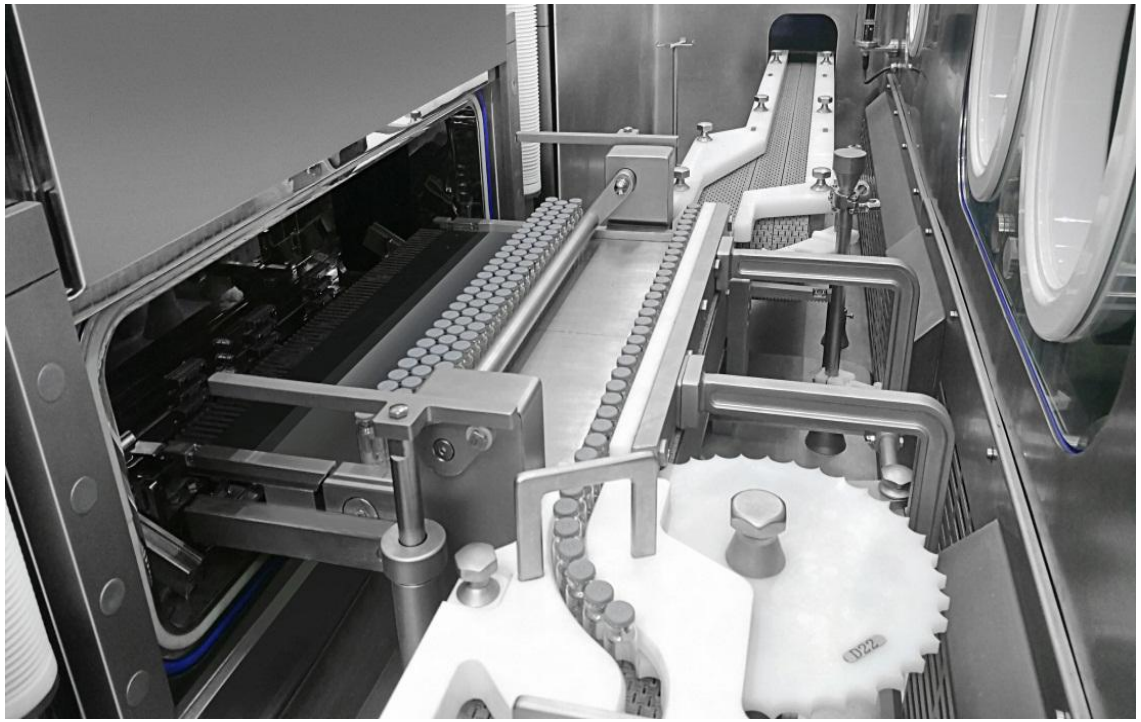
- Better temperature uniformity
- Energy adjustment is more convenient

