Frozen in Time Ltd

Manufacturers of Freeze Drying Machines and Vacuum Cold traps

Operating Manual F25

<u>Operating Manual</u>

<u>F25</u>

Order Number:

Serial Number:

In case of enquiries please state the above

For service please contact:

FROZEN IN TIME LTD
York Road Industrial Park, Sheriff Hutton
York, YO60 6RZ, England
info@freezedriers.com

Telephone: 01347 878158
International: +44 1347 878158

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1. General Information

1.1. Introduction

What is freeze drying (lyophilisation)?

Freeze drying means: Removal of water from frozen material. The drying process takes place by going direct conversion from ice to vapour. This process is called sublimation. This happens under vacuum when the temperature in the product is less than -10°C.
The aim of freeze drying is to obtain a readily water-soluble product which has the same characteristics as the original product after the addition of water. As the drying process takes place in the frozen state at low temperatures it is possible to dry proteins which will not denature. Also most of the other chemical compounds will be unchanged.
Freeze drying products, of biological origin such as tissues, tissue extracts, bacteria, vaccines and sera transforms them into a dry product. During this process enzymatic, bacterial and chemical changes are largely avoided. Freeze drying is the gentlest process for preserving the biological properties of sensitive tissue and tissue components. Freeze drying can also be used for dry some inorganic products.

1.2. Technical data of freeze driers F25

F25 Freeze Drier Specification	
Overall Dimensions W x H x L cm	***120 x 200 x 215***
Tray Area m²	***2.6m²***
Shelves	**6+1 with 60mm spacing**
Shelf Dimensions	**550mm x 800mm**
Ice Condenser Temperature	**-60 ºC**
Shelf Temperature Range ºC	**-50 to +90 ºC**
Defrost	**Hot Gas**
Chamber Door	**Clear Acrylic**
Condenser Ice Capacity	***40 litre***
Cooling system	**Air Cooled**
Refrigerant	**R-449a**
Vacuum Pump	**Pfeiffer Duoline 20M**
Refrigeration m³/h - Hp	**Frigopol 30 – 7.5**
Isolation Valve Ø cm	**Butterfly 25**
Power Requirements	**3ph 380 - 415v**

1.3. Safety instructions

1.3.1. Disconnect the electricity supply before removing panels

The freeze drier must be securely isolated or unplugged or from the mains supply before the panels are removed or any maintenance work is undertaken.

1.3.2. Solvents

Acidic or high solvent concentration products should not be dried because of corrosion risk and damage to the vacuum pump.

1.3.3. Cleaning and Maintenance of the Unit

For infectious, toxic, pathogenic and radioactive substances, the danger information of the associated safety regulations must be observed.

1.3.4. Freezing of skin to surfaces

Make sure skin does not come into contact with freezing surfaces.

1.4. The F25 should not be used when:

1. It is not properly installed.

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2. Panels are missing.
3. The operator is not authorized or trained
4. Highly corrosive or solvent substances are present.
5. In hazardous or dangerous locations.
6. The products are explosive or highly flammable.
7. The products are Infectious, toxic, pathogenic or radioactive unless in suitable vessels and in accordance with the relevant safety data.

2. Description of the Freeze Drying Processes

2.1. General Information on Freeze Drying

Freeze drying is the gentlest process for drying products. It uses the process of sublimation, the direct conversion from solid to vapour state. The frozen product is dried under vacuum without thawing. The condenser chamber works as a cryogenic pump as it takes large volumes of vapour and condenses a small amount of ice. The vacuum pump is only intended to remove the air from the drying chamber but not the vapour. In order to start the sublimation process, energy must be supplied to the product. This energy source comes from the specimen chamber wall.
Primary drying removes the most of the water from the product.
Secondary drying removes the last traces of water by means of deep vacuum.

