



# Liquid Nitrogen-Based Lyophilizers

## Superior Performance and Range of Operation

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**L**yophilization, or freeze drying, is a critical step in the manufacture of pharmaceuticals and biologicals to modify or enhance physiochemical properties, such as dissolution rate and bioavailability. Recently, the use of liquid nitrogen-based systems has increased because it provides greater control over the freezing process, increases the range of operating parameters, and reduces manufacturing time when compared with compressor-driven freezing systems. The increased control and faster freezing rate significantly widens the applicability of a lyophilizer to products with difficult formulations or in specific dosage forms.

### SUPERIOR PERFORMANCE

**High Condenser Capacity:** A liquid nitrogen-based condenser has a higher cooling capacity than a compressor-based system and can achieve more uniform and consistent condenser temperatures throughout the entire process, including the peak load in primary drying.

**High Shelf-Cooling Capacity:** A liquid nitrogen-driven system enables the product to attain a lower shelf temperature at a faster and more constant rate than the compressor-based system. The high capacity in the cooling shelves and the condenser in a lyophilizer will significantly widen the applicability of the lyophilizer in manufacturing products with specific formulations.

**Reduced Mechanical Stress:** Sterilization-in-place (SIP) imposes extensive stress upon mechanical systems in a compressor-based lyophilizer. A liquid nitrogen refrigeration system substantially reduces mechanical stress and reduces freezing time. For example, it takes three and a half hours to cool down to 25 °C in a screw compressor lyophilizer compared with one and a half hours to cool to 15 °C in a liquid nitrogen system.

### MORE PRECISE CONTROL

**Formulations of Biologics:** By contrast with the traditional chemically synthesized drugs, biopharmaceuticals and biologicals (proteins, antibodies, vaccines) require more specialized lyophilization cycles. To minimize in-process deterioration and achieve acceptable shelf life after lyophilization, more precise control of freezing temperature and cooling rate is required, which can be achieved with liquid nitrogen-based lyophilizers.



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Liquid nitrogen systems are also advantageous for parenteral pharmaceuticals, which incorporate a nonaqueous solvent to modify physical properties of the formulation, and for high fill-depth/volume dosage products. Both of these types of products place an increased cooling demand on the lyophilizer, but the flexibility of the liquid nitrogen system makes it possible to handle these products without capacity increases.

### REDUCED MANUFACTURING TIME

In these state-of-the art production-scale lyophilizers, faster freezing with liquid nitrogen (up to 2 °C per minutes) can be achieved, and the condenser temperature can be well controlled to as low as -75 °C. The use of liquid nitrogen cooling systems in lyophilizers is only one of the features of the Lyo-Advantage™ system in the sterile operation facility of DSM Pharmaceuticals, Inc. This level of control is in direct response to the large demand for lyophilization by the biopharmaceuticals industry.

DSM Pharmaceuticals, Inc. has made a major investment in expanding its lyophilization manufacturing capacity. Now over 3700 ft<sup>2</sup> of shelf area for lyophilization are available for freeze drying on three sterile filling lines with over two thirds of the capacity driven by liquid nitrogen-based systems.

