FTS Systems

SP SCIENTIFIC

Making Time for Science

LYOPHILIZER OPERATOR'S MANUAL

FTS SYSTEMS LYOSTAR™ 3

RESEARCH & DEVELOPMENT / PILOT-SCALE FREEZE DRYER

FTS Systems Genevac Hull National-Hotpack VirTis

Part Number 100004448

Rev 006, 01/14

Original Instructions

The U.S. English version of this document is the original instructions.

All other languages are a translation of the original instructions.

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Important Symbols

WARNING! INJURY OR EVEN DEATH MAY RESULT IF RECOMMENDATION MARKED WITH THIS SYMBOL IS NOT HEEDED.

CRUSH HAZARD. KEEP HANDS CLEAR WHEN OPERATING DOOR.

ELECTRIC SHOCK DANGER! USE APPROPRIATE CAUTION TO AVOID INJURY OR DEATH.

CORROSIVE CHEMICAL. WEAR SUITABLE GLOVES, SAFETY GLASSES, AND PROTECTIVE CLOTHING.

BURN DANGER! POTENTIALLY HOT SURFACE. USE APPROPRIATE CAUTION.

PROPERTY CAUTION! TO PREVENT DAMAGE TO CHAMBER EQUIPMENT AND/OR LOAD, ADHERE TO PROCEDURES MARKED BY THIS SYMBOL.

DO NOT STORE FLAMMABLE MATERIALS IN CHAMBER.

PRACTICAL OPERATING TIP. THESE RECOMMENDATIONS STREAMLINE UNIT OPERATION AND PREVENT COMMON OPERATOR ERRORS.

ALWAYS WEAR APPROPRIATE PERSONAL PROTECTIVE EQUIPMENT (PPE) SUITED FOR THE TASK YOU ARE PERFORMING.

EXPLOSIVE MATERIALS HAZARD! KEEP OBJECTS AWAY FROM HEAT.

Freeze Dryer Safety Warnings

- ✓ *Do not freeze-dry explosive or highly flammable substances.*
- ✓ *Always assume that shelf, condenser and internal parts may be very cold or very hot. Wear protective equipment to avoid burns.*
- ✓ *Always ensure that only an authorized technician services the refrigeration, heat transfer, vacuum and electrical systems.*
- ✓ *Always ensure that refrigeration air intake is clear and clean.*
- ✓ *Always ensure vacuum pump exhaust is properly ventilated and/or contained.*
- ✓ *Always practice team lifting when moving heavy equipment.*
- ✓ *Always regulate maximum pressure to 1 psig when backfilling from an inert gas.*
- ✓ *Always wear appropriate personal protective equipment (PPE) suited for the task you are performing.*
- ✓ *Be sure to carefully read the entire instruction manual before attempting to operate the freeze dryer.*
- ✓ *Be sure to verify that the electric service and other utilities match the unit's requirements before connecting to power.*
- ✓ *Never allow hand or body contact with open vacuum ports.*
- ✓ *Never clean with solvents. Use mild detergent and water only.*
- ✓ *Never operate the unit without all covers in place.*
- ✓ *Never pressurize a freeze-drying chamber unless it has been specially designed and coded as a pressure vessel (e.g., displays an ASME-coded certificate).*

Never stopper vials unless the chamber door is tightly closed.

Never use acrylic closures if they are cracked or crazed.

Never use with toxic, corrosive, flammable or organic materials unless special precautions are in place to prevent injury to personnel or damage to equipment.

Warranty Information

FTS Systems LyoStar™ 3 Lyophilizers are warranted by SP Scientific to be free of defects in material and workmanship when operated under normal conditions as specified in the instructions provided in this manual. Please take this opportunity to locate the serial tag on your new FTS Systems LyoStar™ 3 and record the information below for future reference. SP Scientific also recommends that you complete and return your unit's warranty registration card.

Model Number _____

Serial Number _____

Part Number _____

Limited Warranty

SP Scientific (the "Company") shall warrant each of its products against defects in material or workmanship for a period of 12 months from the date of installation or 15 months from the date of shipment (whichever comes first) provided that the product is used in a reasonable manner under appropriate conditions and consistent with the applicable operating instructions. In addition, the Company shall warrant the refrigeration system for a period of 24 months provided that the system is used in a reasonable manner under appropriate conditions and consistent with the applicable operating instructions.

The obligation of the Company shall be, at its option, to repair or replace, without charge any parts that prove to be defective within the warranty period, if the purchaser notifies the Company promptly in writing of such defect. No product shall be returned to the Company without prior approval of the Company.

This limited warranty shall cover the costs of parts and labor to repair or replace all defective product(s) at the Seller's factory. For all products installed by the Company and located within the Company service travel areas, this warranty shall cover transportation charges to ship the product to and from the Company's factory and/or the costs of travel, room and board if the Company's employees conduct repair at the Buyer's location. In lieu of repair or replacement at the Company's factory, the Company may, in its discretion, authorize a third party to perform the repair or replacement at the Buyer's location, and at the Company's sole expense.

The Company shall not be responsible for labor charges payable with respect to persons other than Company employees. Replacement or repair of parts pursuant to this warranty shall not in any way extend the original warranty period. The Company shall not be responsible for any unauthorized repairs, replacements or product modifications, nor will it be responsible for any product failures resulting from such unauthorized repairs, replacements or product modifications negligently or otherwise made by persons other than Company employees or authorized representatives of the Company. The buyer shall assume transportation charges to ship the product to and from the Company's factory and the costs of travel, room and board if the Company's employees conduct repair at the Buyer's location within the warranty period if the product was not installed by the Company's and/or is not located within the Company's service travel areas.

THE COMPANY DOES NOT MAKE AND EXPRESSLY DISCLAIMS ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER WARRANTY, EXPRESSED OR IMPLIED, WITH RESPECT TO THE SALE, INSTALLATION, DESIGN OR USE OF ITS PRODUCTS. ADDITIONALLY, THE COMPANY SHALL NOT BE LIABLE FOR ANY CONSEQUENTIAL DAMAGES RESULTING FROM THE USE OF OR ANY DEFECTS IN ITS PRODUCTS.

The Company's employees are available to provide general advice to customers concerning the use of the Company's products; however, oral representations are not warranties with respect to particular products or their uses and may not be relied upon if they are inconsistent with the relevant product specifications for the items set forth herein.

Notwithstanding the above, the terms and conditions set forth in the Company's formal sales contracts shall be controlling and supersede any inconsistent terms contained herein, and any changes to such contracts must be made in writing and signed by an authorized executive of the Company.

WARNING! THE DISPOSAL AND/OR EMISSION OF SUBSTANCES USED IN CONNECTION WITH THIS EQUIPMENT MAY BE GOVERNED BY VARIOUS FEDERAL, STATE OR LOCAL REGULATIONS. ALL USERS OF THIS EQUIPMENT ARE URGED TO BECOME FAMILIAR WITH ANY REGULATIONS THAT APPLY IN THE USERS AREA CONCERNING THE DUMPING OF WASTE MATERIALS IN OR UPON WATER, LAND OR AIR AND TO COMPLY WITH SUCH REGULATIONS.

Contents

Chapter 1

Introduction

Introducing the LyoStar™ 3—the pinnacle of freeze dryer engineering. Designed and built like a full-scale production freeze dryer, this pilot-scale lyophilizer offers superior shelf mapping, rapid shelf freezing, a robust 5.5 hp cascade refrigeration system, unmatched process accuracy and reliability, and a sophisticated instrumentation set. In short, the LyoStar™ 3 is the ultimate R&D lyophilizer.

Standard Features

Hydraulic stoppering system with shelf-latching for various vial sizes.

- Two-stage rotary vane vacuum pump with oil mist eliminator.
- Durable, long-lasting 316L stainless steel chambers and product shelves.
- High capacity external coil condenser.
- High-performance cascade refrigeration system.
- Powerful scroll compressors.
- Isolation valve for chamber isolation during barometric endpoint testing, condenser defrost and periodic leak checking.
- Sixteen (16), 24 AWG Type T product temperature-monitoring thermocouples. Eight (8), 36 AWG Type T product temperature-monitoring thermocouples provided with resin caps with O-rings for use with 13 mm vials. Eight (8), 36 AWG Type T product temperature-monitoring thermocouples encased in polytetrafluoroethylene (PTFE) sheathing and provided with PTFE caps for use with 20 mm vials.
- Two (2) 100 Ohm Resistance Temperature Detectors (RTDs) (*i.e.,* for monitoring the shelf inlet and shelf outlet temperatures).
- Two (2) Capacitance Manometers (*i.e.*, for monitoring vacuum in both the product and the condenser chambers)
- Pirani vacuum transducer (*i.e.*, for pressure monitoring in the product chamber).

Two-stage rotary vane vacuum pump with oil mist eliminator.

Advanced cycle development and optimization tools, including Barometric Endpoint and Pirani Capacitance Differential Feedback (PRCM) testing.

Equipment Options

Stainless steel product and/or condenser chamber doors.

Water-cooling for enhanced performance.

Stainless steel Bio-seal flange for cleanroom installation.

- Liquid nitrogen trap.
- Sample Extractor Assembly.
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-
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Chapter 2

Getting Started

Initial Inspection

Your LyoStar™ 3 lyophilizer was carefully packed and thoroughly inspected before leaving the factory. However, in the unlikely event that shipping damage has occurred, retain all packing material and contact your freight carrier immediately.

DO NOT ACCEPT DAMAGED SHIPMENTS FROM A CARRIER WITHOUT A SIGNED NOTIFICATION OF DAMAGES.

Upon receiving your shipment, inspect all contents of your equipment for damage. Check packing material for small accessory items. Remove all packing material carefully and inspect for concealed shipping damage. Inspect the inside of the machine for any visible damage. If concealed damage or loss is discovered, contact the freight carrier immediately.[1] Keep all contents, packing material and related paperwork intact until a written report is obtained.

Note: *SP Scientific will cooperate in the matter of collecting your claim, but is not responsible for the collection or free replacement of the material. When possible, replacement parts will be shipped and invoiced to you, making them a part of your claim.*

Setup Procedure

The LyoStar™ 3 research & development lyophilizer is designed for single level installation in either a machine room or cleanroom. The unit should be installed in a location that is convenient for both operation and service.

Note: *SP Scientific recommends installing your LyoStar™ 3 lyophilizers in an area equipped with an adequate fire suppression system, as the system's pressure relief devices are not intended to withstand substantial increases in pressure due to extreme external temperatures (e.g., such as in the event of a facility fire).*

1.

The following procedure will guide you with the setup of your LyoStar™ 3 lyophilizer.

Uncrate and unwrap the unit.

Note: *The LyoStar™ 3 and the control system workstation and peripherals (e.g., printer) supplied with the control system are typically packaged separately.*

[1] "Concealed damage or loss" refers to damage or loss that does not become apparent until the merchandise has been unpacked and inspected. Should damage or loss be discovered, you may make a written request for inspection by the carrier's agent within 15 days of the delivery date. You may then file a claim with the freight carrier or SP Scientific, depending on the terms of your shipment. If your shipment was "FOB Destination" file your claim with SP Scientific and include the inspection report and any other supporting documents. If your shipment was "FOB Shipping Point" file your claim with the freight carrier and include the inspection report and any other supporting documents.

Inspect the inside of the unit for any visible damage. Check refrigeration lines, heat transfer lines and vacuum lines for damage. Check for visible liquid at or near the base of the unit.

2. Open the product and condenser chamber doors. Remove all packing material from chambers.

Note: *LyoStar™ 3 lyophilizers are equipped with stoppering, therefore, it may be necessary to power up the unit and adjust the shelves before removing all packing material. At this point, leave the shelf packing in place. Wait until you have completed the installation procedure before powering up the unit.*

3. Inspect chamber parts for possible damage and leaks. Check the bottom of the product chamber for traces of oil. The heat transfer fluid contains a fluorescent dye, making leaks easily visible with a black light. The condenser and chamber should be clean and dry. The condenser drain valve should be closed.

4. **Services and Utilities.** Review the Layout Drawing from your equipment and confirm that the services and utilities available at your facility meet a standard voltage configuration requirement:

- 208/230 VAC, 50/60 Hz, 1 phase, 40 A
- 220 VAC, 60 Hz, 1 phase, 40 A
- 240 VAC, 50 Hz, 1 phase, 40 A
- 400 VAC, 50 Hz, 3 phase, 30 A
- 480 VAC, 60 Hz, 3 phase, 30 A

5. Ensure that the voltage, phase, frequency and amperage listed on the lyophilizer's serial tag match your facility's available power supply (*i.e.,* the power outlet you intend to use must meet the voltage and amperage requirements listed on the serial tag).

Note: *LyoStar™ 3 includes two Uninterruptible Power Supplies (UPS), which permit the control system software to continue operating in the event of a power failure. One UPS provides backup power to the computer workstation (HMI/SCADA and peripherals) and one UPS provides backup power to the PLC and all critical instruments.*

DO NOT CONNECT THE SYSTEM TO POWER AT THIS TIME.

6. CAUTION! ONLY A QUALIFIED ELECTRICIAN SHOULD CONNECT THE UNIT TO THE AVAILABLE ELECTRICAL SUPPLY.

Position the unit on a firm, level floor in an area that provides adequate air circulation. The LyoStar™ 3 is designed for installation and operation in a room with a controlled temperature of between 19 °C and 25 °C and a maximum relative humidity of 70%.

Note: *Do not allow the intake air for the LyoStar™ 3 to exceed 30 °C. If the ambient room temperature exceeds 30°C, do not operate the lyophilizer until adequate cooling or ventilation is established.*

Clearance. Twenty-four (24) inches (61 cm) of obtainable clearance is recommended on all sides of the unit for serviceability and efficient operation. If multiple machines are being operated in a single area, position them so that the hot exhaust from one does not blow into the intake of another. If machines are placed side-by-side, increase the minimum clearance to 48 inches (122 cm).

7.

Cleanroom systems: Position the freeze dryer so that the wall flange is flush against the periphery of the wall opening. Screw, caulk and secure it to the wall.

Heat Transfer System. The heat transfer system is shipped with heat transfer fluid. The fluid circuit is a sealed system and under normal setup or operating conditions does not require additional fluid. The heat transfer fluid level may be monitored through the sight glass located on the side of the heat transfer fluid reservoir. This sight glass is visible through the upper rear grill panel.

8.

Note: *The heat transfer fluid level should be approximately ¾ full when the system is at 25 °C.*

Door Gaskets. Ensure that the chamber and condenser door gaskets are clean and free of defects (*e.g.*, cuts, cracks, tears). If the gasket shows any signs of cracks or tears replace it immediately. Failure to do so shall result in poor vacuum integrity. As a minimum, gaskets should be inspected quarterly and replaced annually.

9.

Note: *The door gaskets do not require vacuum grease for pre-seal or operation.*

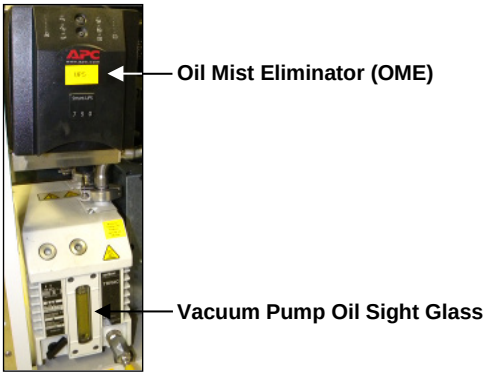
Vacuum System

10.

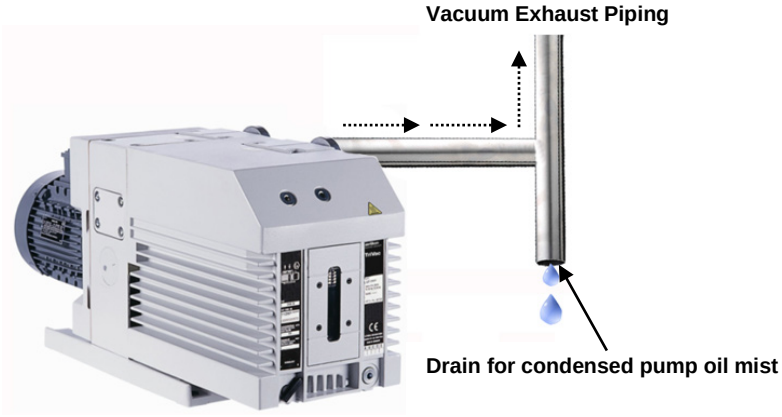
Vacuum Pump Oil. Check the vacuum pump oil. The vacuum pump is shipped with oil in it. The vacuum pump oil should be clearly visible in the sight glass on the front of the pump. The oil level should read between the center and top of the sight glass while the pump is off and to the top of the sight glass while the pump is in use. Add oil only if necessary. DO NOT OVERFILL!