The main components of a freeze dryer are:

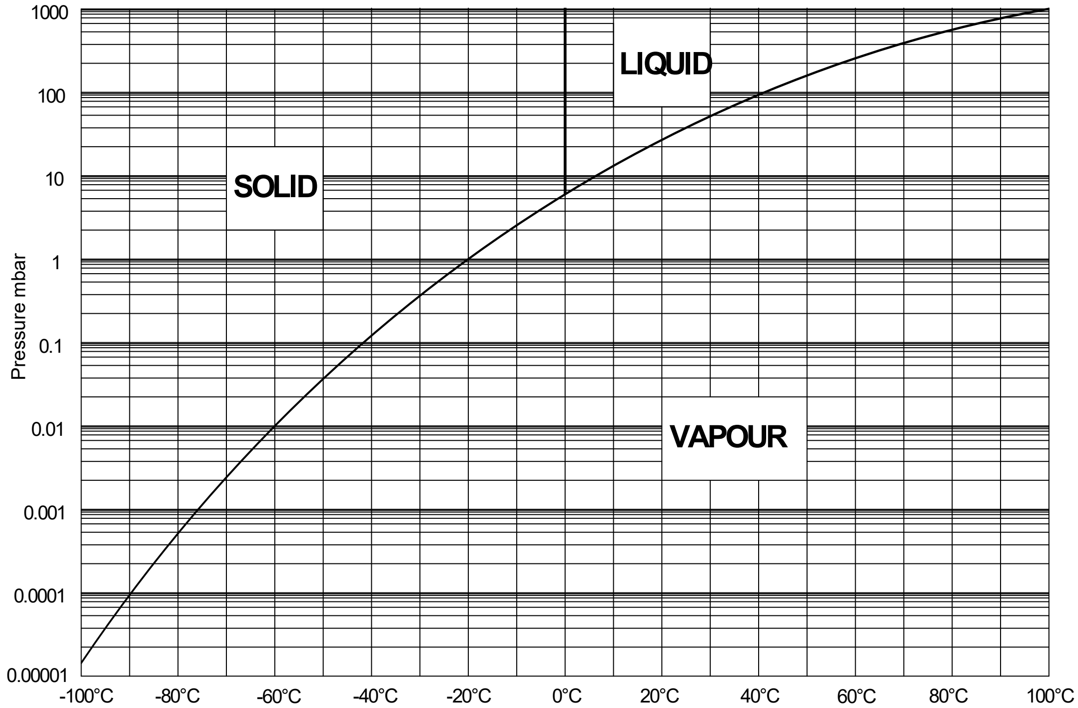
- Vacuum drying chamber with product shelves
- Vacuum pump to evacuate air.
- Ice condenser with temperature of -55°C to condense water vapour.