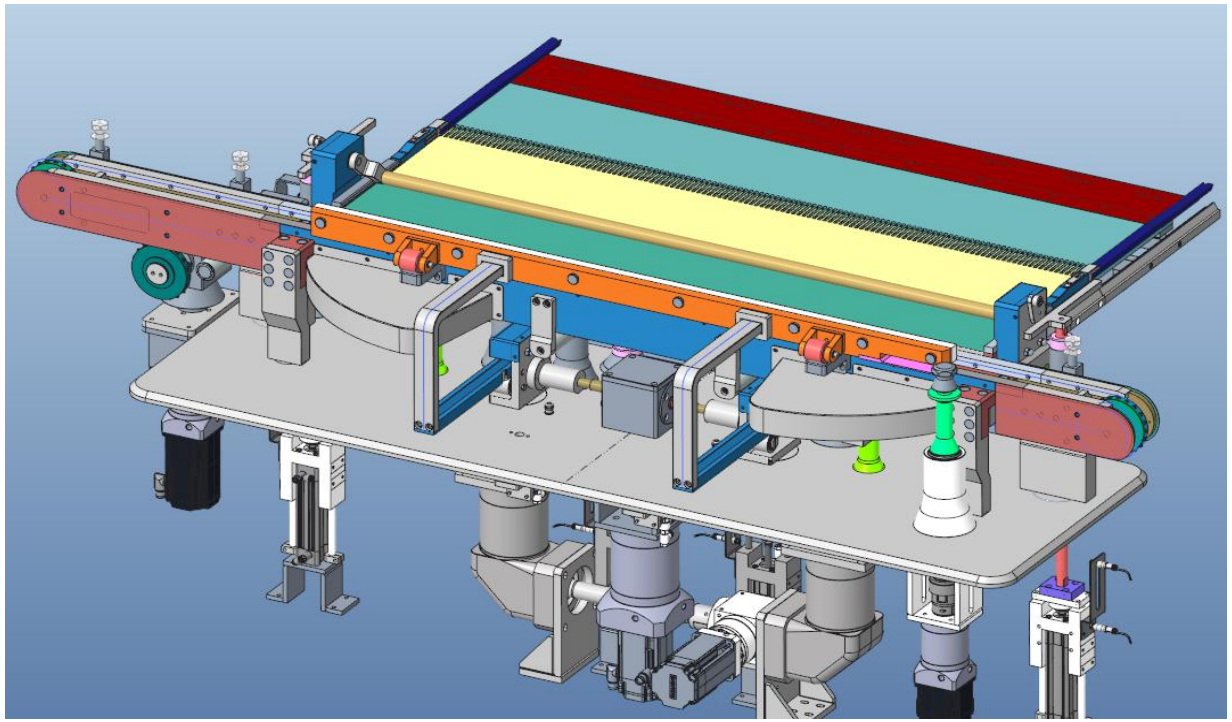




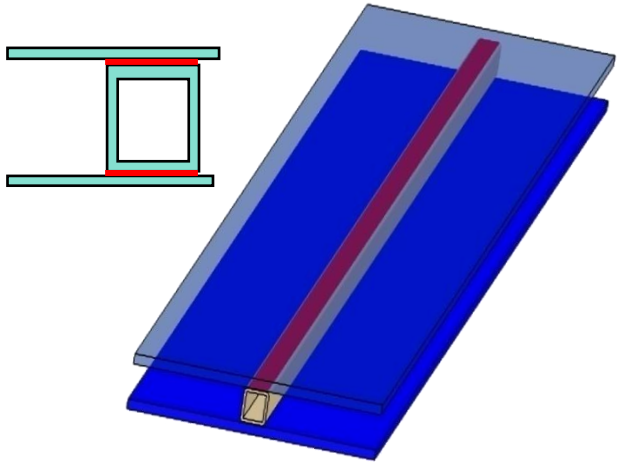
Alpha ALUS System

Dividing the motion of the earlier straight long pusher rod into two sets of execution devices, the first pushing rod is responsible for combining the star wheel to perform a bottle assembly matrix; and the second pushing rod supports the vial to push on to the shelves.

