HTD
BIOSYSTEMS INC.
High Throughput Development

Lyophilization



Custom Lyophilization Services

HTD provides customized lyophilization services and development in the San Francisco Bay area. Our complete lyophilization services include:

Formulation development and lyophilization of proteins, peptides, DNA, RNA, antibodies, antibody-polymer conjugates, vaccines, liposomes, diagnostic kits and small molecules.

Lyophilization Cycle Development

We characterize the pre-lyo solution by Differential Scanning Calorimetry (DSC) to determine glass transition temperature or collapse temperature in the frozen concentrate (Tg'). We then use a lab scale Vertis freeze-dryer to lyophilize the product. The product is usually sealed under vacuum or under a flow of an inert gas such as Nitrogen.

Characterization of solid-state properties

We use DSC and Karl Fischer to monitor solid-state structure (amorphicity) and moisture content of the lyophilized cake, respectively. The cakes are also reconstituted and reconstitution time is measured. The cakes are reconstituted and the molecular conformation of the API and its bioactivity is compared before and after lyophilization. Our experience in lyophilization and detailed characterization of the product during lyo development provides our clients with the necessary information for rationalizing the lyophilization cycle during development.

Stability studies

Lyophilized cakes are stored at cold, under ambient or accelerated condition and their stability is determined by different techniques.

Fill Finish For Tox Studies

We provide manufacturing of TOX lots for GLP testing. We use a Vertis pilot scale lyophilizer (Genesis 12 XL) with a capacity of 1,000 vials (3 mL). HTD has successfully manufactured several Tox lots for its customers.

Scale-up of Lyo cycles

Successful scale-up to a large production size dryer is critical for developing a pharmaceutically-acceptable product. Using our specially configured lyophilizer, we develop a robust lyo cycle that can be easily tech-transferred to a production scale.

Tech Transfer to large GMP lyophilizers

HTD has successfully lyophilized numerous drug products and transferred the process into manufacturing. Our pilot scale lyophilizer is specifically designed to mimic large production lyophilizers. We provide a rationale approach to the lyophilization cycle that becomes a critical component of the CMC section for submission to the regulatory agencies and manufacturing groups.

1061 Serpentine Lane, Suite E , Pleasanton CA 94566
Tel. 510.367.0528, www.htdcorp.com

Lyophilization Process

Lyophilization Cycle

Lyophilization comprises of a series of process steps that include

- **Freezing** at a controlled rate to ensure minimal perturbation of protein structure,
- **Annealing** of the frozen matrix to ensure a consistent frozen matrix across the vials.
- **Primary drying** to sublime the bulk water from the frozen matrix.
- **Secondary drying** to remove more tightly bound water molecules, ensure low moisture content in the product, and have the right solid-state properties in the final lyophile to obtain a stable product.

Criteria for a Stable Lyophilized Biopharmaceutical

- A glass transition temperature above the storage temperature
- Moisture content below 2 %
- Maintain as much native structure of the protein in the solid state
- Minimize phase separation of the protein from the amorphous phase

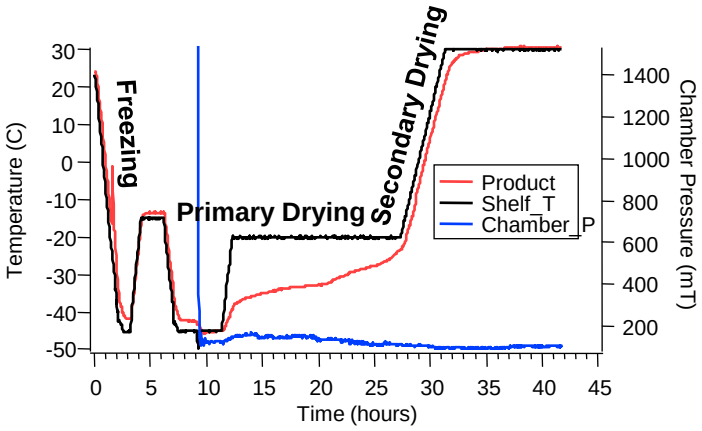

Fig 1. Vertis lyophilizer. **Fig 2**. Steps in a freeze-drying cycle. **Fig. 3**. Lyophilized product

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