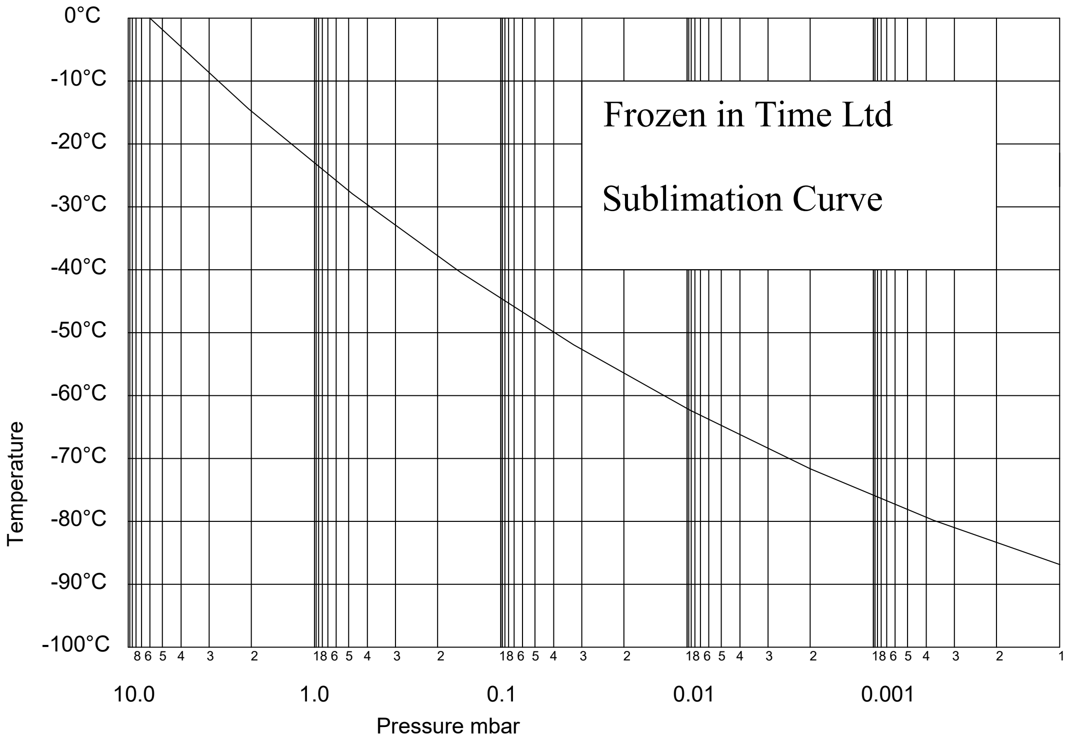
Sublimation

The principle of sublimation is briefly explained using the phase diagram of solid liquid and vapour. If the pressure is higher than 6.1 mbar, water can exist in all three phases (solid, liquid, vapour) when the temperature is lowered or raised. At 6.1 mbar and 0ºC all three lines meet, this is called the triple point where all three phase can occur simultaneously. Below this point when the pressure is lower than 6.1 mbar, the ice is converted directly from a solid to a vapour on reaching the sublimation pressure curve.

The sublimation curve shows the vapour pressure of water as affected by temperature and pressure.

Phase diagram for solid, liquid and vapour




Frozen in Time Ltd
Sublimation Curve
0°C
-10°C
-20°C
-30°C
-40°C
-50°C
-60°C
-70°C
-80°C
-90°C
-100°C
Temperature
10.0
1.0
0.1
0.01
0.001
Pressure mbar

2.2. Freezing the product.

Product can be frozen directly in the chamber . This is the usual option for product to be freeze dried in trays or vials. The product is placed on the shelves and the chamber iscooled down to the desired temperature. The freezing can be done in stages, at a controlled rate or just as quickly as possible.

2.3. Primary drying

The condenser drops to its operating temperature.
The isolation valve is open
The vacuum pump is switched on.

The duration of the main drying phase depends mainly on:

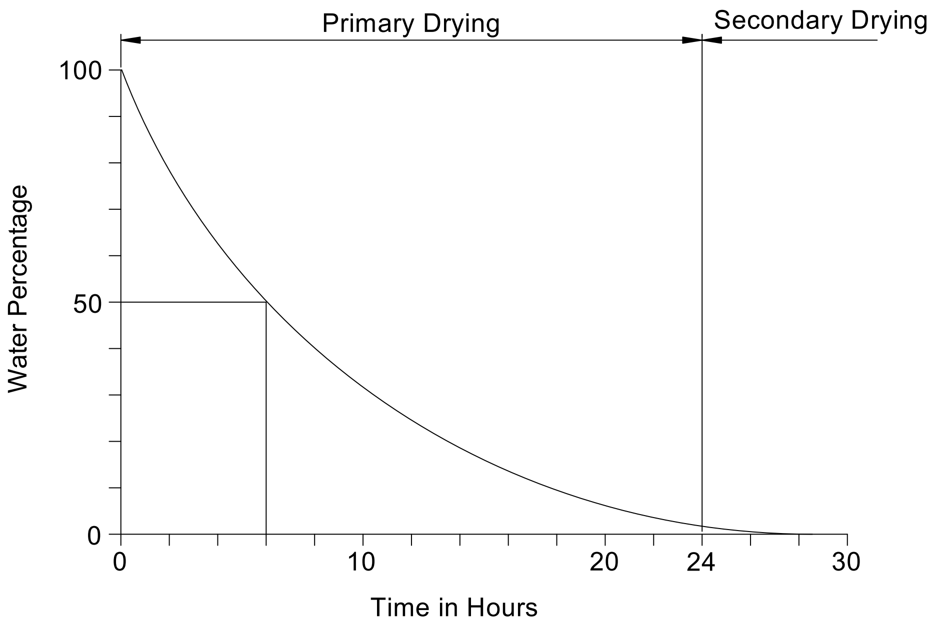
- the layer thickness of the product,
- the solid content of the product,
- the heat supplied to the product during the drying process,
- the vacuum pressure inside the drying chamber during the drying process.