Note: *For information on vacuum system maintenance, refer to Chapter 10: General Maintenance, Vacuum System .*

Oil Mist Eliminator. The LyoStar™ 3's vacuum system is equipped with an Oil Mist Eliminator. Ensure that it is properly attached to the vacuum system before operating the lyophilizer.



Vacuum Pump Exhaust. If applicable, check your facilities vacuum pump exhaust piping. SP Scientific recommends an adequate vacuum pump exhaust system be installed, as pump vapors can be unpleasant in the lab and are not typically permitted in a clean room environment. SP Scientific suggests vacuum pump exhaust piping travel horizontally from the pump across to a "T" equipped with a drainable trap and then 90 degrees vertically to an outside vent. Always place the drain trap as close to the pump as possible. Exhaust lines should have an inside diameter no smaller than the discharge of the pump. Filters are also available. If you cannot exhaust directly outside the facility, a hood may be used.



11. **Doors and Ports.** Ensure that all ports, including the condenser drain port, are closed and/or sealed. Close the product and condenser chamber doors.

12. **Optional Water-Cooled Units.** If your unit is equipped with an optional water-cooled refrigeration system, ensure that the flow rate and temperature of the water meets the lyophilizer's specified requirements. During warmer months, water temperature may increase. If water from a controlled temperature source is not used, take steps to ensure that the water temperature is maintained within the unit's specified temperature range.

    Attach the cooling water supply to the cooling water inlet connector and a water return line to the cooling water outlet connector. SP Scientific recommends installing manual shut off valves and pipe unions on both the cooling water inlet and cooling water outlet connectors for ease of service.

13. ***Note:*** *SP Scientific recommends installing a 30 x 40 mesh or finer strainer on the cooling water supply (reference: McMaster Carr 98775K45).*

14. **Pneumatic Isolation Valve.** Standard LyoStar™ 3 lyophilizers are equipped with a pneumatic isolation valve. This valve requires a water-free compressed air source. Ensure that your air source meets the unit's specified requirements. Connect the compressed air source at this time.

    Inert Gas for Backfill. Nitrogen or other inert gas may be used to backfill the product chamber prior to stoppering. When using inert gas for backfill, ensure that the source meets the specified requirements. Connect the source to the sterile air inlet port.

Inert Gas for Systems with Praxair's ControLyo™ Nucleation On-Demand Technology. LyoStar™3 lyophilizers equipped with ControLyo™ Nucleation On-Demand Technology require an inert gas source for system pressurization. Argon (preferred), nitrogen or other suitable inert gas should be supplied with the gas pressure capable of delivering 4 scfm when
15. regulated between 50 and 60 psig. Connect the source using a ¾-inch male NPT fitting.

Notes: *Without proper ventilation , operation of ControLyo™ may cause the oxygen concentration of ambient air to drop below acceptable levels. To ensure that ventilation is adequate for the depressurization process, the volume to vent percentage ratio (V_V/V_R) must be less than 6.5%, where V_V equals the product chamber volume multiplied by 10, and V_R equals the total volume of the room in which the lyophilizer is located. In addition, SP Scientific recommends the use of an O_2 sensor to monitor oxygen concentration while operating ControLyo™.*

For additional information, refer to Chapter 9: Praxair's ControLyo™ Nucleation On-Demand Technology.

Vacuum Level Control and Vacuum Release. Nitrogen, room air or customer specified inert gas should be provided within a pressure range of
16. atmospheric to 5 psig maximum for vacuum level control and/or vacuum release.

Control System Connections.

17. ***Note:*** *For additional information, refer to the setup procedure included in your control system operator's manual.*

VERIFY THAT THE RED VOLTAGE-SELECTING SWITCH LOCATED ON THE BACK OF THE WORKSTATION TOWER IS APPROPRIATELY CONFIGURED FOR YOUR INPUT POWER (115 VAC OR 230 VAC). CONNECTING THE WORKSTATION TO POWER WHILE THE SWITCH IS IN THE WRONG POSITION COULD CAUSE SEVERE DAMAGE TO THE WORKSTATION.

Connect the supplied data communications cable(s) (*e.g.*, RS-232, Ethernet, etc.) between the LyoStar™ 3 lyophilizer and the control system workstation.

Your LyoStar™ 3 includes an Uninterruptible Power Supply *(UPS)* to be used with control system workstation. Connect the power cables of the monitor, PC and peripherals to the open electrical sockets on the UPS. Plug the UPS into
18. the available power supply and enable power.

19. Ensure that all electrical control panel switches, as well as the main circuit
20. breaker are in the off position.

Connect remaining utilities and/or attach additional equipment.

Connect the lyophilizer to the available power supply (check available power supply against the lyophilizer's requirements as stated on the serial tag).

Note: *The UPS which provides backup power to the PLC and all critical instruments is installed within the LyoStar™ 3 frame.*

21.

CAUTION! ONLY A QUALIFIED ELECTRICIAN SHOULD CONNECT THE UNIT TO THE AVAILABLE ELECTRICAL SUPPLY.

Turn on the main circuit breaker and all remaining control panel switches, if applicable.

Chapter 3

The Freeze-Drying System

PRACTICAL OPERATING TIP. REFER TO YOUR CONTROL SYSTEM OPERATOR'S MANUAL FOR SPECIFIC DETAILS REGARDING THE OPERATION OF YOUR UNIT.

Components and Subsystems

Before operating your LyoStar™ 3 for the first time, take a few moments to familiarize yourself with the lyophilizer's components and subsystems. The LyoStar™ 3 lyophilizer consists of the following main components:

- Product drying chamber.
- Product shelves.
- Ice condenser.
- Shelf heat-transfer system.
- Stoppering system.
- Condenser cooling system.
- Removable spool piece for optional installation of TDLAS apparatus.[2]
- Isolation valve.
- Refrigeration system.
- Vacuum system.
- Aeration and vacuum level control.
- Electrical system and associated wiring.
- Control system software and related hardware components.

[2] Tunable diode laser absorption spectroscopy (TDLAS) is a method of measuring the concentration of a gas or gas component.

Product Drying Chamber

Standard Chamber

The standard product-drying chamber is a horizontally mounted square vessel manufactured from grade 316L stainless steel. The chamber is designed for and provided with reinforcement capable of withstanding full vacuum. It is insulated to limit energy loss and includes all ports and connections required for connecting the lyophilizer's necessary sub-systems and components. An inert gas port is located on the lyophilizer's rear panel.

ControLyo™ Chamber

LyoStar™ 3 lyophilizers equipped with Praxair's ControLyo™ Nucleation On-Demand Technology require a specially designed product chamber. The ControLyo™ product chamber is similar in design to the standard chamber. However, it also meets the design, fabrication, inspection, testing, and certification of pressure vessels operating at either internal or external pressures exceeding 15 psig as stated by the American Society of Mechanical Engineers (ASME) Boiler and Pressure Vessel Code, Section VIII, Division I. The Maximum Allowable Working Pressure (MAWP) of the product chamber for systems equipped with Praxair's ControLyo™ Nucleation On-Demand Technology is 28.5 psig.

Note: *For additional information, refer to Chapter 9: Praxair's ControLyo™ Nucleation On-Demand Technology and/or your control system operator's manual.*

Standard Chamber Door

The standard product chamber door is a full-view acrylic door. A split-ring gasket surrounds the chamber opening allowing the chamber to be sealed under vacuum when the door is closed.

ControLyo™ / Stainless Steel Chamber Door

LyoStar™ 3 lyophilizers equipped with Praxair's ControLyo™ Nucleation On-Demand Technology are equipped with a stainless steel drying chamber door that meets the design, fabrication, inspection, testing, and certification of pressure vessels operating at either internal or external pressures exceeding 15 psig as stated by the American Society of Mechanical Engineers (ASME) Boiler and Pressure Vessel Code, Section VIII, Division I. The Maximum Allowable Working Pressure (MAWP) of the product chamber door for systems equipped with Praxair's ControLyo™ Nucleation On-Demand Technology is 28.5 psig.

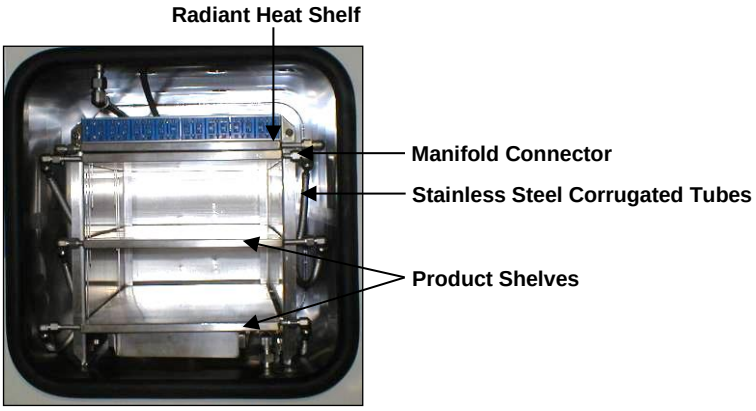
Note: *For additional information, refer to Chapter 9: Praxair's ControLyo™ Nucleation On-Demand Technology and/or your control system operator's manual.*

Stainless Steel Chamber Door

Standard LyoStar™ 3 lyophilizers may be configured with an optional stainless steel drying chamber door.

Product Shelves

The LyoStar™ 3 lyophilizer is offered with up to four usable shelves and one radiant heat shelf. The radiant heat shelf is mounted above the top product shelf to provide uniform heating to product located on the uppermost useable product shelf. All shelves are manufactured from grade 316L stainless steel.



Shelf Stack and Latching

The product shelf assembly is designed with a moveable shelf stack, which when utilized may facilitate the stoppering of product vials. The moveable shelf stack may also be modified to increase the distance between shelves using the provided shelf-latching kits. This flexibility is beneficial when processing in large vials. The use of a shelf-latching kit, however, will reduce the total number of usable shelves in your product chamber.

Note: *For additional information, refer to Chapter 8: Shelf-Latching.*

Stoppering

The stoppering system provides bottom-up shelf collapse allowing you to fully seat partially inserted stoppers into product vials at the end of a freeze dry cycle.[3]

Note: *For additional information, refer to Chapter 7: Stoppering.*

Product Trays

LyoStar™ 3 lyophilizers are supplied with removable bottom stainless steel trays, one for each usable product shelf. These trays allow for greater heat transfer from the shelf to the vial sample. After loading trays filled with vials into the product chamber, remove the bottom to allow for better heat transfer to the vials. Before unloading the trays, replace the tray bottoms and remove the tray with the vials.

Note: *Product trays for bulk processing are also available from SP Scientific. Do not use removable bottom trays when bulk drying.*

[3] Siliconized rubber stoppers are recommended. Standard rubber stoppers used in dry vials may increase the required pressure.

Shelf Heat-Transfer System

The shelves are hollow to allow heat transfer fluid to circulate through them, and connected in parallel with inlet and outlet manifolds by stainless steel corrugated tubes. Both the inlet and outlet manifolds are located within the chamber.

The temperature of the shelves is controlled by the heating or cooling of the heat transfer fluid circulating through them. Two (2) 100 Ohm Resistance Temperature Detectors (RTDs) are used to monitor the shelf inlet and shelf outlet temperatures.

The heat transfer system is comprised of the following components:

- A heat exchanger cooled by the lyophilizer's refrigeration system.
- An immersion heater to heat the system's heat transfer fluid.
- A fluid pump to circulate the heat transfer fluid.
- A fluid expansion tank with a level indicator allows for changes in the volume of the heat transfer fluid across the full temperature range. A pressurized nitrogen gas blanket facilitates fluid circulation.

TDLAS Spool Piece

LyoStar™ 3 lyophilizers are considered TDLAS-ready. Equipped with a special vapor port that includes a removable spool piece, your lyophilizer can be easily converted for use with tunable diode laser absorption spectroscopy equipment.

Note: *For information about converting your system for use with TDLAS equipment, contact SP Scientific.*

Isolation Valve

LyoStar™ 3 lyophilizers include a butterfly-type isolation valve, installed in the vapor port between the product and the condenser chambers. The isolation valve is used to isolate the condenser chamber from the product chamber. It permits controlled defrosting of condensate and/or loading and unloading of product while the condenser is under vacuum or being defrosted, allows for periodic barometric endpoint (pressure-rise) testing during a freeze-dry cycle, and can assist operators when conducting leak checks of the vacuum system.[4]

Isolation Valve Utility Requirements

The standard isolation valve is equipped with a pneumatic actuator and requires a regulated supply of compressed air. Refer to the lyophilizer's specifications.

[4] Barometric End Point testing can be a useful method of determining product dryness. It relies on closing an isolation valve between the product chamber and condenser chamber and consequently observing the rise in pressure. The time that the isolation valve is closed is generally small (*i.e.,* 15 to 30 seconds). The rate and speed of rising pressure while the isolation valve is closed is an indication of product dryness. Typically, the slower and smaller the rise in pressure, the drier your product. For more information, refer to your control system operator's manual.

Condenser System

The external ice condenser consists of a continuous, multiple loop coil located inside a horizontally mounted, cylindrical vessel manufactured from grade 316L stainless steel. The condenser chamber, which is designed for and provided with reinforcement capable of withstanding full vacuum, is located below the product-drying chamber.

The condenser is connected to the drying chamber via a 4-inch (102-mm) diameter vapor port. A condenser drain is located on the front panel, below and to the left of the condenser door.

Condenser Cooling

The condenser cooling coils are mounted inside the chamber. The coils are continuous for optimal flow of refrigerant. Cooling of the condenser coils is achieved by the direct expansion of refrigerant in the condenser coils. The chamber is insulated to protect against external heat gain. A Type T thermocouple probe located on the cooling coil is used to monitor the temperature of the condenser.

Standard Condenser Door

The standard condenser chamber door is a full-view acrylic door. A split-ring gasket surrounds the chamber opening allowing the chamber to be sealed under vacuum when the door is closed.

Defrost

Defrosting of the condenser is achieved by pumping hot refrigerant gas through the condenser coils.

Refrigeration System

The LyoStar™ 3 includes a robust 5.5 hp cascade refrigeration system consisting of two scroll compressors—one 3.5 hp high-stage compressor and one 2 hp low-stage compressor. The refrigeration capacity is split to allow cooling of both the shelf and condenser simultaneously depending on demand, which is determined by the control system automatically during operation. The low-stage circuit discharges heat to the high-stage circuit via a cascade condenser at a temperature well below ambient. The heat is removed from the high-stage circuit by either a water- or air-cooled heat exchanger, depending on the purchased option. The low-stage circuit is used to provide cooling for the shelf and the condenser. A Type T thermocouple probe monitors the interstage temperature of the refrigeration system.

Refrigeration System Utility Requirements

Lyophilizers with air-cooled refrigeration systems require suitable ventilation and/or conditioning of the room. Water-cooled refrigeration systems require an adequate cooling water supply. Refer to the lyophilizer’s specifications.

Aeration and Vacuum Level Control

You may 'break' vacuum in the product and condenser chambers by aeration using nitrogen, room air or other suitable gas. A single inert gas port, which is located on the freeze dryer's rear panel, is provided for vacuum release, vacuum level control and backfill (*e.g.*, prior to stoppering). Room air or an inert gas supply is fed through a 0.2 micron sterile air filter to the product chamber during vacuum level control and backfill processes, or to the condenser chamber during vacuum release. The valve used for vacuum level control and backfill is located on the product chamber, while the valve used for vacuum release is located on the condenser chamber.

Vacuum System

The purpose of the vacuum system is to provide vacuum and vacuum level control at the setpoint required by the freeze-dry cycle. An adequately-sized two-stage rotary vane vacuum pump is typically supplied with LyoStar™ 3 lyophilizers. The vacuum system also includes an oil mist eliminator which traps or filters out oil mist created by the vacuum pump before the mist is expelled into the ambient environment.

Vacuum Pump Exhaust

As vacuum pump vapors can be unpleasant in the lab and are not typically permitted in a clean room environment, SP Scientific recommends installing an adequate vacuum pump exhaust system. Vacuum pump exhaust piping should travel horizontally from the pump across to a "T" equipped with a drainable trap and then 90 degrees vertically to an outside vent. Always place the drain trap as close to the pump as possible. Exhaust lines should have an inside diameter no smaller than the discharge of the pump. If you cannot exhaust directly outside the facility, a hood may be used.

LyoS™ Control System

The LyoS™ Control System is designed to meet the lyophilization requirements of pharmaceutical and biotechnology companies. The system is based on GE's Proficy HMI/SCADA iFIX solution for Windows® and utilizes an Allen-Bradley CompactLogix programmable logic controller (PLC).

The GE Proficy operator interface is designed for ease of use as a Human-Machine Interface (HMI), which presents process data to the operator and allows the operator to monitor and control all process parameters. The iFIX SCADA engine is ideally suited for process-driven applications, offering you faster, more intelligent control of your lyophilization cycle and related functions. Installed on a Microsoft® Windows®-based PC, the software provides visualization, data acquisition and supervisory capabilities directly to the PLC. All process control is completed via the PLC.