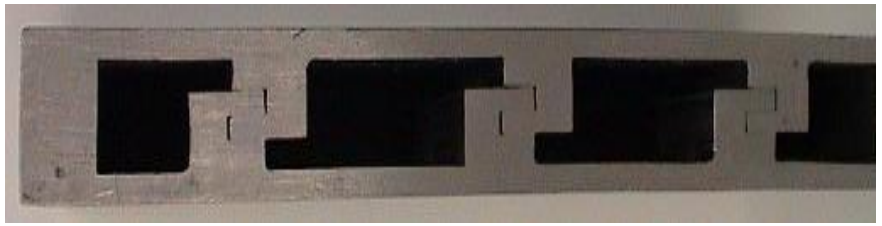




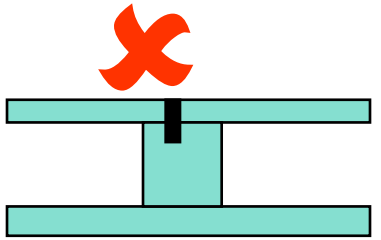
Brazing(Fusion) Shelves



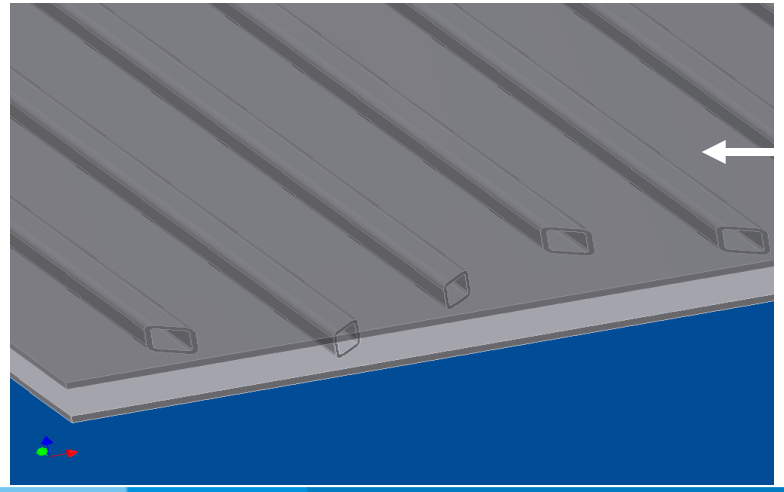
Fusion

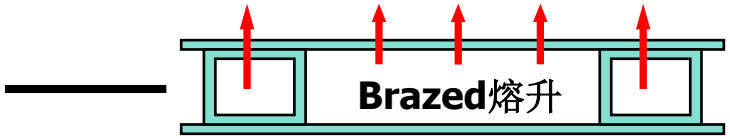


(Intetnal welding Shelf)