With increasing pressure the rate of sublimation rises as long as it stays below the vapour pressure of the product. This is because at higher pressures the heat energy reaches the sublimation front of the ice core sooner. Therefore the drying period is shortened. The water vapor generated during the main drying phase is not intended to be removed by the vacuum pump. It is to be collected by the ice condenser. The purpose of the vacuum pump is to lower the partial pressure of the non-condensable gases so that the water vapor can be transported from the product to the ice condenser. However, small quantities of water vapor will be removed by the vacuum pump. The vacuum pump is equipped with a gas ballast valve that when open, removes traces of condensable vapors from the pump. For this reason the gas ballast valve can be open during the main primary phase. The gas ballast valve is not required for secondary drying and closing it will help achieve a lower level of vacuum.
During primary drying the moisture is removed by sublimation and during secondary drying the bound moisture is removed by desorption. The recommended vacuum pump should reach with open gas ballast valve, a vacuum level lower than the relevant water vapour pressure.
Specimen chamber temperatures can be raised in stages or set to maximum for fastest heat transfer. The heat input must of course not be enough to damage or melt the product. Too much heat will increase the amount of vapours to a point where the vacuum level diminishes to above the eutectic point of the product.

The residual moisture of the dried product depends mainly on:

- The temperature of the dried product during the final drying process,
- The final vacuum reached during the final drying process.

The end of the primary drying phase is reached, when the product temperature is nearly the same as the shelf temperature (temperature difference between shelf and product approximately 3 to 5ºC). Once the primary drying is completed the secondary drying will remove the bound water from the product. The following diagram shows the drying process for a product containing approximately 10 % solid matter. During the first quarter of the primary drying phase 50% of the water content is condensed. During the next quarter of the primary drying phase 50% of the remaining water content is condensed. This continues until the drying curve approaches the time axis asymptotically. This typical drying curve is due to the fact that the area of sublimation recedes into the product and the remaining water vapour must pass through the already dried layers. During the drying process the resistance increases. The drying curve is determined by the latent heat of sublimation and the amount of vapour transported. In order to increase the specific heat conduction properties of the product and to keep the water vapour volume as low as possible it is necessary that drying takes place as close as possible to the solidification point or eutectic point.



The drying time depends heavily on the vacuum level. The nearer the vacuum to the solidification point in accordance with the vapor pressure curve the shorter the drying time.

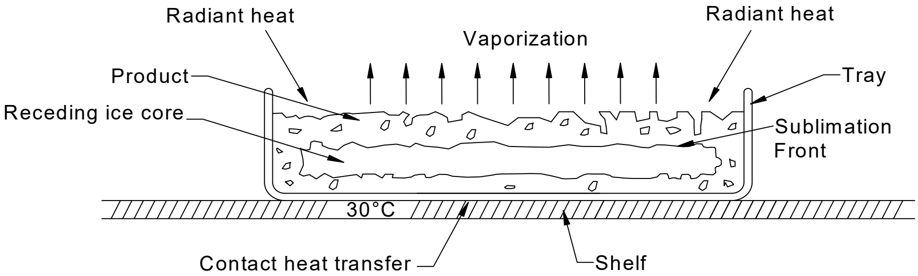
Facts regarding ice in a vacuum:

1.0 gram of ice at;
1.0 mbar assumes a volume of 1 m³ vapor
0.1 mbar assumes a volume of 10 m³ vapor
0.01 mbar assumes a volume of 100 m³ vapor

Heat supply during drying

The required heat supply to the product to be dried takes place by;
Conduction through contact in the drying chamber
Mild conduction through low pressure vapour
Radiant heat energy.

Effects of freeze drying of a product in a dish



Heat transfer takes place via the heated shelves by direct contact with the bottom of the tray. At the beginning of sublimation the transfer of heat is very effective from the wall of the tray to the frozen product. However, soon an area develops which is ice-free, porous, dried and has an insulating effect between the wall of the tray and the product. This slows down the heat energy transfer available to the ice core. The porous dried layer enables the passage of vapour from the ice core. If it is restricted the temperature will increase and ice core will thaw rather than sublimate. This applies especially to inhomogeneous products and to great layer thicknesses. During this drying phase it is important to regulate the heat supply and control temperature and pressure precisely.