Note: *For more information, refer to your control system operator's manual.*

Programmable Logic Controller (PLC)

For every LyoStar™ 3 lyophilizer there is a Programmable Logic Controller (PLC) running a computer program configured to that system. There is a set of master PLC code, from which the PLC code for each individual project is derived.

Note: *For more information, refer to your control system operator's manual.*

Chapter 4

Operating your Lyophilizer

PRACTICAL OPERATING TIP. YOUR LYOPHILIZER IS SUPPLIED WITH A SOPHISTICATED CONTROL SYSTEM. REVIEW YOUR CONTROL SYSTEM OPERATOR'S MANUAL BEFORE OPERATING YOUR FREEZE DRYER.

WHEN IN OPERATION, ALWAYS ASSUME THE LYOPHILIZER CHAMBERS ARE UNDER VACUUM. ALL GLASSWARE UNDER VACUUM REPRESENTS A SIGNIFICANT IMPLOSION HAZARD. INSPECT ALL GLASSWARE USED IN THE LYOPHILIZER FOR VISIBLE DEFECTS (CRACKS, CHIPS, OR SCRATCHES) PRIOR TO USE. DO NOT USE GLASSWARE THAT IS DEFECTIVE.

LIQUID NITROGEN IS A HAZARDOUS MATERIAL THAT BOILS AT -194 °C. LIQUID NITROGEN PRESENTS A SEVERE FROSTBITE HAZARD. WHEN USING LIQUID NITROGEN, WEAR PROPER EYE PROTECTION AND PROTECTIVE GLOVES.

WEAR APPROPRIATE EYE PROTECTION AT ALL TIMES WHEN WORKING WITH OR ANYWHERE NEAR A LYOPHILIZER.

Leak Rate and Function Testing

Once LyoStar™ 3 is fully installed and operational, SP Scientific recommends performing automatic leak rate and function tests using your control system software. Refer to the lyophilizer's performance specifications when determining whether or not the results of these tests are successful. Consider successful test results baseline performance data. Maintain copies of test results for reference during routine testing of the lyophilizer.

Note: *For additional information regarding the automated Leak Rate and Function Test, refer to your control system operator's manual.*

Preparation and Pretreatment

Your LyoStar™ 3 lyophilizer is a high-performance R&D and pilot-scale tray freeze dryer, allowing you to process product in many ways including in bulk trays or vials. If you choose to process your product sample in a container, note that your container volume should always be at least two to three times the volume of your sample (*i.e.*, use 80 ml containers or larger when preparing 40 ml samples).

PRIOR TO OPERATING YOUR FREEZE DRYER, ENSURE THAT THE PRODUCT CHAMBER, SHELVES AND CONDENSER ARE CLEAN AND DRY. ENSURE THAT THE STOPPERING ASSEMBLY IS IN THE RETRACTED POSITION BEFORE PROCEEDING.

Product Temperature-Monitoring Probes

LyoStar™ 3 lyophilizers are equipped with ANSI Type T temperature-monitoring thermocouple probes, allowing you to monitor product temperature throughout the lyophilization process. The probe ends may be inserted directly into your product samples prior to freezing. When placing product probes, it is important to be uniform and consistent in order to obtain the best representative readings.

Supplied Product Probes

LyoStar™ 3 lyophilizers, with the standard configuration, are supplied with the following ANSI Type T temperature-monitoring thermocouple probe:

- Sixteen (16) temperature-monitoring thermocouple probes constructed of 24 AWG (0.0201 inches in diameter) Type T (copper, constantan) thermocouple wire with standard miniature two-pin male connectors.
- Eight (8) temperature-monitoring thermocouple probes constructed of 36 AWG (0.0050 inches in diameter) Type T (copper, constantan) thermocouple wire with standard miniature two-pin male connectors. Probes include resin caps with O-rings for use with 13 mm vials.
- Eight (8) temperature-monitoring thermocouple probes constructed of 36 AWG (0.0050 inches in diameter) Type T (copper, constantan) thermocouple wire encased in polytetrafluoroethylene (PTFE) sheathing with standard miniature two-pin male connectors. Probes include PTFE caps for use with 20 mm vials.

Placement in Bulk Samples

When processing bulk product samples, tape the thermocouple probe to the center of the product tray with the tip of the thermocouple just barely touching the bottom of the tray. Product may then be poured into the tray.

Placement in Serum Bottles or Vials

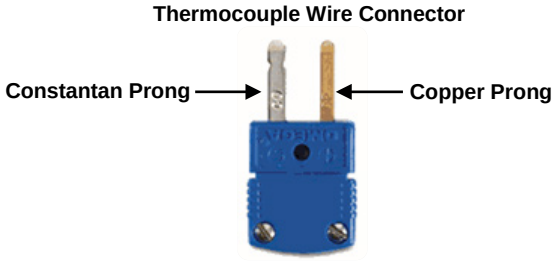
When processing product samples in vials or similar glassware, the thermocouple should be placed so that its tip is just touching the bottom center of the container. When possible, the sample with the thermocouple should be placed in the center of the product tray.

Placement in Unusual Containers or Samples

If an atypical container or product is being processed, place the thermocouple toward the bottom center of the product. The product should then be placed in the center of a product tray.

Thermocouple Connection

Once thermocouples are properly placed, the product may be loaded into the chamber. When connecting the thermocouple wire connector to the corresponding outlet on the product chamber jack panel, make sure that you achieve a copper-to-copper connection. A copper-to-constantan connection in the system will give erroneous readings.



Pre-Freezing

Product samples must be frozen before the start of the drying process. In many cases product samples are frozen before they are placed into the lyophilizer. Pre-freezing methods include, but are not limited to, using a laboratory freezer, dry ice, methanol, or liquid nitrogen.

Stoppers

The stoppering system allows you to fully seat stoppers into product vials upon completion of your freeze-dry process. Stoppers must be partially inserted into product vials prior to stoppering. Note that product vials must be loaded evenly across shelves for stoppering to occur correctly. SP Scientific recommends using the supplied removable bottom trays when processing in vials.

***Note**: For additional information, refer to Chapter 7: Stoppering.*

Freeze Drying

A typical freeze-drying cycle consists of two phases: freezing (which may include thermal treatment) and 17 drying steps. Conditions within the lyophilizer are varied throughout the cycle to ensure that the resulting product has the desired physical and chemical properties, and that the required stability is achieved.

***Note:** For information on how to perform a freeze-dry cycle, refer to your control system operator's manual.*

Once product samples have been prepared and loaded into the product chamber, ensure that the product and condenser chamber doors are securely latched, and the condenser drain valve is closed. Vacuum may be used to pre-seal the product and condenser chambers. When pre-sealing the product and condenser chambers, allow the vacuum to run for at least 30 seconds to create a verifiable seal.

Freezing / Thermal Treatment

Product samples must be frozen before the start of the drying process. Freezing can be accomplished directly in the product chamber as part of an automated cycle, or in a shell bath or laboratory freezer. The temperature required for freezing is dependent on the characteristics of the product sample. Typical freezing temperatures range between 10 °C and 20 °C below the product's eutectic or collapse point.[5]

Praxair's ControLyo™ Nucleation On-Demand Technology

ControLyo™ Nucleation On-Demand Technology is a new technology developed by Praxair, Inc., which utilizes a series of pressurization and depressurization events within the product-drying chamber using a gas to enable controllable instantaneous and homogeneous nucleation of the freezing event for all product containers in the chamber. Systems configured with Praxair's ControLyo™ Nucleation On-Demand Technology provide the option of performing these events during the Freezing / Thermal Treatment phase of a freeze-dry cycle.

Note: *For additional information, refer to Chapter 9: Praxair's ControLyo™ Nucleation On-Demand Technology and/or your control system operator's manual.*

Drying Steps 1-16

Once your product samples have been frozen, moisture must be extracted from the product through a process called sublimation. During the transition from freezing to drying steps 1-16, the condenser is typically cooled to its lowest possible temperature under the load. A cold condenser chamber, typically -40 °C or below, provides a surface on which the water vapor can re-solidify during the drying phases.

Using the lyophilizer's control system, the chamber pressure is lowered, and adequate heat is supplied to the product samples allowing the water within the product to sublimate. Temperature is controlled by the cooling and heating systems, while chamber pressure is controlled via the vacuum level control valve.

An inert gas may be used for vacuum level control, if desired. When using an inert gas for vacuum level control, be sure to use an accurate two-stage pressure regulator set to a maximum of 1 psig. Bleed gas should be connected to the lyophilizer's inert gas port.

Note: *SP Scientific recommends the use of nitrogen for vacuum level control with an inert gas. Gases other than nitrogen may cause inaccurate sensor readings.*

During drying steps1-16, about 95% of the product's water should sublimate. Note that these drying steps may take several days. When drying step 16 has completed, both the condenser and vacuum should reach a stable low reading.

Note: *For additional information, refer to your control system operator's manual.*

[5] A product's eutectic point is the point on phase diagram where three or more phases are present and the temperature and composition of the liquid phase cannot be altered without the disappearance of one of the solid phases. The reference to eutectic point assumes that the product being frozen has a crystalline structure. Amorphous materials, which are non-crystalline and structure-less in nature, do not have a eutectic point. Instead, they have what is referred to as a liquid-glass transition temperature (or simply glass transition temperature). However, amorphous materials do have a similar point, below which the product must be maintained to prevent melt-back or collapse during the freeze-drying process.

Drying Step 17

Some products may require an additional drying step even when they appear dry. It is during this phase that any remaining unfrozen water is removed from the product.

Using the lyophilizer's control system, the temperature is typically increased during this step to remove bound water until the residual water content falls to the range required for optimum product stability. The shelf temperature setpoint should be set higher than the temperature setpoint used in step 16 of drying for several hours in order to remove residual water. Some products may also benefit from an increased pressure setting during this step. The pressure setpoint may be modified as needed during this phase based on product characteristics.

Completing the Cycle

When the cycle completes, both the vacuum and condenser systems must be shut down.

If your system is equipped with stoppering and you are processing product in vials, activate the stoppering mechanism to seal your product vials. Stoppering may be executed at any desired pressure, using air or an inert gas for backfill, or while the system is under vacuum. Stoppering must be performed with evenly distributed vials of equal height to ensure uniform stoppering force and to prevent vial shifting.

***Note**: For additional information, refer to Chapter 7: Stoppering.*

Release, or break, vacuum from the system prior to unloading your product. Do not attempt to open the product or condenser chamber doors until the system pressure returns to ambient pressure.

Unplug product probes and remove your product from the product chamber.

Defrost

The condenser should be defrosted after each freeze-drying cycle. LyoStar™ 3 lyophilizers utilize hot gas from the compressor to warm the condenser coils during the defrost process.

CAUTION! DO NOT CHIP AWAY AT ICE WITHIN THE CONDENSER AS DAMAGE TO THE CONDENSER MAY RESULT.

After removing the ice and melted condensate from the condenser chamber, thoroughly clean and rinse the condenser with a mild detergent or baking soda solution to neutralize any acids that may be present.

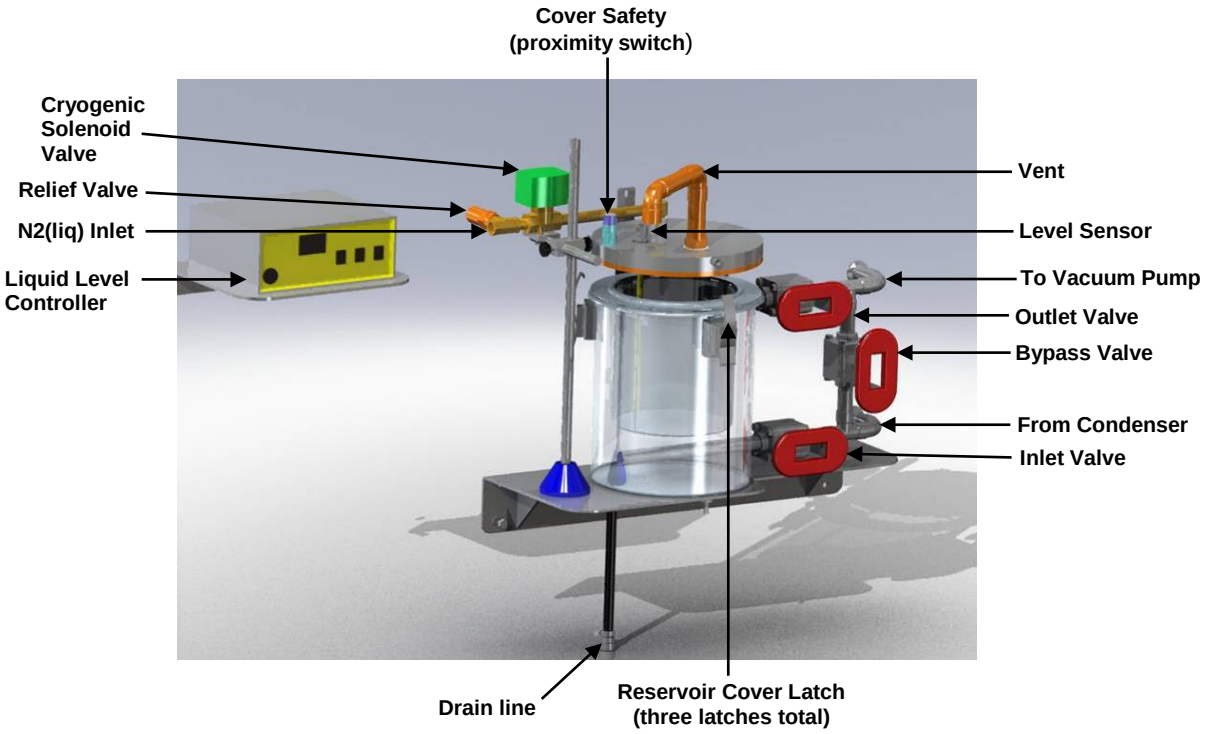
Liquid Nitrogen Trap

The optional auto-fill Liquid Nitrogen ($N_{2(liq)}$) Trap is designed to protect the vacuum pump from the corrosive properties of acid and alkaline vapors, as well as the low temperatures and organic solvents associated with the freeze-drying process.

A liquid level controller with a thermistor-type level sensor is provided with the Liquid Nitrogen Trap. The controller helps to maintain between 1 and 4 inches (2.54 and 10.16 cm) of liquid nitrogen in the reservoir. Low- and high-level alarms are preset at 0 and 6 inches (0 to 15.24 cm).

Note: *Refer to the liquid level controller operator's manual for further information.*

The following drawing illustrates the components of the liquid nitrogen trap.



WARNING! LIQUID NITROGEN, DUE TO ITS EXTREMELY LOW TEMPERATURES CAN CAUSE SEVERE CRYOGENIC BURNS. EXERCISE CAUTION WHEN HANDLING. WEAR PROTECTIVE GLOVES AND AVOID SKIN CONTACT. BEFORE OPERATING THE SYSTEM, READ THE LIQUID LEVEL CONTROLLER MANUAL AND COMPLETELY FAMILIARIZE ALL PERSONNEL WITH THE SAFE HANDLING AND STORAGE OF LIQUEFIED GASES.

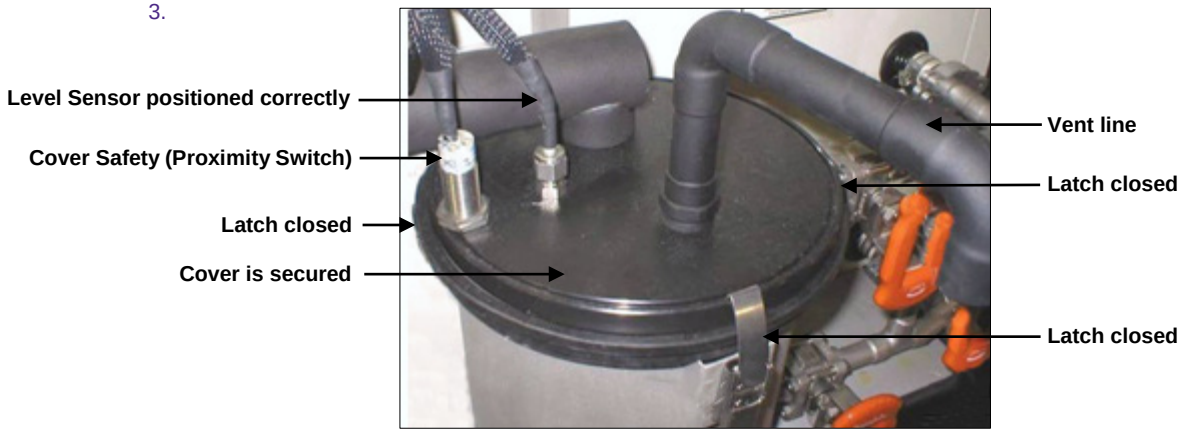
WARNING! INERT GASES RELEASED IN A CONFINED SPACE CAN DISPLACE SUFFICIENT AIR AND MAKE THE ATMOSPHERE INCAPABLE OF SUSTAINING LIFE. ENTERING AN OXYGEN DEFICIENT ATMOSPHERE MAY CAUSE UNCONSCIOUSNESS WITHOUT WARNING.