Penetration weld Shelf

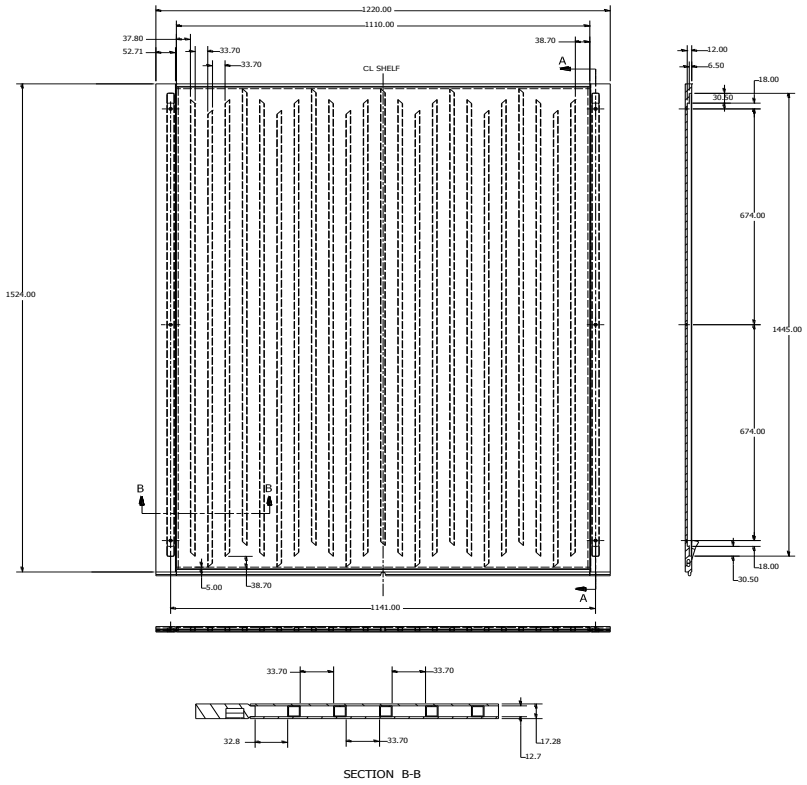




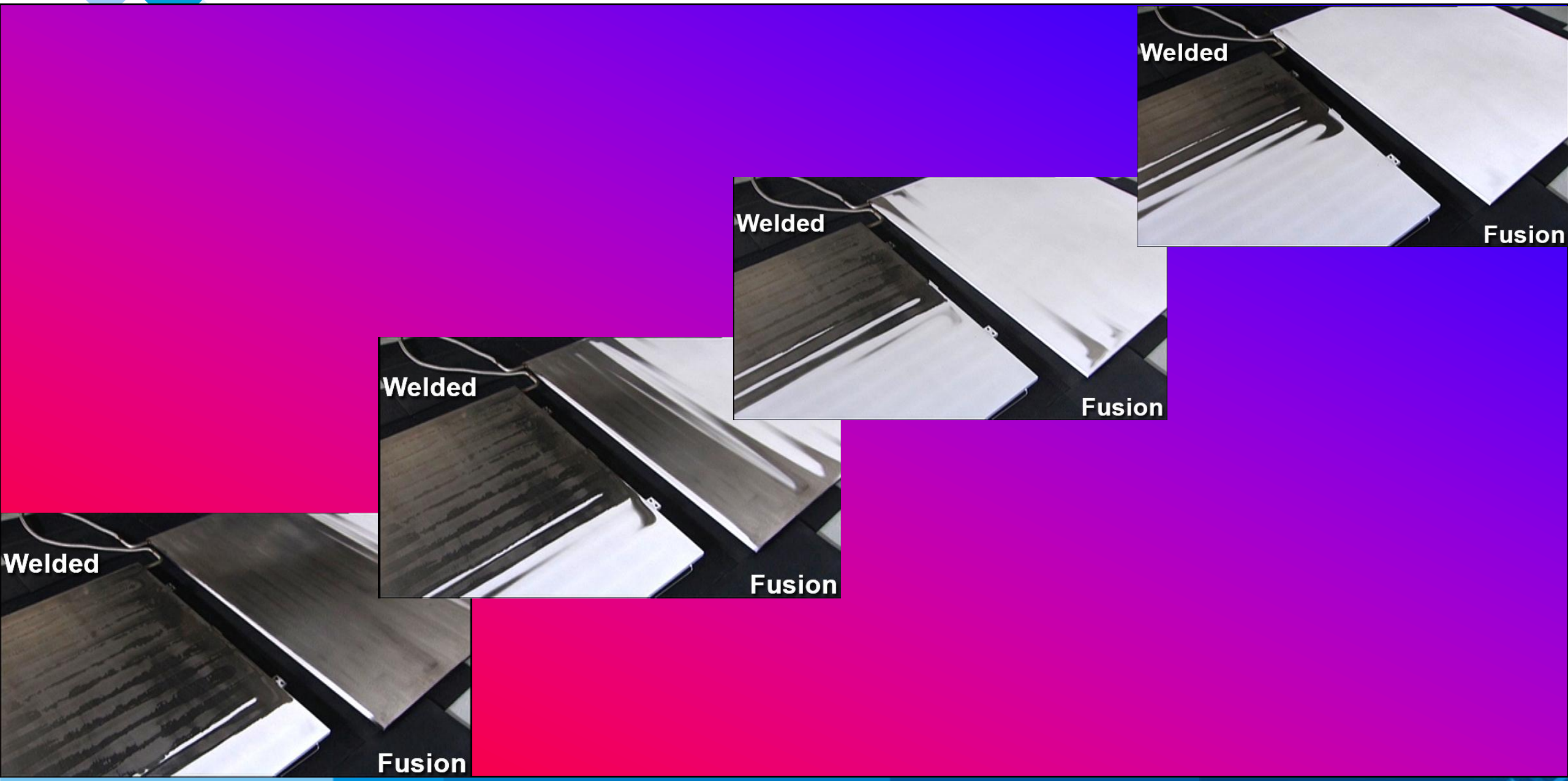
Brazing(Fusion) Shelves

Advantages of Brazing Shelves

- Provide Increased Flatness
  - ✓ Metal-to-metal bonding area for a brazed shelf is ***6 times*** greater than for a welded shelf
  - ✓ Reduces risk of non-alignment with automated loading systems
- Hollow interstitial supports provide 20% greater heat exchange area
- Tougher, hence improved performance against load
- Reduction In Weight & Silicon oil volume
  - ✓ Faster response to temperature changes
  - ✓ Reduced energy consumption during freeze drying and sterilization
  - ✓ Faster cool down after sterilization
  - ✓ Better temperature uniformity



Brazing(Fusion) Shelves



Production and manufacturing - quality improvement (Shelf welding)

Thank you