2.4. Secondary drying

The final pressure in the drying chamber depends on the ice condenser temperature according to the vapor pressure curve above ice :
e. g. 1.030 mbar correspond to -20°C
0.370 mbar correspond to -30°C
0.120 mbar correspond to -40°C
0.040 mbar correspond to -50°C
0.01 mbar correspond to -60°C

The unit is in operating condition if the temperature of the ice condenser is lower than -50°C and the pressure is lower than 0.12 mbar. The final pressure measured when there is no product in the unit and its corresponding ice temperature is determined by the warmest ice surface in the condenser chamber.

2.5. Pressure rise test

The pressure rise test is a good way to confirm that there is no more vaporizing ice in the product It can be performed manually by the operator. When the secondary dying stage is considered to be finished, a pressure rise test will ensure it is. The isolation valve is closed and the operator will watch to see the rate at which the vacuum level in the product chamber increases. The vacuum level will rise even with dry product, however the rate at which it rises when ice is still vaporizing is much greater. The operator must perform tests to become familiar with these rates of pressure rise.

2.6. Air admittance

After the product is dry the vacuum in the chamber must be released by admitting air.
Air will enter through the air admittance valve until the pressure is equalized and the door will release. This may take a few minutes.

2.7. Defrosting

Defrosting of the ice condenser is carried out manually by pressing the defrost button. The condenser door must be opened to allow the water/condensate out.
Defrost can only be done after the process has finished and the product has been removed. The defrost will run for a one hour to melt the ice, it will then switch off. If any ice remains then it can be switched on again and it will run for another hour. This ensures that defrost does not get forgotten about and left to run for excessive amounts of time. Pressing the upward pointing temperature control button sets the defrost target temperature. One touch of this button displays the cut out temperature of the defrost condenser chamber. To set this temperature, you can adjust with the up or down pointing buttons..

3. Installation and Commissioning of the Unit

3.1. Site of installation

In order to ensure the air circulation of the heat exchanger, do not place items behind the unit that could restrict air flow. The ambient temperature should be between approximately +5°C and +30°C. The refrigeration compressor of the freeze dryer is air-cooled. Sufficient air circulation must be ensured. A distance of at least 30cm to the wall should be kept. The unit should not be positioned near radiators or heat sources. In the case of insufficient air circulation or too high ambient temperatures, the temperature and the pressure in the refrigerating system will increase. If the maximum permissible operating pressure is exceeded, this may cause the refrigeration unit to switch off.

3.2. Mains power

The operating voltage on the name plate must correspond to the local supply voltage. Frozen in Time freeze dryers are units of safety class I. The **F-Series** freeze driers require a three-phase power supply 380 to 415 Volts.

3.3. Air admittance

Filtered air can be admitted into the product chamber. If an inert gas is needed such as nitrogen then a supply of this is required usually a gas cylinder. Take care not to over pressure the system.

3.4. Vacuum pump exhaust gases

The oil mist from the vacuum pump is normally trapped in an exhaust filter.
If this is not the case, the oil mist has to be discharged outside. A hose can be connected to the exhaust flange of the vacuum pump that leads into the open air or a vent. During installation of the pipe special care must be taken that condensate cannot flow back into the pump.

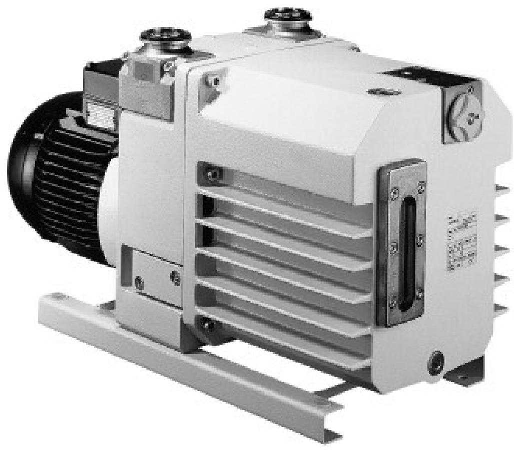
4. Operating the F25

4.1. Loading Trays

The trays slide on to the fixed shelves inside the chamber. There are two trays per shelf.

4.2. Vacuum Pump

The vacuum pump fitted to the F25 has a 24m³/h displacement.