Operation

Before you begin operating the Liquid Nitrogen Trap, read the Liquid Level Controller manual and familiarize all personnel with the safe handling and storage of liquefied gases.

1. Ensure that all three reservoir cover latches have been closed and the reservoir cover is secure.

2. Fully insert the level sensor through the reservoir cover. If the sensor is not fully inserted, liquid nitrogen may overflow and spill out of the vent. Do not obstruct the vent line, as it could result in a pressure build up.

3. 

4. Open the liquid nitrogen supply valve.

5. Switch on the Liquid Level Controller and allow time for the liquid nitrogen reservoir to fill. Ensure that the reservoir cover is properly seated. If it is not, the proximity sensor will prevent the cryogenic solenoid valve from opening. When the liquid level in the reservoir reaches 4 inches (10.16 cm), the controller will close the solenoid valve.

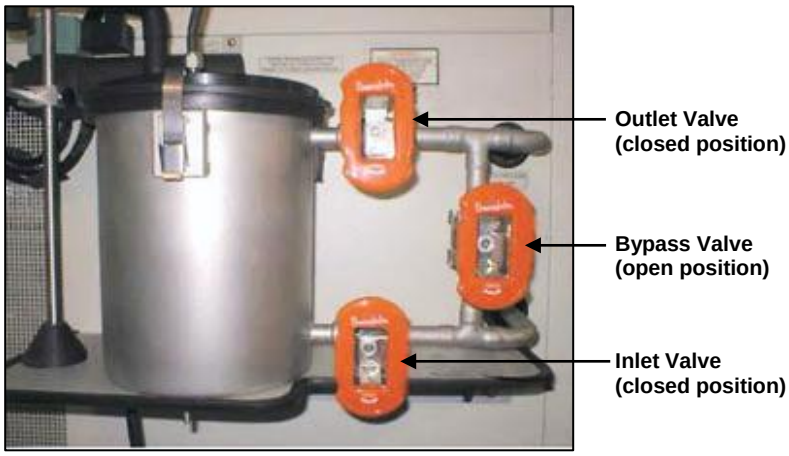
   Note: *The controller will activate the low-level audible alarm until liquid level rises above the end of the sensor. It may be muted.*

To activate the liquid nitrogen trap, open the inlet and outlet valves. Ensure that the bypass valve is closed. When the liquid nitrogen trap is in use, all valves should be parallel as shown below.

6.

To bypass the liquid nitrogen trap, open the bypass valve and close the inlet and outlet valves.

7.



8.

When liquid nitrogen is no longer needed, shut off the supply line and then depress the fill button several times to bleed the supply line.

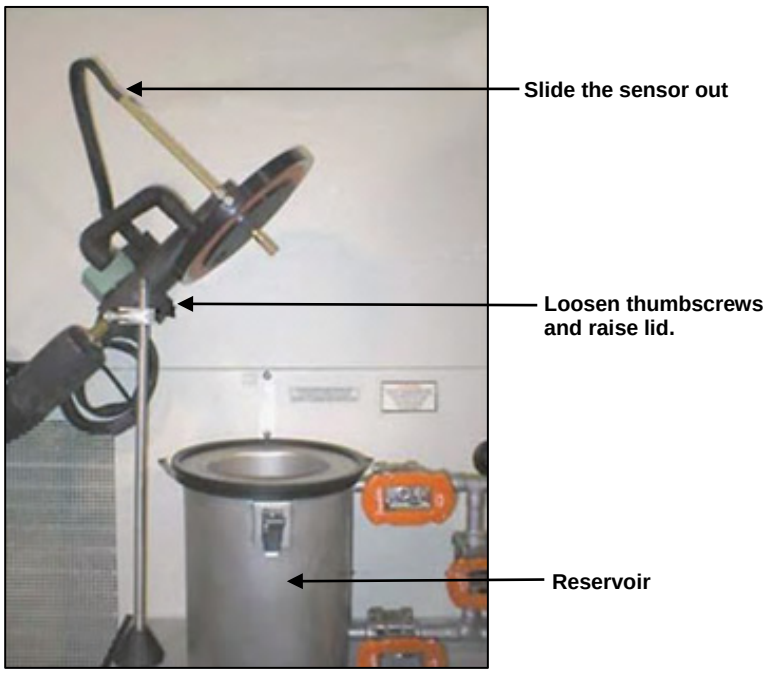
Cleaning

The accumulation of condensed vapors may result in a loss of vacuum, which typically indicates that defrosting is required. Check the trap by isolating the trap (*i.e.*, closing the inlet and outlet valves) and breaking vacuum to the trap, which is accomplished by removing the drain plug from the drain hose located under the stainless steel vessel. Carefully slide the sensor out of the lid. Loosen the black thumb screws and lift the lid. Attempt to lift the center well slightly. If the well does not move easily, your trap may require defrosting.

To clean your liquid nitrogen trap:

Make sure that the trap is offline and that the level controller has been powered off.

1. Remove any liquid nitrogen left in the center well.
2. Place an appropriate container under the trap.
3. Remove the drain hose plug.
4. Carefully raise the sensor.
5. ***Note:*** *The sensor tube material is fragile. Use care when raising and lowering the level sensor.*
6. Loosen the black thumbscrews and raise the lid up the shaft. Do not lift the lid off the top of the shaft.



7. Retighten the thumbscrews to hold the lid in the elevated position.
8. If the trap is frozen, allow it time to defrost. You may accelerate condensate melting by pouring hot water into the inner reservoir.

Note: *Under no circumstances should thawed condensate remain in the trap.*

When possible, remove the inner reservoir. Rinse off and clean any remaining condensate.

Drain the condensate using the drain line and wipe the outer reservoir clean.

Loosen the thumbscrews again and lower the lid.

9. Align and secure the reservoir cover latches and retighten the thumbscrews.
10. Carefully lower the sensor all the way back down into the reservoir.
11.
12.
13.

Sample Extractor Assemblies

The optional Sample Extractor Assemblies for LyoStar™ 3 lyophilizers allows you to select and remove a serum bottle or vial from the product chamber at any time during a freeze-dry run. The selection and removal process is accomplished with virtually no interruption to the drying process. The simplicity of the design and ease of use provides a cost effective methodology for periodic removal of product for sample analysis. The Sample Extractor Assembly is often pivotal in product development or stability studies.

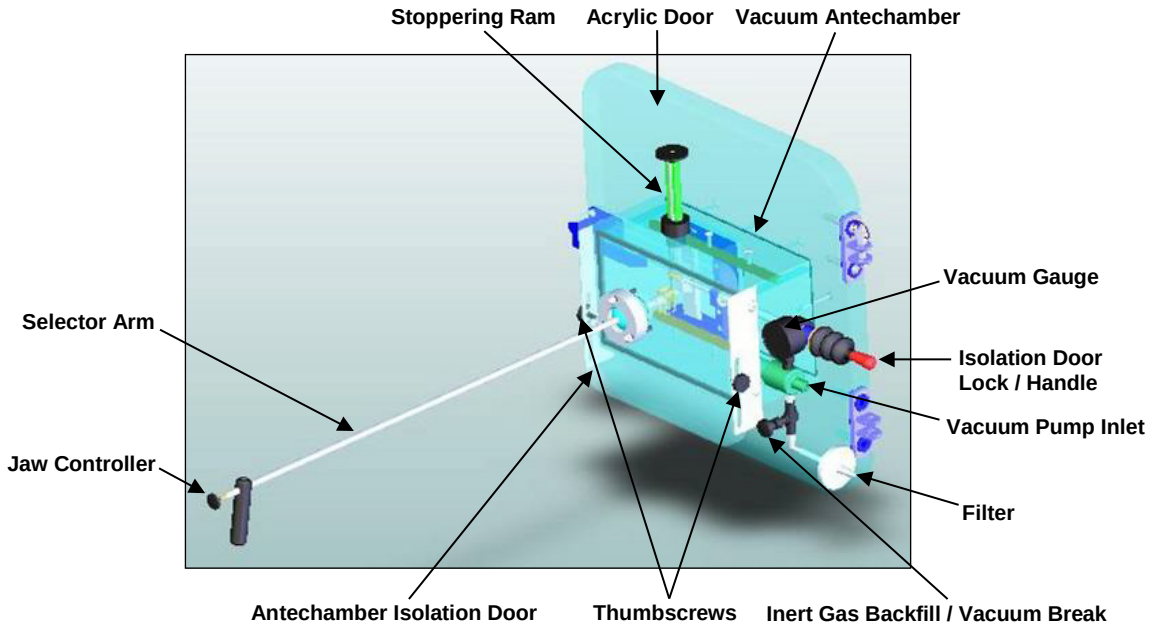
If your unit is equipped with a Sample Extractor Assembly, but does not feature optional Praxair ControLyo™ Nucleation On-Demand Technology, the Standard Sample Extractor (Acrylic) will be supplied and may be installed on site. If your unit is equipped with both a Sample Extractor Assembly and Praxair ControLyo™ Nucleation On-Demand Technology, the ASME-Coded Stainless Steel Sample Extractor will be supplied and installed at the factory. The Stainless Steel Sample Extractor is coded to the same ratings as the vessel and must not to be removed from the unit.

Note: *The Sample Extractor Assemblies use an auxiliary vacuum pump to depressurize the antechamber. This pump requires an additional electrical receptacle operating at either 115 VAC (for 60 Hz frequencies) or 230 VAC (for 50 Hz frequencies).*

Standard Sample Extractor Assembly (Acrylic)

Sample Extractor Assembly Components

The Standard Sample Extractor Assembly is comprised of a modified acrylic door with the following components:



Sample Extractor Installation

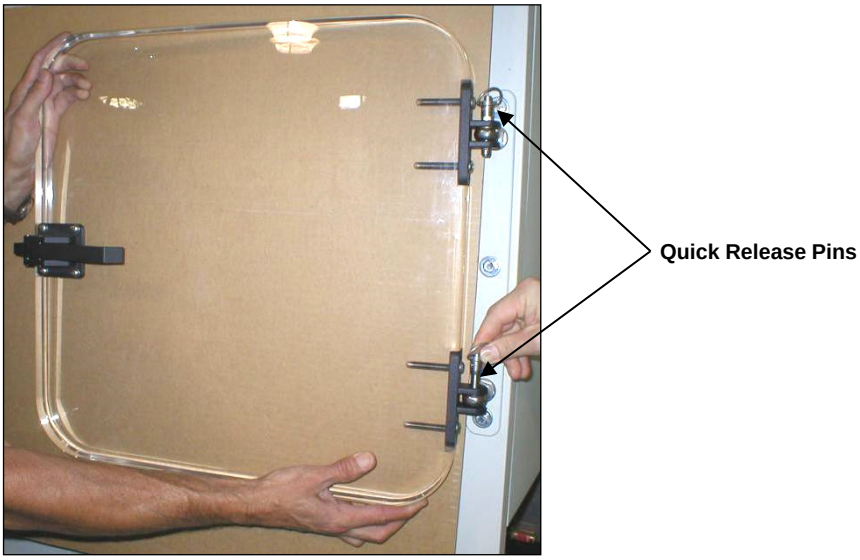
Standard Door Removal

Before installing the Sample Extractor Assembly, the standard acrylic door must be removed from the freeze-dryer.

Ensure that the unit is not in operation and that the product chamber is not under vacuum.

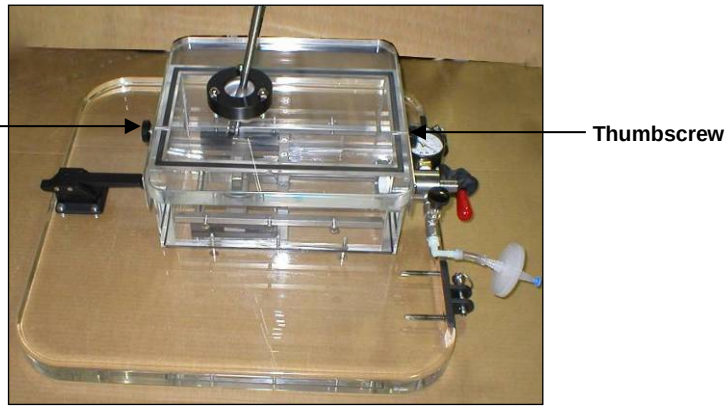
1. Open the product chamber door. Have an assistant in position to support the door.

2. Remove the upper and lower quick release pins from the hinge assembly, and remove the standard door.

3. 

1. Sample Extractor Installation

Prepare the Sample Extractor Assembly door for installation by unscrewing and removing both thumbscrews from the front panel.

2. 

Remove the front antechamber plate and selector arm.

Align the Sample Extractor Assembly door with the hinge brackets and reinstall the quick release pins.

3.

Sample Extractor Assembly Door Without Front Antechamber Cover And Selector Arm.

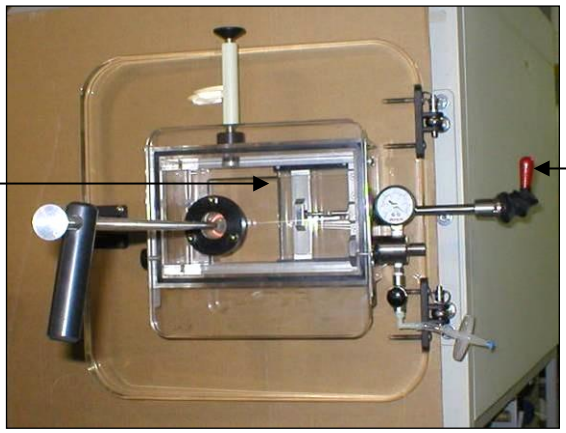
4. Reinstall the front antechamber plate with the selector arm using the thumbscrews.

Sample Extractor Operation

Before beginning operation of the Standard Sample Extractor Assembly, ensure that the front plate is closed and that the inert gas/vacuum break valve is closed.

To operate the Sample Extractor Assembly:

1. Activate the auxiliary vacuum pump to pull vacuum in the antechamber.
2. After the vacuum gauge stabilizes at the maximum position, allow the vacuum pump to operate for an additional 15 minutes.
3. Open the antechamber isolation door. With locking handle in the up position (unlocked), slide the antechamber door open.

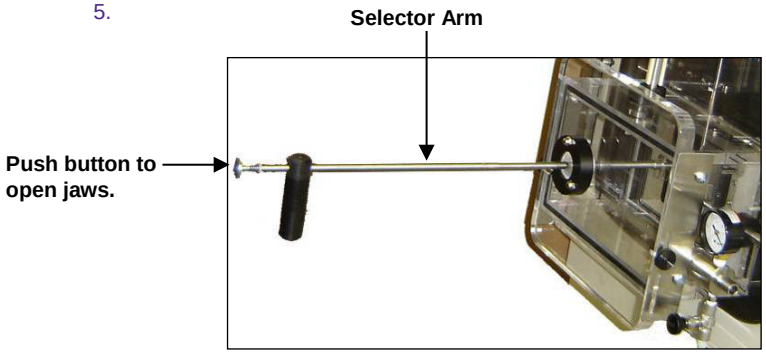


4. When the antechamber isolation door is fully open, lower the handle to lock the isolation door in position.

Manipulate the selector arm to select and extract a vial(s).

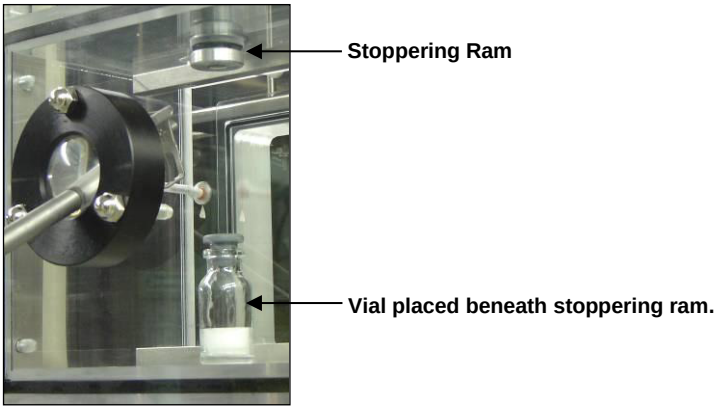
To extract a vial(s), push the button on the end of the selector arm to open the spring-loaded jaws. Place the open jaws around the top of the selected vial and release the button to close the jaws and secure the vial.

5.



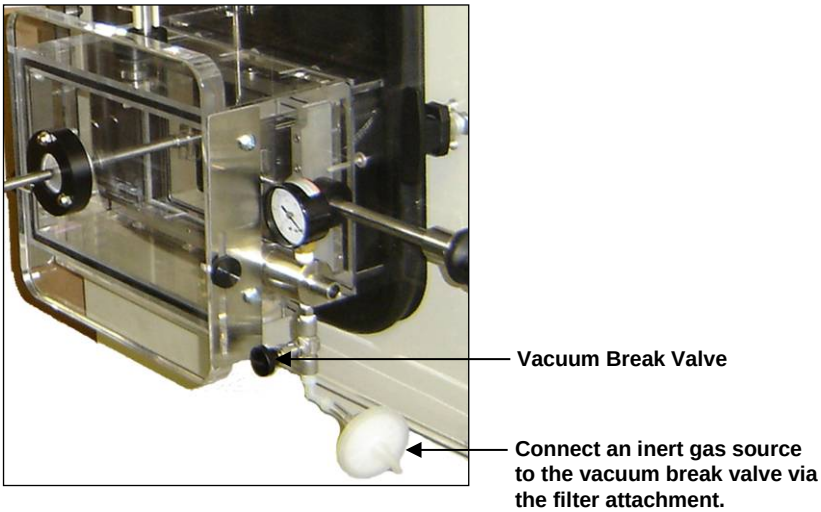
6.

Place a sample in the antechamber directly beneath the stoppering ram.



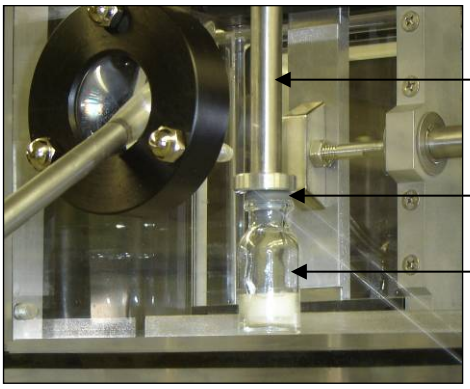
7. Slide the isolation door closed and lower the handle to lock it into position. Remove the plastic shroud from the stoppering ram.

8. Prior to stoppering the sample, you may backfill the antechamber with an inert gas, such as nitrogen ($N_{2(gas)}$) via the vacuum break valve. Connect your inert gas source to the vacuum break valve via the filter attachment.



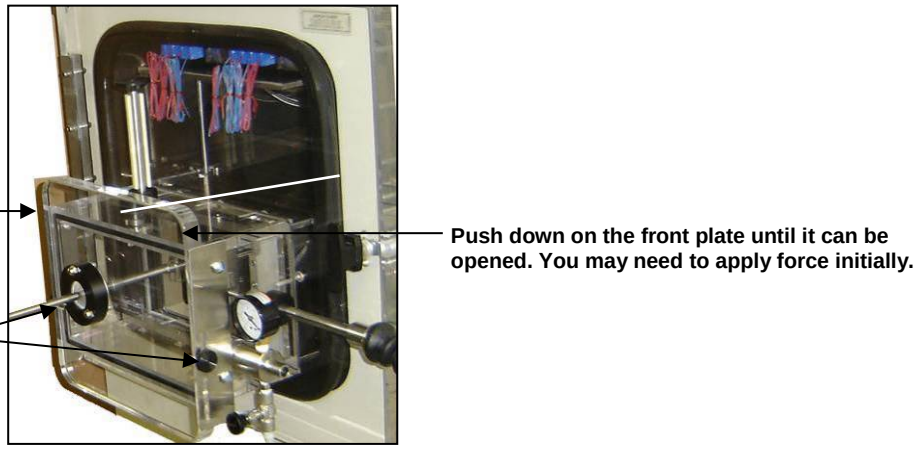
Press down on the stoppering ram to manually stopper the vial.

9.



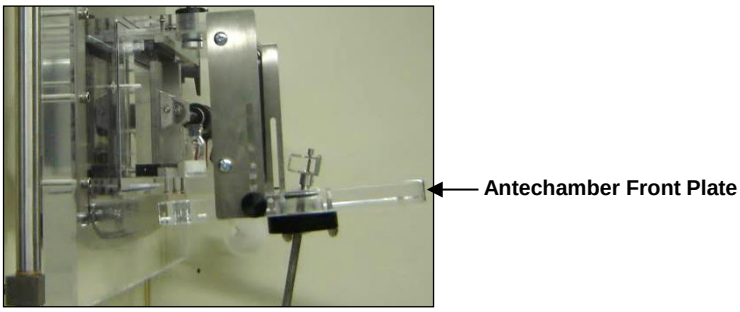
10. Before the sample can be removed from the antechamber, the antechamber pressure must be returned to atmospheric pressure. If you connected an inert gas source for backfilling, remove it now. Open the vacuum break valve to release vacuum from the antechamber. Allow the antechamber to return to atmospheric pressure.

11. Loosen the thumbscrews on each side of the antechamber and push down on the front plate until it can be opened.



12. ***Note:*** *Vacuum pressure in the chamber will cause the antechamber front plate gasket to seal. In order to break the seal, you may need to apply force initially when sliding down the front plate.*

Flip down the front plate.



Remove the vial(s).

13.

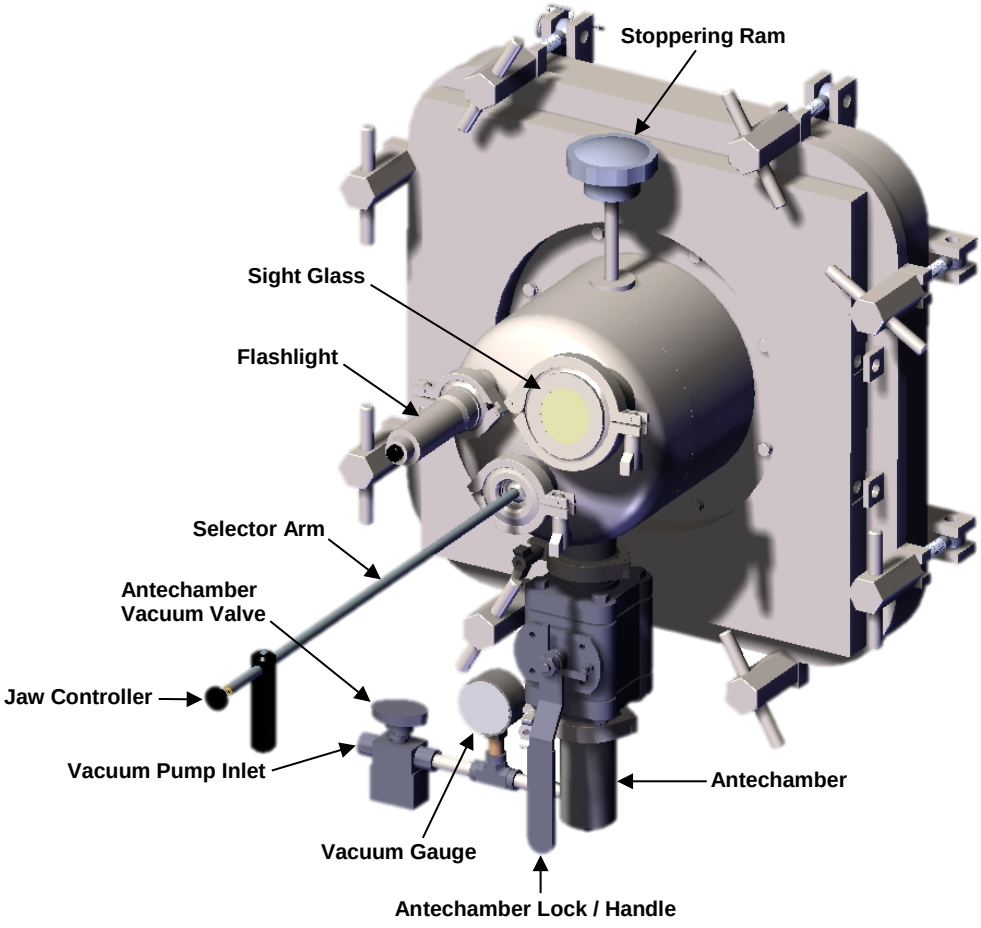
Close the front plate to reseal the antechamber.

14.

ASME-Coded Stainless Steel Sample Extractor Assembly

Sample Extractor Assembly Components

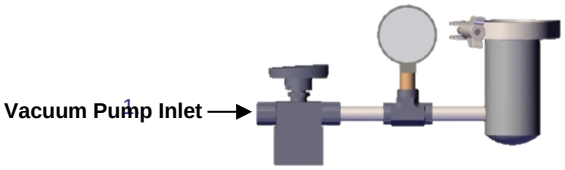
The ASME-Coded Stainless Steel Sample Extractor is comprised of a stainless steel door with the following components:



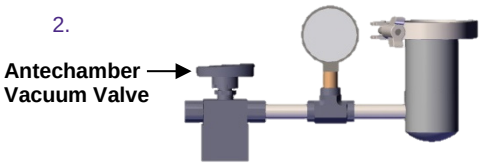
Sample Extractor Operation

To operate the Sample Extractor Assembly:

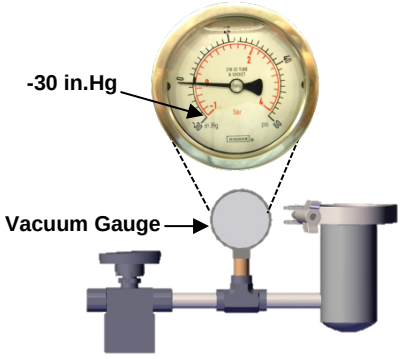
1. Ensure that the auxiliary vacuum pump is connected to vacuum pump inlet.



2. Activate the auxiliary vacuum pump and open the antechamber vacuum valve (by turning it to the right) to pull vacuum in the antechamber.

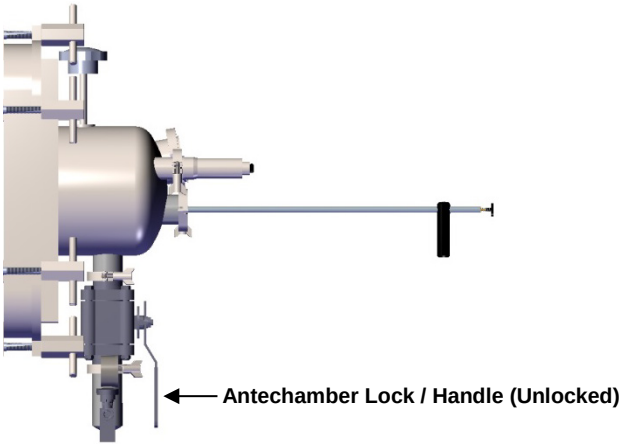


3. When the vacuum gauge reads approximately -30 inHg, close the antechamber vacuum valve (by turning it to the left) and deactivate the auxiliary vacuum pump.



4. Turn the antechamber lock / handle so it is parallel to the sample extractor (unlocked).

Note: *Unlocking the antechamber may cause the lyophilizer's primary vacuum reading to increase. The system's vacuum pump may activate to compensate for the sudden change in pressure.*

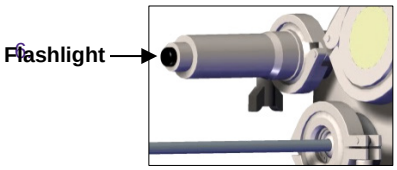


From the LyoS™ control system, ensure that the lyophilizer's parameters are stable before proceeding.

Ensure that the flashlight is securely fitted to the sample extractor assembly then press the black button on the back of the flashlight to illuminate the chamber.

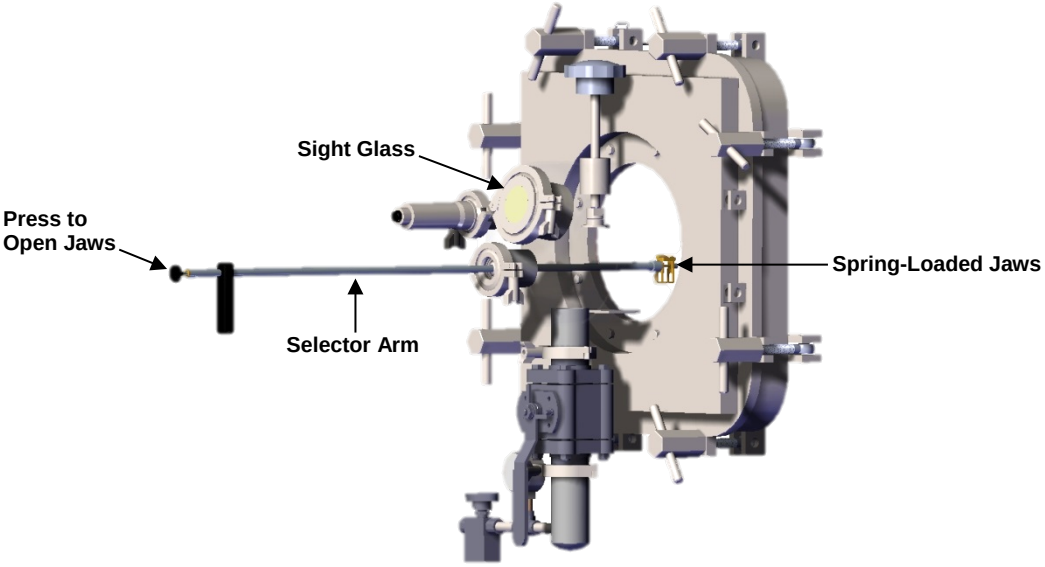
5.

6.



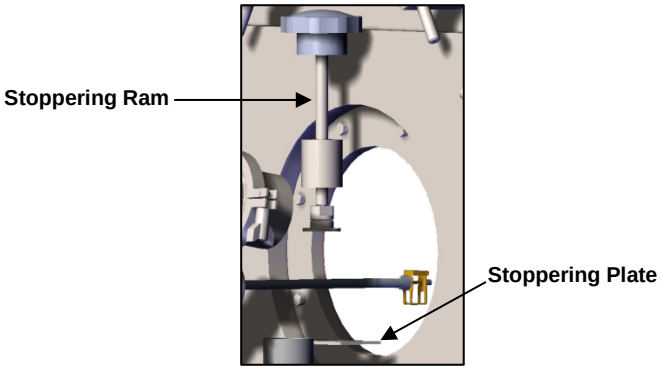
While looking through the sight glass, manipulate the selector arm to select and extract a vial.

7. To extract a vial, push the button on the end of the selector arm to open the spring-loaded jaws. Place the open jaws around the top of the selected vial and release the button to close the jaws and secure the vial.



8. ***Note:*** *For more information on sample extraction, refer to the Standard Sample Extractor Operation (Acrylic), Sample Extractor Operation section of this chapter.*

Using the selector arm, place the vial directly beneath the stoppering ram on the stoppering plate. Push the button on the end of the selector arm to open the jaws and release the vial.



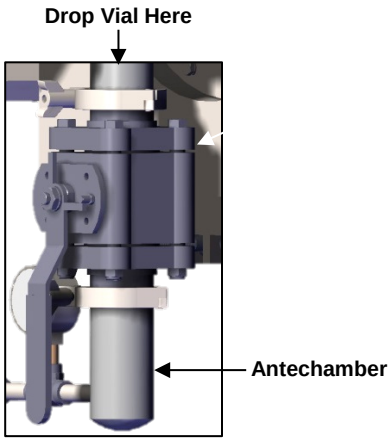
Once the vial is directly beneath the stoppering ram, press down on the stoppering ram to manually stopper the vial.

Once stoppered, use the selector arm to pick up the vial and bring it directly over the antechamber.

9. Once directly over the antechamber, release the vial dropping it into the antechamber.

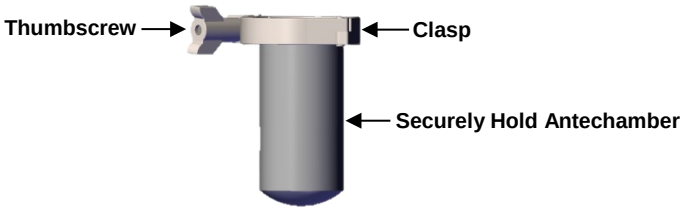
10.

11.

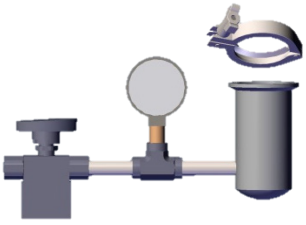


12. Once the sample is in the antechamber, turn the antechamber lock / handle so it is across the sample extractor (locked).

13. Securely hold the base of the antechamber and remove the clasp by loosening the thumbscrew.



Once the clasp is removed, the antechamber and vacuum components will separate from the Sample Extractor.



14.