The vacuum pump oil should be changed when the pump is warm. The oil level should be visible in the sight glass. The intervals for changing the oil will depend upon the products being freeze dried. The condenser chamber temperature must be lower than the temperature corresponding to the vapour pressure that the product is going to freeze dried at. In the case of water vapour the following is a good guide:

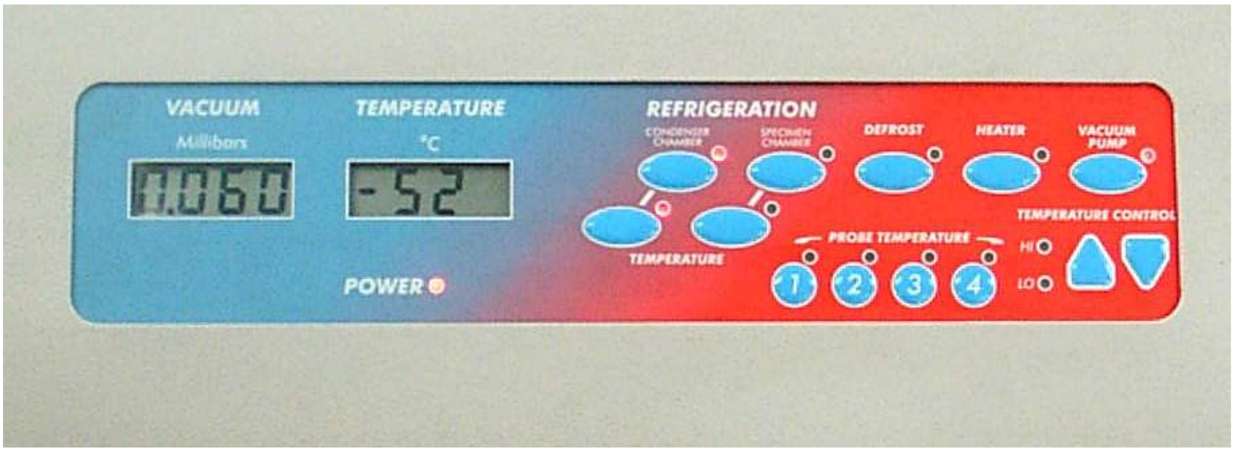
1.030 mbar correspond to -30°C
0.370 mbar correspond to -40°C
0.120 mbar correspond to -50°C
0.040 mbar correspond to -60°C
0.01 mbar correspond to -70°C
0.003 mbar correspond to -80°C

If the product contains large quantities of chemicals that are more volatile than water then lower temperatures in relation to vacuum levels are required.
An oil mist filter should be fitted to the exhaust port of the vacuum pump.
For extra information on the pump please see the separate operating manual.

4.3. Vacuum release/Air admittance valve

Air can be admitted into the chambers after drying or during defrost. Releasing the vacuum is the only way to it will be possible to open the doors.

4.4. Control System



4.4.1 LED`s

Indicator LED`s will show which functions are active on the freeze drier. If a button is pressed and the LED does not illuminate then the function has not been activated due to an interlock. An interlock will block incorrect functions from being selected. When temperatures are being selected the LED will indicate which temperature is being displayed.

4.4.2. Condenser Chamber Refrigeration

When the condenser chamber button is pressed, the condenser refrigeration will start, the LED will light up and the condenser chamber temperature will initially be displayed. When it is switched off the LED will switch off however the refrigeration system will continue to run for a few minutes. This delay in switching off the refrigeration will enable the compressor to evacuate the suction pipes.

4.4.3. Specimen Chamber Refrigeration

When the specimen chamber button is pressed, the condenser refrigeration will start, the LED will light up and the specimen chamber temperature will initially be displayed. When it is switched off the LED will switch off however the refrigeration system will continue to run for a few minutes. This delay in switching off the refrigeration will enable the compressor to evacuate the suction pipes. Pressing the downward pointing temperature control button sets the specimen chamber target temperature. One touch of this button displays the cut out temperature of the chamber. To set this temperature, you can adjust with the up or down pointing buttons. This set point is also used for controlling the heater temperature.

4.4.4. Defrost

The defrost may only be selected when all other buttons have been switched off. On the A-series driers a defrost can be done during or after the process has. The defrost will run for one hour to melt the ice, it will then switch off. If any ice remains then it can be switched on again and it will run for another hour. This ensures that defrost does not get forgotten about and left to run for excessive amounts of time. Pressing the upward pointing temperature control button sets the defrost target temperature. One touch of this button displays the cut out temperature of the defrost condenser coils. To set this temperature, you can adjust with the up or down pointing buttons.