15. ***Note:*** *The clasp is not attached to the antechamber. It may be necessary for two (2) people to complete step 13.*

Remove the vial from the antechamber.

Reattach the antechamber and vacuum components to the Sample Extractor by placing the clasp around the top of the antechamber and tightening the thumbscrew.

Note: *The clasp is not attached to the antechamber; therefore, it may be necessary for two (2) people to complete step 15.*

Shelf Spacing

Certain applications of the Sample Extractor Assemblies may require shelf spacing adjustments. Latching one (1) shelf up will position the other shelves so that a 20 ml vial may be used. It also increases the accessible shelf area to 240 in^2 (0.15 m^2).

Notes: *When removing 20 ml vial samples, select the vial and rotate the selector rod 90 degrees so that the vial is held horizontally as it is removed from the shelf.*

For additional information, refer to Chapter 8: Shelf-Latching.

Chapter 7

Stoppering

The LyoStar™ 3's stoppering system provides bottom-up shelf collapse allowing you to fully seat partially inserted stoppers into product vials at the end of a freeze dry cycle.[6]

A compact hydraulic power unit, mounted below the product chamber, is used to create the required stoppering pressure. The pump is typically preset to apply enough force on each shelf to fully stopper three full trays of 5 milliliter (ml) or larger vials.

Note: *If you intend to stopper full trays of vials smaller than 5 ml, the stoppering pressure may need to be increased. This adjustment should only be made by an SP Scientific authorized service technician. Please contact SP Scientific Service for assistance.*

While it is possible to process product in vials of different sizes simultaneously, to avoid glassware breakage and/or damage to your product never place vials of different heights on the same shelf.

PROPERTY CAUTION! TO PREVENT GLASSWARE BREAKAGE, DO NOT PLACE VIALS OF DIFFERENT HEIGHTS ON THE SAME SHELF.

The stoppering mechanism applies significant force to the vials when stoppering, therefore, SP Scientific does not recommend stoppering partially loaded shelves. In cases where you only have enough product to process a partially loaded shelf, consider positioning empty vials and stoppers around the product-filled vials to load the shelf completely.

Main Components

The main components of the stoppering system for LyoStar™ 3 lyophilizers include a hydraulic power unit (pump) with internal check valve and pressure gauge, a hydraulic cylinder and a method of operation such as a rocker switch or stoppering controls accessible from the control system human-machine interface (HMI).

The hydraulic cylinder rod is attached to the compressing platform. The terminal / top shelf is stationary, but all other shelves are moveable. The hydraulic cylinder rod raises and compresses the shelves during the stoppering process. Stoppering is achieved when the compressing force is fully transferred to the terminal shelf, pressing the shelves together.

[6] Siliconized rubber stoppers are recommended. Standard rubber stoppers used in dry vials will increase the required pressure.

Stoppering

The hydraulic stoppering mechanism may be operated under vacuum or after backfilling the chamber with inert gas. Operation of the stoppering system while the unit is at low temperatures is not recommended (*i.e.*, below -5° C).

Shelf spacing may need to be adjusted to accommodate various size vials. The LyoStar™ 3's shelf-latching kits may be used to modify the interdistance between shelves allowing you to process and adequately stopper vials of various sizes.

To stopper:

1. Press and hold the stoppering switch.

   ***Note**: The stoppering system is equipped with a safety interlock. Movement of the stoppering mechanism up or down can only be achieved with the product chamber door in the closed position.*

   The compressing shelf shall stop after the vials are fully seated.

2. After stoppering, return the shelves to the original position. The compressing shelf will stop at the initial position.

3. ***Note**: Shelves must be properly aligned and level to fully insert the stoppers. Incomplete stoppering across the shelf area may indicate that the shelf assembly is not properly aligned or level.*

4. Once vials have been stoppered and the product shelves have returned to their original loading position, chamber vacuum may be broken and the chamber door may be opened.

5. If removable bottom trays are used, samples shall be removed by reinserting the tray bottoms under the sample containers and then removing the full trays from the chamber.

   ***Note:** LyoStar™ 3 lyophilizers are supplied with removable bottom stainless steel trays. These trays allow for greater heat transfer from the shelf to the vial sample. Do not use removable bottom trays when bulk drying.*

Inert Gas Backfill

Some processes benefit from an oxygen-free atmosphere within product vials. This can be accomplished by backfilling with an inert gas prior to stoppering.

To backfill your product chamber with an inert gas:

1. From a gaseous nitrogen source, attach rubber tubing to the port labeled “INERT GAS”.

   Note: *SP Scientific recommends the exclusive use of nitrogen for this process. Any gas other than nitrogen may cause false readings on the vacuum sensors.*

2. Disable and release vacuum. Inert gas shall begin to bleed into the chamber. The amount of gas allowed into the chamber is arbitrary. You may fill the chamber to atmospheric pressure, if desired.

WARNING! NEVER CONNECT A GAS SOURCE WITHOUT A PRESSURE REGULATOR. THE PRESSURE REGULATOR MUST BE CAPABLE OF REDUCING SUPPLY PRESSURE TO 1 PSIG (70 MBAR OR 7 KPA) OR LESS.

WARNING! THE CHAMBER IS NOT DESIGNED FOR POSITIVE PRESSURE. OVERFILLING MAY CAUSE A SAFETY HAZARD.

Notes: *Some systems are programmed to allow for automatic backfill and automatic stoppering to be part of the freeze-dry cycle.*

For additional process information, refer to your control system operator’s manual.

Shelf-Latching

The product shelf assembly used in the manufacture LyoStar™ 3 lyophilizers is designed with a moveable shelf stack, which is primarily used to facilitate the stoppering of product vials. However, the ability of the shelf stack to move up and down also serves a second purpose. Using the shelf-latching kits that are provided with your unit, the shelf arrangement may be modified to increase the distance between shelves when processing product in large vials that do not fit into the standard shelf clearance of the unit.

Note: *The use of a shelf-latching kit will reduce the total number of usable shelves in your product chamber while increasing shelf clearance.*

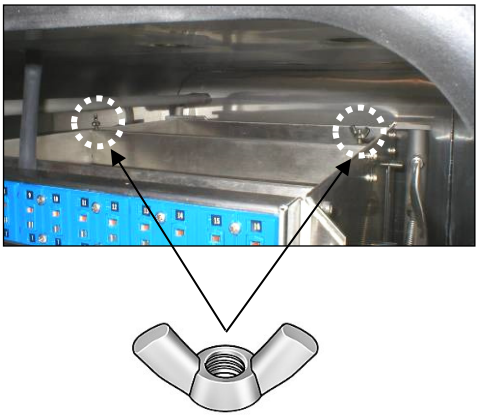
The shelf-latching kits with allow for:

- 2 to 1 shelf-latching on a 2-shelf unit.
- 3 to 2 and 3 to 1 shelf-latching on a 3-shelf unit.
- 4 to 3, 4 to 2 and 4 to 1 shelf-latching on a 4-shelf unit.

The following procedure demonstrates the use of a shelf-latching kit that allows the operator of a three-shelf LyoStar™ 3 lyophilizer to process and stopper on only two shelves within the product chamber. The instructions are essentially the same for each latching kit.

1. To install the shelf-latching kit:
2. Close the product chamber door and use the stoppering system to manually move all of the shelves into the full upright position.

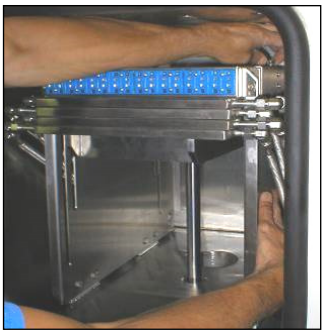
   Locate the threaded rods and wing nuts on the top of the shelf assembly.



Wing Nuts

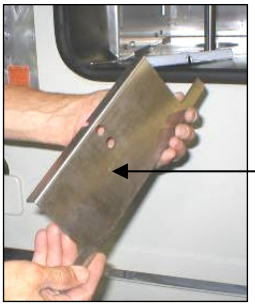
Loosen the wing nuts.

3.

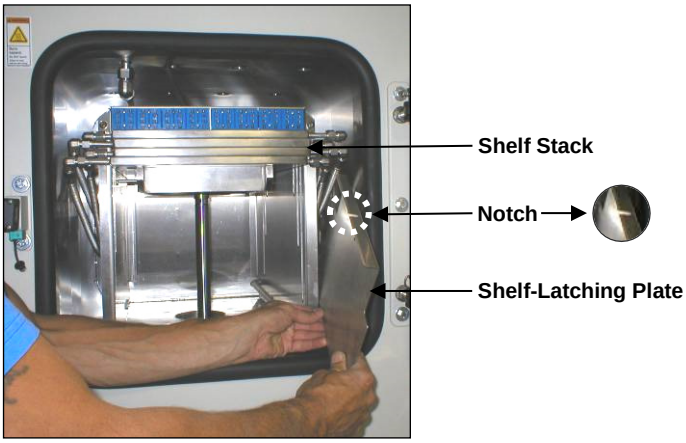


Obtain the shelf-latching plates.

4.

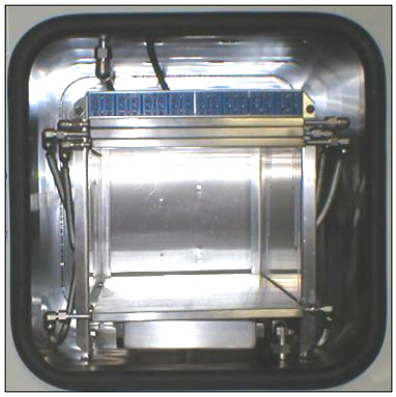


5. Slide the shelf-latching plates on either side of the shelf stack between the shelf fluid hoses and the shelf assembly so that the lip of the plate rests on top of the shelf assembly. Ensure that the notch fits around the tie rod.

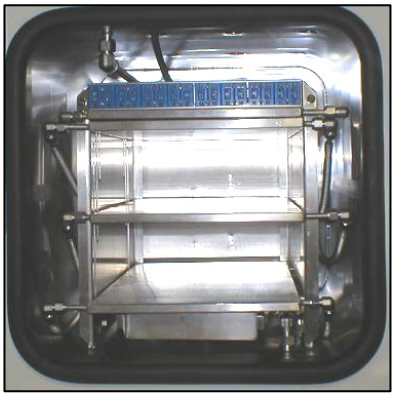


Secure wing nuts. Operate the stoppering system and return the shelves to their full down position (only the usable shelves will travel). The shelves are then available for loading. See examples.

6.



Three-Shelf Unit Converted To Single Usable Shelf Using Shelf-Latching Kit.



Three-Shelf Unit Converted To Two Usable Shelves Using Shelf-Latching Kit.

Chapter 9

Praxair's ControLyo™ Nucleation On-Demand Technology

THE FOLLOWING SECTION IS INTENDED FOR LYOSTAR™ 3 LYOPHILIZERS CONFIGURED WITH PRAXAIR'S CONTROLYO™ NUCLEATION ON-DEMAND TECHNOLOGY. FOR ADDITIONAL INFORMATION, REFER TO YOUR CONTROL SYSTEM OPERATOR'S MANUAL.

ControLyo™ Nucleation On-Demand Technology is a new technology developed by Praxair, Inc., which utilizes a series of pressurization and depressurization events within the product-drying chamber using a gas to enable controllable instantaneous and homogeneous nucleation of the freezing event for all product containers in the chamber.

Note: *For information on Praxair's ControLyo™ Nucleation On-Demand Technology, read the following section and refer to your control system operator's manual.*

WARNING! WITHOUT PROPER VENTILATION, OPERATION OF CONTROLYO™ MAY CAUSE THE OXYGEN CONCENTRATION OF AMBIENT AIR TO DROP BELOW ACCEPTABLE LEVELS. TO ENSURE THAT VENTILATION IS ADEQUATE FOR THE DEPRESSURIZATION PROCESS, THE VOLUME TO VENT PERCENTAGE RATIO (V_V/V_R) MUST BE LESS THAN 6.5%, WHERE V_V EQUALS THE PRODUCT CHAMBER VOLUME MULTIPLIED BY 10, AND V_R EQUALS THE TOTAL VOLUME OF THE ROOM IN WHICH THE LYOPHILIZER IS LOCATED. IN ADDITION, SP SCIENTIFIC RECOMMENDS THE USE OF AN O_2 SENSOR TO MONITOR OXYGEN CONCENTRATION WHILE OPERATING CONTROLYO™.

Note: *The volume of a standard LyoStar™ 3 chamber is 3.99 ft^3 / .113 m^3.*

NOISE FROM THE EQUIPMENT UNDER NORMAL OPERATING CONDITIONS SHALL NOT EXCEED 85 DBA WHEN MEASURED AT ANY POINT THREE (3) FEET AWAY FROM THE EQUIPMENT. LYOPHILIZERS EQUIPPED WITH CONTROLYO™ SHALL EXCEED THE SPECIFIED NOISE LEVEL RATING FOR APPROXIMATELY 3 TO 5 SECONDS DURING DEPRESSURIZATION. SP SCIENTIFIC RECOMMENDS THE USE OF BOTH HEARING AND EYE PROTECTION DURING THE CONTROLYO™ PROCESS.

The Praxair ControLyo™ Nucleation On-Demand Technology Process

Pressurization

The pressurization process for controlled nucleation involves the introduction of a sterile filtered inert gas into the lyophilizer product chamber. The control of the pressurization process is based on a pressurization setpoint and the measured product chamber pressure.

The pressurization function is designed to maintain the pressure in the product chamber to accommodate small leaks or changes in pressure due to gas temperature. The system will automatically re-pressurize the product chamber if pressure falls below the preset deadband, but only after the chamber has reached the pressure setpoint. The pressurization process will stop if the Pressurization Time Out (PTO) timer expires before the chamber pressure reaches the pressure setpoint. The PTO timer is started when a pressurization process is initiated. Pressurization is stopped after receiving a depressurization signal.

Depressurization

The depressurization process for controlled nucleation involves the rapid depressurization of the pressurized product chamber to a controlled setpoint above atmospheric pressure. This rapid depressurization induces controlled nucleation of freezing for materials contained within the product chamber. The depressurization process is completed in less than three seconds and requires a control system with a suitably fast processing speed. The control of the pressurization process is based on a depressurization setpoint and the measured chamber pressure.

Purging

The purge operation is triggered by the pressurization process above and follows the same logic. The only difference is that the pressurization and depressurization setpoints are changed to correspond to a purging operation. The purging operation is typically repeated 2 to 5 times based on the freeze dry recipe being used. The pressurization purge and depressurization purge, as well as the delay between purges and the number of purges are the configuration parameters that determine the purge cycle operation.

Importance of Controlled Nucleation

"Nucleation" denotes the onset of ice crystallization as the formulation is cooled during the Freezing / Thermal Treatment phase of the lyophilization cycle. The temperature at which nucleation occurs plays a key role in the outcome of the lyophilization process. In a conventional lyophilization process, nucleation occurs randomly at a temperature below the formulation's thermodynamic freezing point.

The degree of super-cooling required for an aqueous solution can be defined as the temperature difference between the thermodynamic freezing point of the solution and the temperature at which ice nucleation first occurs. The onset of ice nucleation is a stochastic event with the range of super-cooling depending on the solution properties and process conditions. In lyophilization of pharmaceutical formulations, the degree of super-cooling is normally higher in production than it is at the laboratory scale, due to the cleaner conditions and significantly reduced airborne particles in cGMP manufacturing environments. Nucleation occurs randomly from container to container with super-cooling of -10 °C to -20 °C being common. The degree of super-cooling is important because it determines the number of ice nuclei formed and thus the number and size of ice crystals in the frozen material. As a result, the degree of super-cooling can have a significant effect on the drying process and resulting cake structure.

Praxair's ControLyo™ Nucleation On-Demand Technology enables nucleation of all containers in the freeze-dryer at a defined time and temperature below the thermodynamic freezing point of the formulation and thereby provides much improved control over super-cooling. It should be noted that Praxair's ControLyo™ Nucleation On-Demand Technology cannot arbitrarily prevent the contents of a container from nucleating, especially if foreign particles are present in the formulation that could act as nucleating agents. Praxair's ControLyo™ Nucleation On-Demand Technology can make a container nucleate at the desired conditions prior to its spontaneous nucleation. As such, it is very useful for achieving uniform nucleation of all product containers at warmer nucleation temperatures than might otherwise occur.

Previous investigations have shown that nucleation behavior can significantly influence important lyophilization process and product attributes, including cake microstructure, drying rate, protein aggregation, reconstitution, vial cracking, product uniformity, and cake elegance. Praxair's ControLyo™ Nucleation On-Demand Technology therefore represents a potentially powerful tool for improving lyophilization processes. A full discussion of the potential benefits achievable with nucleation control is outside the scope of this document; only some general comments are provided below. It should be understood that the specific impact of nucleation control on any process or product attribute will depend on the nature of the formulation and the other lyophilization process steps.