4.4.5. Heater

The heater function refers to the specimen chamber heater. Switching this on will heat up the specimen chamber. This function is subject to an interlock. It can only be activated when the vacuum pump is running. (the vacuum pump can only be activated when the condenser chamber is below -30°C) When it is activated the LED will illuminate. The heater output itself is controlled by a temperature set point and a vacuum control set point.

Setting the heater temperature uses the same set point as the specimen chamber refrigeration. Pressing the downward pointing temperature control button sets the specimen chamber target temperature. One touch of this button displays the cut out temperature of the chamber. To set this temperature, you can adjust with the up or down pointing buttons.

When the vacuum is above a settable level the heater will not produce heat. The reason for this is that when freeze drying, it is necessary not to go above a certain vacuum level.

For example if you do not want the vacuum to go above 0.4 mbar then you would set it at 0.4 If the level went above this the heater would not produce heat. This would cause the sublimation to slow down and the vacuum level would recover.

This vacuum control set point is settable between 0.1 mbar and 1.0 mbar. If vacuum control above 1.0 mbar is required or if heaters are to be tested with no vacuum level at all then the set point needs to be turned off.

To change the set point press and hold the vacuum sensor selector button for specimen chamber until the displays change. The display on the right will say either Off or a number between 1.0 and 0.1. Scroll up with the arrow keys until you reach OFF and then wait until it returns back to normal mode. It takes a few seconds.

4.4.6. Vacuum Pump

The condenser chamber refrigeration must be running before the vacuum pump can be activated. The Vacuum pump can only be activated when the condenser temperature is below -30°C. When the vacuum pump is running the indicator light will be illuminated.

4.4.7. Vacuum Display

The display is in Millibars. It shows the level of vacuum in the system and this will vary throughout the drying cycle. This is because the products are giving off water vapour and gases that raise the vacuum level. Near the end of the cycle the pressure will be lower. The display will read OFF while the vacuum pump is switched off. When the vacuum pump is switched on, the display will read ON. When the pressure has dropped to below 500 Millibars (half of atmospheric pressure) it will start to register the pressure.

4.4.8. Temperature Display

The temperature is displayed in °C. The display will switched between the condenser chamber, the specimen chamber and the 4 mobile probes.
To select the condenser chamber temperature press the oval button below the condenser chamber refrigeration activation button.

To select the specimen chamber temperature press the oval button below the specimen chamber refrigeration activation button.
To select a probe temperature press the round buttons labeled 1 to 4.
When temperatures are being selected the LED will indicate which temperature is being displayed.
Temperature probes 1 to 4 are the loose probes in the specimen chamber that can be inserted into samples chosen in different areas of the specimen chamber.

4.5. Drainage of the defrost condensate

The dried products in the trays should be removed first of all.

A suitable container should be placed under the drain port in the back of the chamber or a pipe connected from the drain port to a suitable drainage point.

Select defrost, this will start the refrigeration in defrost mode. The ice will melt and run out the drain port. The defrost will run for one hour. If ice remains after the defrost has turned off select defrost again to allow extra time.

5. Troubleshooting

5.1. Power failure

The freeze drier will resume settings after a power failure. In the event of a power failure in the drying phase, the batch may become unusable. Whether the batch can be saved or not depends on the drying phase in which the product was in when the power failure occurred. If power returns within a few minutes then it is unlikely that any damage will have occurred. It is important to distinguish between the primary drying phase and the secondary drying phase. The product is in the secondary drying phase if the residual moisture has reached approximately 5 %. Below this value, the product is generally not damaged by a power failure.
If the product is in the primary drying phase, it is recommended that the product is refrozen.
It is also advisable to defrost the condenser chamber at this point.
If the product is considered to be still usable then freeze drying can restart.

5.2. Insufficient vacuum

Is the vacuum pump is running? If not:

- Check that the pump motor switch is on
- Check that the IEC connection lead is connected
- Check that the vacuum pump circuit breaker has not switched off.
- Check that the contactor is operating.

If the vacuum pump is running:

- Check that air admittance is closed.
- Check all vacuum connections on specimen chamber including door seal. Repair or replace.
- Check for water from cleaning or spilled product residue, this may vaporize preventing vacuum.
- Remove panels and listen for leaks after a vacuum evacuation has been tried.
- Check the vacuum pump is pulling an adequate vacuum, test with a separate vacuum sensor.