A lower degree of super-cooling (*i.e.*, warmer nucleation) generally produces larger ice crystals, which upon sublimation in drying steps 1-16 leave behind larger pores. Larger pores can significantly reduce the mass transfer resistance of the cake to shorten the drying time and lower the product temperature during drying steps 1-16 compared to the smaller pores resulting from uncontrolled, colder nucleation conditions. Proteins tend to aggregate on the surface of ice, and the larger ice crystals obtained with warmer nucleation temperatures can alleviate aggregation stress on sensitive proteins. Additionally, larger pores in the cake structure can result in a faster reconstitution of the cake. Furthermore, one of the important goals of the freezing step during lyophilization is to produce a uniform batch, which is often difficult to achieve because of the stochastic nature of nucleation. By removing nucleation heterogeneity, ControLyo™ technology can significantly improve homogeneity of the lyophilization process to within the limits of the heat transfer uniformity of the freeze-drying equipment and containers.

Key Steps

Key steps for utilizing Praxair's ControLyo™ Nucleation On-Demand Technology are outlined below:

1. Load product containers into the lyophilizer and securely latch the chamber doors.
2. Connect the supply gas source to the compressed gas inlet of the lyophilizer.

Note: *The identity of the gas can significantly impact the efficacy of Praxair's ControLyo™ Nucleation On-Demand Technology. Inert gases are generally recommended for lyophilization processes. Both argon and nitrogen are suitable gases with argon possessing superior efficacy. For laboratory-scale freeze-dryers, the gases may be supplied from a gas cylinder or from a liquid dewar in combination with an appropriately sized vaporizer.*

3. Purge the drying chamber with the same inert gas used for nucleation control to make sure the majority of the gas atmosphere in the freeze-dryer has the desired identity.
4. Pressurize the product chamber with the same inert gas to the highest pressure permitted by the Maximum Allowable Working Pressure (MAWP) of the lyophilizer (*e.g.*, the MAWP of the LyoStar™ 3 is 28.5 psig). A higher initial pressure is more favorable for product nucleation.

Cool product containers to the target nucleation temperature (*e.g.*, 1 to 2 °C below the thermodynamic freezing point of your product). The shelf temperature should be set at a temperature such that the product is maintained below the target nucleation temperature during depressurization.

5. ***Note:*** *The pressurization and cooling events do not need to follow a certain sequence prior to the depressurization step that induces nucleation (e.g., pressurization followed by product cooling or product cooling followed by pressurization). To optimize batch uniformity, it is generally recommended that product temperatures and chamber pressure be approximately equilibrated at the desired values prior to depressurization.*

6. Allow samples to cool until warmest sample temperature is -1 °C or colder, as dictated by the thermodynamic freezing point of your product. To improve nucleation uniformity, hold the shelf temperature for a minimum of 60 minutes to achieve temperature equilibration in all samples.

7. Depressurize the chamber to approximately 1 to 2 psig to induce nucleation. To avoid possible back-flow of material from the environment into the product chamber, it is recommended that you close the valves through which the depressurization is achieved at a positive chamber pressure (*i.e.*, final pressure in the product chamber is greater than ambient pressure). Praxair's ControLyo™ Nucleation On-Demand Technology is considered effective when all product containers within the lyophilizer nucleate and begin freezing within seconds of triggering the depressurization event. The rate and magnitude of the pressure drop are important factors in determining the efficacy of Praxair's ControLyo™ Nucleation On-Demand Technology. Praxair's ControLyo™ Nucleation On-Demand Technology is generally more effective for greater and more rapid pressure drops.

8. The product temperature profile following the nucleation event can impact the final ice crystal structure. It is generally recommended that you maintain the product containers at the target nucleation temperature for additional time after nucleation to allow the ice crystals to grow larger. The optimal post-nucleation shelf cooling profile for a given product should be determined via experiments.

9. Reduce shelf temperature to complete the freezing step.

10. Complete the freeze-dry cycle, monitoring critical cycle characteristics of the drying phase.

Mechanism

The exact mechanism by which Praxair's ControLyo™ Nucleation On-Demand Technology induces nucleation is not fully understood, but there are hypotheses as to what may give rise to nucleation. The gas in the product chamber undergoing expansion during depressurization will cool, and the cold gas contacting the surface of the metastable liquid in the vial might induce nucleation. Another hypothesis is that depressurization may cause local evaporation of some surface liquid, and the resultant evaporative cooling may trigger nucleation. Another possibility is that sudden depressurization may generate a pressure wave or vibrational disturbance that mechanically induces nucleation. Other mechanisms may be envisioned, and multiple mechanisms may contribute to the successful control over the initiation of nucleation. The mechanism remains speculative, though, and additional research is needed.

Guidelines and Performance Expectations

The target nucleation temperature should be a few degrees (usually 1 or 2 °C) below the thermodynamic freezing point of the formulation to accommodate potential inaccuracies in product temperature measurement or estimation. Therefore, the freezing point should be accurately determined experimentally prior to lyophilization with analytical methods such as DSC (differential scanning calorimetry) or FDM (freeze-drying microscopy).

The efficacy of ControLyo™ technology generally improves with the following:

- Increasing magnitude and rate of the pressure drop.
- Use of argon gas instead of nitrogen gas.
- Colder target nucleation temperature.
- Larger product container size.
- Lower fill volume.

The ControLyo™ technology is designed for a given lyophilizer's pressure rating and available depressurization orifices to provide effective nucleation control for as wide a range of nucleation temperatures, container sizes, fill volumes, and gas types as possible. If a lyophilizer can accommodate a sufficiently large and rapid pressure drop, the ControLyo™ technology can controllably induce nucleation in all product containers and fill volumes of practical interest for lyophilization using nitrogen gas at temperatures within 1 °C of a formulation's thermodynamic freezing point (*i.e.*, the typical measurement capability of a thermocouple). If the ControLyo™ technology cannot achieve uniform nucleation control in a difficult application (*e.g.*, 1.5 mL fill in a 2 mL vial) using nitrogen gas at a temperature close to the formulation's thermodynamic freezing point, it may be necessary to decrease the target nucleation temperature or use argon gas instead of nitrogen gas to achieve nucleation control.

The ControLyo™ technology has been designed for SP Scientific's LyoStar™ 3 lyophilizers to provide robust nucleation control capabilities. It is anticipated that the ControLyo™ technology should be able to achieve the following in a LyoStar™ 3 lyophilizer:

- Nucleate any lyophilization container greater than or equal to 2 mL in nominal volume having a fill volume less than or equal to 75% of the nominal container volume using argon gas at a temperature within 3 °C of the formulation's thermodynamic freezing point.
- Nucleate any lyophilization container greater than or equal to 5 mL in nominal volume having a fill volume less than or equal to 75% of the nominal container volume using nitrogen gas at a temperature within 3 °C of the formulation's thermodynamic freezing point.

It is necessary to confirm experimentally the nucleation control capabilities for a given combination of freeze-dryer and ControLyo™ system. As such, it will be necessary to confirm experimentally the expectations provided above for the implementation of the ControLyo™ technology.

Chapter 10

General Maintenance

Proper routine maintenance is the key to an efficiently operating lyophilizer with minimal downtime, and will likely extend the life of your equipment, sub-systems and components.

Maintenance should be performed a minimum of four times a year. Because system use and application varies from one facility to another, system maintenance may need to be performed more frequently.

Vacuum System

Vacuum Pump

Clean oil is necessary for optimal vacuum and overall efficiency of the vacuum system. Checking and changing the oil on a regular basis will greatly extend the life of the vacuum pump. Check the vacuum pump oil after each freeze-dry cycle by draining a small amount (~100 mL) from the pump drain line. Use a clear container to capture the sample. Oil should be changed as needed.

When visually checking the oil, use the following guidelines:

- Pale yellow or clear vacuum pump oil indicates good condition.
- Dark vacuum pump oil indicates acid contamination.
- Cloudy gray vacuum pump oil indicates water contamination.

Changing Vacuum Pump Oil

1. Change the oil immediately after shutting down the pump while the oil is still hot.
2. Protect your hands from the hot oil. Make sure vacuum is released from the system.
3. Remove the top fill plug and open the drain valve located at the bottom of the pump. Drain the contaminated oil into a suitable container.
4. When the oil has completely drained, close the valve and add new oil to the pump while visually checking the sight glass to ensure proper level (near the MAX line). Reinstall the fill plug.

   If pump oil is particularly contaminated, operate the vacuum pump for 10 to 15 minutes to flush any residual oil from the system's interior components. Repeat steps 2 and 3 to complete the process.

PROPERTY CAUTION! IF YOUR PRODUCT CONTAINS CORROSIVE MATERIALS OR ORGANIC SOLVENTS, OIL MUST BE CHECKED AND CHANGED MORE FREQUENTLY. IN ADDIATION, A FILTER TRAP MAY BE INSTALLED TO PROTECT THE VACUUM PUMP AND PUMP OIL.

Scheduling Oil Changes

After clean oil is loaded into the vacuum pump and all necessary connections have been made between the vacuum pump and the freeze dryer, perform a full capacity test cycle.

Have a qualified technician check the oil after the test cycle. If the oil appears dirty, you may need to change the oil after every use. If the oil appears clean, check the oil again after two uses or cycles. If the oil remains clean after two cycles, check the oil again after four cycles. Continue to monitor the vacuum pump oil after each cycle until a change of condition is noted or a period of one month elapses. If the oil remains clean after several cycles, changing the oil once per month may be sufficient.

Gas Ballast Valve on the Vacuum Pump

The gas ballast valve removes some contaminants from the pump oil. During freeze-drying, vapors may bypass the condenser and end up in the vacuum pump. If this occurs, the vapors will degrade the oil, causing excessive wear and higher vacuum pressure.

When the ballast is open, it allows a controlled amount of air into the second stage pump cylinder. This reduces the partial pressure, increases the pump's operating temperature and releases the vapors.

Note: *Refer to the vacuum pump manual for the location of the gas ballast valve.*

Vacuum Tubing and Gaskets

Inspect tubing and gaskets periodically for signs of wear. Check gaskets by removing and inspecting interior surfaces for potential problems.

Door Gasket

Ensure that the chamber and condenser door gaskets are clean and free of defects (cuts, cracks, tears). If a gasket shows signs of cracks or tears replace it immediately. Failure to do so shall result in poor vacuum integrity. As a minimum, gaskets should be inspected quarterly and replaced annually.

Note*: The door gaskets do not require vacuum grease for pre-seal or operation.*

1.
2. To check the door gasket:
3. Remove the door gasket.
4. Grip the gasket with both hands and turn it inside out.
5. Inspect the inside of the gasket, which has the highest potential for developing a problem.

   If any inconsistencies are found in the material (*e.g.*, cuts, cracks, dry rot, rippling), replacement is necessary.

   Reinstall door gaskets on a clean, grease-free metal rim. Remove excess grease from the metal using isopropyl alcohol on a clean paper towel or cloth. The gasket may be cleaned with isopropyl alcohol as well.

Refrigeration System

The LyoStar™ 3 is designed for installation and operation in a room with a controlled temperature of between 19 and 25 °C. If the ambient temperature is routinely higher than the equipment specifications, the amount of refrigerant gas being condensed as it passes through the condenser will be less. This could lead to premature failure of the compressor(s) or compressor efficiency problems such as an inability to reach maximum low temperature.

Air-Cooled Condenser

It is very important to keep the air-cooled condenser clean. This is where high-pressure vapor from the compressor is converted to liquid refrigerant by rejecting the heat gained from the vapor condenser into the ambient air. Reduced airflow over the condenser can result in severely reduced performance and may shorten the life of the compressor.

To maintain the air-cooled condenser and compressor:

1. Do not allow any paper, cloth or Kimwipes® to slip underneath the unit. These items obstruct airflow.
2. Always maintain at least 24 inches (61 cm) of clearance around all sides of the unit. If machines are installed side-by-side, increase the minimum clearance to 48 inches (122 cm).
3. Maintain a room temperature of between 19 and 25 °C. Higher temperatures may result in reduced performance and shorten compressor life.
4. Clean the fins on the unit. Dust buildup may cause the unit to malfunction.

Water-Cooled Condenser

The optional water-cooled condenser consists of a highly-efficient heat exchanger, which removes up to 90 percent of the energy consumed by the compressor. If your unit is equipped with a water-cooled refrigeration system, ensure that the water supply is on and providing cooling water within a temperature range of 5 to 25 °C. Do not operate the LyoStar™ 3 with a cooling water supply above 30 °C (86 °F). If the water supply is off, the resulting high pressure in the system may damage the compressor.

The water-cooled condenser may require occasional flushing to remove deposits, depending on the quality of the water supplied to the system. Periodically examine connections for leaks or cracks.

Condenser Chamber

The condenser chamber is fabricated from stainless steel. Under normal use, it may be rinsed and kept clean with a mild detergent. If corrosive materials are being processed in the lyophilizer, thoroughly clean and rinse all parts of the freeze dryer that come in contact with product moisture. This shall prevent the residual build-up of corrosive and contaminating materials on interior surfaces, protecting the lyophilizer, as well as the next product batch to be processed.

You may add baking soda or any mild buffering agent to the rinse water to help neutralize acidic residue. A siphon type squeeze bottle can be used to direct rinse spray into difficult to reach areas.

Acrylic Parts

Clean acrylic parts with a mild detergent. Use a soft cloth or Kimwipes® to avoid scratching the acrylic.

CAUTION! DO NOT USE ORGANIC SOLVENTS OR ABRASIVE CLEANERS.

Chemical Resistance Chart

Chemical	Code	Chemical	Code	Chemical	Code
Acetic Acid (5%)	R	Ethyl Alcohol (50%)	LR	Nitric Acid (10%)	R
Acetic Acid (Glacial)	N	Ethyl Alcohol (95%)	N	Nitric Acid (40%)	LR
Acetic Anhydride	LR	Ethylene Dichloride	N	Nitric Acid (Conc.)	N
Acetone	N	Ethylene Glycol	R	Oleic Acid	R
Acetonitrile	N	2-Ethylhexyl Sebacate	R	Olive Oil	R
Ammonium Chloride (Saturated)	R	Formaldehyde (40%)	R	Phenol Solution (5%)	N
Ammonium Hydroxide (10%)	R	Gasoline (Regular, Leaded)	LR	Soap Solution (Ivory)	R
Ammonium Hydroxide (Conc.)	R	Glycerine	R	Sodium Carbonate (2%)	R
Aniline	N	Heptane	R	Sodium Carbonate (20%)	R
Battery Acid	R	Hexane (Commercial Grade)	R	Sodium Chloride (10%)	R
Benzene	N	Hydrochloric Acid	N	Sodium Hydroxide (1%)	R
Benzyl Alcohol	N	Hydrofluoric Acid (40%)	R	Sodium Hydroxide (10%)	R
Butyl Acetate	N	Hydrogen Peroxide (3%)	R	Sodium Hydroxide (60%)	R
Calcium Chloride (Sat.)	R	Hydrogen Peroxide (28%)	N	Sodium Hypochlorite (5%)	R
Calcium Hypochlorite	R	Isooctane	R	Sulfuric Acid (3%)	R
Carbon Tetrachloride	N	Isopropyl Alcohol	LR	Sulfuric Acid (30%)	R
Chloroform	N	Kerosene	R	Sulfuric Acid (Conc.)	N
Chromic Acid (40%)	N	Lacquer Thinner	N	Toluene	N
Citric Acid (10%)	R	Methyl Alcohol (50%)	LR	Transformer Oil	R
Cottonseed Oil (Edible)	R	Methyl Alcohol (100%)	N	Trichloroethylene	N
Detergent Solution (Heavy Duty)	R	Methyl Ethyl Ketone (MEK)	N	Turpentine	LR
Diesel Oil	R	Methylene Chloride	N	Water (Distilled)	R
Diethyl Ether	N	Mineral Oil	R	Xylene	N
Dimethyl Formamide	N	Naphtha (VM&P)	R	Trifluroacetic Acid	N
Dioctyl Phthalate	N				
Ethyl Acetate	N				

CODES

R = Resistant (withstands long periods of exposure at temperatures up to 50 °C).

LR = Limited Resistance (withstands short periods of exposure at room temperature).

N = Not Resistant (immediate damage may occur upon exposure).

Routine Maintenance Schedules

The typical lyophilizer is a sophisticated instrument used for processing pharmaceutical and/or biotechnology products. Each lyophilizer includes, as a minimum, a refrigeration system, vacuum system, shelf system, condenser system, electrical system, control system and a heat transfer system, as well as optional systems.

Complex mechanical systems require routine maintenance to guarantee trouble-free product processing and long equipment life. SP Scientific recommends incorporating routine maintenance schedules into your production schedules as per your company's Standard Operating Procedures (SOPs).