If the vacuum pump cannot achieve a sufficient vacuum then replace it or get it repaired.

5.3. Insufficient cooling of the condenser chamber

If the condenser chamber is not reaching the relevant temperature -55ºC
(Please allow 15% for high load conditions)

- Check to see if there is liquid flow in the refrigeration sight glass. Contact the manufacturer, supplier or a local refrigeration engineer.
- Check the circuit breakers for the compressor
- Check that the contactors are operating.

5.4. Insufficient defrosting of the condenser chamber

If defrost is not heating up.

- Check the circuit breaker for defrost
- Check that the contactor is operating.
- Check that the settings in the on the control panel are allowing its activation
- Check that temperature control is not controlled by a sensor that is malfunctioning and reading an incorrectly high temperature.

5.5. Insufficient cooling of the specimen chamber

If the shelves are not reaching low set points or relevant temperature -35ºC

- Check to see if there is liquid flow in the refrigeration sight glass. Contact the manufacturer, supplier or a local refrigeration engineer
- Check the circuit breakers for the compressor
- Check that temperature control is not controlled by a sensor that is malfunctioning and reading an incorrectly low temperature.

5.6. Insufficient heating of the specimen chamber

If the shelves are not reaching high set points or the relevant temperatures 60ºC to 80ºC.

- Check the circuit breaker or fuse for the heater
- Check that all the contactor or relay is operating.
- Check that shelf temperature control is not controlled by a sensor that is malfunctioning and reading an incorrectly high temperature.
- Check that there is not an vacuum set point entered lower than the present vacuum level preventing the heater from being activated.
- Check that the settings in the control panel are allowing its activation

5.7. Door will not seal under vacuum

If the door will not seal under vacuum

- Check that the vacuum pump is running
- Check that the air admittance valve is closed
- Clamp the product chamber door and check that it is pushed up against its seal all around.

Does the door still open?

5.8. Incorrect probe temperature

Incorrect probe temperatures can be due to

- Unplugged probes
- Broken thermocouples
- Thermocouples with loose connections

6. Maintenance

6.1. Product chamber
Before each start-up, ensure that product chamber is drained.

6.2. Heat exchanger

The refrigeration heat exchanger is used to cool the refrigerant compressed by the refrigeration unit. The heat exchangers are located on each side of the unit and should be kept free of dust or dirt residues. The heat exchanger can be cleaned by brushing, using a vacuum cleaner from the outside or by using compressed air from inside of the unit. Excessive build up on the heat exchanger leads to a decrease in performance and may cause a failure of the unit.

6.3. Rubber seals

Special attention must be paid to the rubber seals. If the seals are dirty, they must be removed, cleaned and slightly greased with vacuum grease. If they show signs of cracking they must be replaced.

6.4. Vacuum pump

Clean up any oil spills on or around the freeze drier from oil changes.
For the maintenance of the vacuum pump, please refer to the separate operating manual.
Additionally:
The oil level of the vacuum pump must be regularly checked at the sight glass (in case of continuous operation at least once a day). Top up oil to the required level via the oil inlet. Due to possible operation with gas ballast, oil consumption cannot be avoided. For topping-up see the operating manual of the pump. The oil change should always be carried out with warm pump.

6.5. Exhaust filter

The exhaust filter should be replaced if it becomes saturated. Where possible there should still be a pipe after the exhaust filter leading into open air. Take care that the condensate in the filter does not rise too high.

6.6. Cleaning

Use soapy water or other water-soluble, mild cleaning agents to clean the freeze dryer. Avoid corrosive and aggressive substances. Do not use alkaline solutions, solvents or agents with abrasive particles. Remove product residues from the ice condenser chamber using a cloth. It is recommended to open the doors of the freeze drier when it is not in use so that moisture can evaporate.
If there is the risk of toxic, radioactive or pathogenic contamination, special safety measures must be considered and adhered to.

6.7. Checks by the operator

The operator has to ensure the important parts of the freeze dryer and those necessary for safety are not damaged. This especially refers to:

- Doors and hinges
- Seals
- Oil level of vacuum pump
- Heat exchangers
- Exhaust filter