Each of the following Recommended Maintenance Schedule items includes the skill level of the individual designated to complete the task.

- **Level 1** tasks can be accomplished by the operator or someone within your maintenance department.
- **Level 2** tasks require an individual trained in refrigeration, vacuum and/or electronic control systems.
- **Level 3** tasks normally require a Service Engineer or an individual trained and certified in lyophilizer testing and repair procedures. **Level 3** items may be performed by SP Scientific.

Notes: *Monthly, Quarterly, Annual and Five-Year Maintenance Schedules may differ slightly from unit to unit due to the options purchased and the original system configuration.*

For more information, contact SP Scientific Service.

Recommended Monthly Maintenance Schedule

SP Scientific recommends performing the following maintenance tasks monthly. If additional assistance is required, please contact SP Scientific Service.

Recommended Monthly Maintenance	Task Level
Inspect the product chamber and condenser door gaskets and ensure that they are clean and free of defects (cuts, cracks, tears). If a gasket shows signs of cracks or tears replace it immediately.	Level 1
Check the operation of the temperature-monitoring thermocouple probes. An approximate ambient temperature reading should be observed on the temperature display.	Level 1
Clean the interior surface of the product chamber. Remove any broken glass or foreign material.	Level 1
Check the level and condition of the vacuum pump oil. Change oil when required. See the vacuum pump manual supplied with your lyophilizer for instructions. Drain some oil in the sump of the pump and compare it against a clean, unused vacuum oil sample. If the pump oil appears discolored or cloudy, change it.	Level 1
Check for residual water in the drain lines and if evident, remove.	Level 1
Ensure that all automated controls, such as shelf temperature control, operate properly.	Level 1
Check for normal frost patterns on the compressor. Report any anomalies to your maintenance department.	Level 1
If your unit is equipped with a water-cooled refrigeration system, check cooling water flow and temperature, if possible. Report the low flow or high temperature conditions to your maintenance department.	Level 1
Check air supply pressure if utilized for valve actuation.	Level 1

Recommended Quarterly Maintenance Schedule

SP Scientific recommends performing the following maintenance tasks quarterly. If additional assistance is required, please contact SP Scientific Service.

Recommended Quarterly Maintenance	Task Level
Complete all items outlined on the Recommended Monthly Maintenance Schedule.	Level 1
Check for proper operation and sealing of the condenser and product chamber doors. Adjust as needed.	Level 1
Check the refrigeration air-cooled condensers for dust or foreign material. Clean with a shop vacuum or air source if required. ***Note:*** *Not required for water cooled units*	Level 1
Ensure that at least 10 inches (25.4 cm) of open space exists in the rear and sides of the unit for free air movement.	Level 1
Check the vacuum system for leaks by performing a vacuum leak rate test. Compare the original documented leak rate to the latest results.	Level 1, Level 3
Check the line voltage reading. The indicated value should be within ± 5% of the unit's required voltage when voltage ranges are provided or ±10% for single voltage configurations (see Serial Tag).	Level 1
Check the oil level in each compressor, if provided with a sight glass. The level should read to the maximum fill line. Report low-level conditions to your maintenance department.	Level 1

Recommended Annual Maintenance Schedule

SP Scientific recommends performing the following maintenance tasks annually. If additional assistance is required, please contact SP Scientific Service.

Recommended Annual Maintenance	Task Level
Complete all items outlined in the Recommended Monthly and Quarterly Maintenance Schedules.	Level 1
Inspect all vacuum connections for minor cracks or wear points. Replace as needed.	Level 3
Repeat the calibration of all temperature-monitoring probes (*e.g.,* product temperature probes, shelf temperature probe(s) condenser temperature probe(s), etc.).	Level 2, Level 3
Repeat the calibration of all vacuum-level sensors.	Level 2, Level 3
Check the static pressure in one or, in the case of redundant systems, both refrigeration systems. Pressures should be checked by a qualified refrigeration technician and only after a twenty-four hour stabilization period. Compare obtained readings to the information on the refrigeration charge nameplates. Check for refrigerant leaks if the indicated pressure has deviated more than 10 psig.	Level 2, Level 3
Check the fluid level of the refrigeration system. Check refrigeration system piping and components for fluid leaks.	Level 2, Level 3
Check the fluid level of the heat-transfer system. Check heat-transfer system piping and components for fluid leaks. A special dye was mixed with the heat transfer fluid during manufacture to allow for easy leak detection with a black light. Pay special attention to Swagelok connections and flex hoses, if applicable.	Level 3
If your unit is equipped with a stoppering system, check for proper operation. The stoppering system should move freely. Make adjustments as needed. Check the stoppering system for fluid leaks.	Level 1, Level 3
If your unit is equipped with a water-cooled refrigeration system, remove PENN water regulation valves from condenser receivers and inspect for scale or rust. If scaling or rust is present, clean the valves and chemically clean the plate exchangers as per manufacturer instructions.	Level 2, Level 3
Lubricate all motors that require lubrication.	Level 2
Inspect the product chamber and condenser door gaskets for age cracks, worn spots and/or minor cuts. Replace as needed.	Level 1, Level 2
Inspect all rubber vacuum connections utilized for vacuum-level sensor connections, vacuum bleed and vacuum break connections. Check for age cracks, worn spots or minor cuts. Grease the inside diameter of vacuum tubes with vacuum grease and re-install. Replacement tubing kits are available based on model.	Level 2, Level 3

Recommended Five-Year Maintenance Schedule

SP Scientific recommends performing the following maintenance tasks every five years. If additional assistance is required, please contact SP Scientific Service.

Recommended Five-Year Maintenance	Task Level
Complete all items outlined in the Recommended Monthly, Quarterly and Annual Maintenance Schedules.	Level 1, Level 2, Level 3
Remove the vacuum pump and replace all parts included in the “minor rebuilding kit.” Contact SP Scientific Service for parts or Factory On-Site Assistance.	Level 2, Level 3
Test the volumetric efficiency of the refrigeration system compressor(s).	Level 2, Level 3

Appendix A: Sample Recipe

The sample recipe is provided as a general reference only. The format is based on the Recipe screen of the LyoS™ control system.

The following recipe parameters are intended for use with one (1) liter of water. Before you begin, fill one bulk-processing tray with water, place it on one of the product shelves in the chamber and close the door. Enter the following recipe parameters and run a freeze dry cycle.

Freezing / Thermal Treatment

Step	1	2	3	4	5	6	7	8	9	10	11	12	
	✓	✓	X	X	X	X	X	X	X	X	X	X	
Temp	20	-20	0	0	0	0	0	0	0	0	0	0	°C
Ramp	0	80	0	0	0	0	0	0	0	0	0	0	min
Hold	10	30	0	0	0	0	0	0	0	0	0	0	min

Control with CM	✓	
Guaranteed Soak	X	
Product Driven Mode	X	
Product Temperature	20 °C	
Shelf Load	X	

Extra Freeze

Product Temp SP	-40 °C	Hold Time	60 min	Condenser SP	-45 °C	Initial Vacuum SP	100 mTorr

Drying Phase

Step	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
	✓	✓	✓	✓	✓	✓	X	X	X	X	X	X	X	X	X	X	✓	
Temp	-40	0	10	20	40	0	0	0	0	0	0	0	0	0	0	0	25	°C
Ramp	0	80	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	min
Hold	60	120	240	600	360	0	0	0	0	0	0	0	0	0	0	0	30	min
Vacuum	0	0	100	200	0	0	0	0	0	0	0	0	0	0	0	0	0	mTorr
V.Ramp	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	min
PRISE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	mTorr
PVG/CM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	mTorr

Product Storage		**Backfill/Stoppering**					
Product Temp SP	50 °C	Backfill	X	PVG/CM Diff.	X		
Vacuum SP	0 mTorr	Stoppering	X	Pressure Rise	X	Retest Time	2 min
		End Cycle		Control Action	X	Closure Time	20 sec

Appendix B: Troubleshooting

Troubleshooting Chart

Condition	Possible Cause	Recommended Corrective Action
Freeze-dryer starts hard (*i.e.,* difficulty or rough starting). Makes chugging noises at startup.	Low voltage supply.	Check the voltage and amperage supplied to the unit against the freeze-dryer's serial tag. If supply is low, contact a certified electrician to evaluate.
The system will not respond to the commands sent from the computer	Lyophilizer not powered on.	Check that the lyophilizer is plugged in and the circuit breaker on the rear of the system is switched on.
	Data communications problem.	Check to ensure that the communication cable is connected between the computer and the freeze-dryer. Shut down the computer and power off the LyoStar. Restart the LyoStar™ 3 and the computer.
Vacuum pump will not start.	No power to pump motor.	1) Vacuum pump motor circuit breaker tripped. 2) Automatic control not in vacuum or heat phase. 3) Check the power source in the electrical box at the Solid State Relay or Contactor. (See electrical schematic for reference points.)
	Power to motor OK, but pump will not start.	Vacuum pump may be seized. Motor should be removed (see vacuum pump manual) and started without pump attached. This will determine if the problem is in the motor or the pump. If the pump module is seized, it should be rebuilt or replaced.
Vacuum pump runs, but unit has no vacuum.	Condenser drain left open.	Check plug in drain hose.
	Door gaskets not sealing.	Close door latches snugly. A properly sealed door should show a distinctive ¼ " to ½ " wide dark ring where the gasket comes in contact with the acrylic door.
	Accessory ports, valves or filters not closed tightly.	Check all connections for integrity.
	Water under the door gasket.	Remove door gasket and remove any condensation that may be collected. Door gasket should be dry and grease-free on the inside.
Unit pulls vacuum but system pressure does not register on display or other vacuum gauges.	Defective probe.	Test with McLeod gauge or remote vacuum gauge and replace the probe if necessary.
	Vacuum level not low enough to register	If pump has been running at least 30 minutes, test for vacuum leaks.

Condition	Possible Cause	Recommended Corrective Action
Compressor does not start.	No power to compressor.	Verify that power is connected and refrigeration switch is on. Check for power on compressor wires in electrical panel (See schematic drawing).
	Compressor pulling excessive amperage LRA (Locked Rotor Amps).	Replace Compressor.
Condenser temperature OK, shelf/product chamber temperature will not decrease.	Shelf/product chamber solenoid not opening.	Check voltage to coil – replace coil if necessary.
	Low heat transfer fluid.	Check heat transfer level at service panel. The fluid should fill ½ to ¾ sight glass at room temperature. Add fluid if necessary.
	No or low nitrogen pressure in heat transfer system.	Nitrogen pressure should be 20 psig at nitrogen charge access valve.
	Heat transfer fluid not circulating.	No nitrogen pressure (see above).
	Heat transfer pump not turning.	Check voltage to pump motor. Replace pump if necessary.
	Possible refrigeration system leak.	Find leak, repair, evacuate and recharge to specifications.
Shelf/product chamber temperature OK, condenser temperature will not decrease.	Condenser solenoid not opening.	Check voltage to coil. Replace coil if necessary.
	Condenser expansion valve improperly adjusted (if equipped).	Readjust valve so the compressed suction service valve has frost on it, but not on the body of the compressor. This should be tested at the specified temperature.
	Possible refrigeration system leak.	Find leak, repair, evacuate and recharge to specifications.
Shelf/product chamber temperature will not reach specified low temperature.	Shelf expansion valve improperly adjusted (if equipped).	Readjust valve so the compressed suction service valve has frost on it, but not on the body of the compressor. This should be tested at the specified temperature.
	Low refrigerant.	Check static charge, find leak, repair, evacuate and recharge to specifications.

Additional Troubleshooting: Vacuum System

If a vacuum leak is suspected in your freeze-dryer, perform a preliminary vacuum leak check of your system. The following steps will guide you through troubleshooting your vacuum system.

Vacuum Pump Test

This test will help you determine whether the system has a possible vacuum leak or a defective vacuum pump.

To check the vacuum pump:

1. Isolate the vacuum pump from the system by blocking off the main vacuum port with a rubber stopper. Be sure to block off the main line upstream of the vacuum gauge sensor so that you can use the sensor to monitor vacuum levels.[7] On some models, you may be able to look inside the condenser chamber and place the stopper into the main inlet port.

2. If the pump does not pull vacuum, call SP Scientific Service.

3. If the pump appears to be working properly, but vacuum does not reach the system's specified blank-off, you may have a faulty vacuum gauge. Retest the system with another gauge and/or call SP Scientific Service.

4. If the vacuum pump test is successful and the gauge appears to be operating properly, proceed to the product chamber and condenser vacuum leak test.

[7] The vacuum probe sensor is typically located in the main vacuum line between the vacuum pump and the condenser chamber.

Product Chamber and Condenser Vacuum Leak Check

To check the product and condenser chambers, and related vacuum connections:

Open the product chamber door and visually inspect the shelf assembly for liquid leaks. Use a flashlight if necessary. If a liquid leak is observed, call SP Scientific Service immediately.

1. If liquid leaks are not found, isolate the lyophilizer's external condenser from the product chamber. You may plug the throat of the product chamber using rubber stopper, or close the isolation valve (LyoStar™ 3 lyophilizers are equipped with a pneumatic isolation valve).
2. Start the condenser manually. Wait for the condenser temperature to drop below -40 °C.
3. Start the vacuum pump. Allow the system to stabilize at its lowest specified temperature and vacuum.
4. If the condenser is not able to reach vacuum levels of 20 millitorr or below, begin checking all vacuum system connections between the condenser and
5. the vacuum pump. Ensure that the drain port is closed and that connections are snug. If you need additional assistance, call SP Scientific Service.
6. If the condenser is able to reach vacuum levels of at least 20 millitorr, you can likely rule out any leaks from the condenser area. The suspected vacuum leak may be related to the product chamber area.
7. To check the product chamber for leaks, begin by placing your finger over the vacuum level control port at the rear of the system.
8. If you feel a sucking sensation when your finger is on this valve port, the solenoid valve may be faulty. Call SP Scientific Service.
9. If you do not feel vacuum being pulled through the vacuum level control port, apply a product such as SNOOP® liquid leak detector to the external surfaces of the product chamber door gasket.[8] While applying this liquid, monitor the chamber vacuum reading for fluctuations. Watch the door gasket for leak
10. locations. Replace the door gasket as needed. Call SP Scientific Service.
11. If leaks are not detected, apply the liquid leak detector to all fittings located on top of the product chamber. Again, monitor the chamber vacuum reading for fluctuations and watch for leak locations. If a leak is identified near the fittings, call SP Scientific Service.

If the system is still unable to pull adequate vacuum, call SP Scientific Service.

[8] SNOOP® liquid leak detector is manufactured by the Swagelok Company.

Appendix C: Stainless Steel Cleaners

Cleaning Required	Cleaning Agent[9]	Application Method[10]	Effect on Finish
Heat Tint or heavy discoloration	Penny-Brite or Copper-Brite	Use in direction of polish lines on No. 4 (polished) finish. Wipe with dry cloth.	May scratch No. 2 (mill-rolled) and Nos. 7 and 8 (polished) finishes.
	Paste Nu-Steel, DuBois Temp, Tarnite, or Kelox	Rub with dry cloth or stainless steel wool.	Use in direction of polish lines on No. 4 (polished) finish. May scratch No. 2 and No. 7 and 8 (polished) finishes.
	Revere Stainless Steel Cleaner, Take-Off, or AC-60	Apply with damp sponge or cloth.	Use in direction of polish lines on No. 4 (polished) finish. May scratch No. 2
	Allen Polish, Steel Bright, Wyandotte, Bob-O, Zud, Dubrite, or Prepare Dex	Rub with a damp cloth.	Use in direction of polish lines on No. 4 (polished) finish. May scratch No. 2 (mill-rolled) and No. 7 and No. 8 (polished) finishes.
Tenacious deposits, Rusty Discolorations, Industrial atmospheric stains.	Oakite No. 33, Dilac, Texo 12, Texo N.Y., Flash-Klenz, Caddy Cleaner, Turco Scale 4368, or Permag 57	Swab and soak with clean cloth. Allow to stand 15 minutes or more, per directions on package. Then rinse and dry.	Satisfactory for use on all finishes.
Hard Water Spots and Scale.	Vinegar	Swab or wipe with cloth. Rinse with water and dry.	Satisfactory for use on all finishes.
	Dilac, Oakite No 33, Texo 12, Texo N.Y.	Swab with cloth or soak. Let stand 10-15 minutes. Always follow with neutralizer rinse, and dry.	Satisfactory for use on all finishes. Effective on tenacious deposits or where scale has built up.

[9] Use of proprietary names is only intended to indicate a type of cleaner, and does not constitute any endorsement (nor does omission of any proprietary name imply its inadequacy). All products should be used in strict accordance with instructions and warnings on the product package.

[10] In all applications, a stainless steel wool, sponge fibrous brush, or pad is recommended. Avoid use of ordinary steel wool or steel brushes for scouring stainless steel.

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