Frozen in Time Ltd

Manufacturers of Freeze Drying Machines and Vacuum Cold traps

Operating Manual HS-5 & HSL-5

<u>Operating Manual</u>

<u>HS-5 & HLS-5</u>

Order Number:

Serial Number:

In case of enquiries please state the above

For service please contact:

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Important Safety Instructions

This manual contains instructions which are intended to assist persons installing, operating and servicing the described equipment, machine parts or systems. These instructions have been prescribed to assure personal safety and to avoid personal injury and / or collateral damage. Care should be taken to read and carefully follow all safety instructions and operating procedures described herein.

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1. General Information

1.1. Introduction

What is freeze drying (lyophilization)?

Freeze drying is a process of dehydration where water or liquid is withdrawn from a material though sublimation. Sublimation is the conversion of a substance from a solid state to a gas. This conversion or *phase transition* is carried out in a freeze drying vessel. The material to be dried is frozen to less than -10°C and placed under a vacuum, heat is then introduced to the frozen product which causes the ice to sublime.

Freeze drying is typically used where the preservation of the material is important. It generally does not destroy the physical structure or chemical compounds of a product. Freeze drying is the gentlest process for preserving biological properties of sensitive tissues and tissue components. It is also commonly used for drying food, blood plasma, and pharmaceuticals.

The basic steps involved in freeze drying are the freezing of the product, primary drying and secondary drying.

Products such as wet material, aqueous solutions or suspensions are frozen. The final temperature being below the product's eutectic, or collapse temperature so as to maintain its structural soundness. Once all water is converted to ice the condenser and vacuum systems are energized for the drying process.

Primary drying then removes unbound or easily removed ice by sublimation. The product is under vacuum to maintain a low pressure (of a few millibars) ensuring water vapour remains below its 'triple point' and is able to migrate into the system's ice-collecting condenser. Primary drying removes up to 95% of the product's moisture and is generally a slow, controlled process.

After the initial ice is sublimed, bound water may still be present which can limit the product's stability and shelf life. Secondary drying is required to remove this sorbed water which is strongly bound to the product's solids. Secondary drying usually begins during the primary drying phase but extends beyond it and normally at temperatures higher than during primary drying. Residual moisture is desorbed at this stage and the resulting moisture levels in the product are at 1 to 5% at the end of drying.

1.2. HS-5 & HSL-5 Technical data

Freeze Dryer Specifications		
	HS-5	***HSL-5***
Overall Dimensions W x D x H cm	**190 x130 x 300**	**190 x130 x 300**
Specimen and Condenser Chamber Construction	**Polished 316L Stainless Steel**	**Polished 316L Stainless Steel**
Shelf Area m²	**6**	**6**
Number of shelves	**7 +1**	**7 +1**
Shelf Size W x D in cm	**80 x 107**	**80 x 107**
Maximum Distance between shelves if they are all equally spaced in cm	**6**	**6**
Condenser Chamber Temperature	**-55 ºC**	**-85 ºC**
Shelf Temperature Range ºC	**-50 to +60 ºC**	**-70 to +60 ºC**
Stoppering Device	**Hydraulic**	**Hydraulic**
Mobile Temperature Probes	**6**	**6**
Condenser chamber Defrost	**Hot Gas**	**Hot Gas & Electric**
Condenser Ice Capacity	**80 litre (60litres / 24hour)**	**80 litre (60litres / 24hour)**
Refrigerant	**R-507**	**R-507 – R-23**
Vacuum Pump	**Duo 65**	**Duo 65**
Vacuum level obtainable	2×10^{-2} **(0.02mbar)**	2×10^{-2} **(0.02mbar)**
Refrigeration	**Single Stage Refrigeration**	**Two Stage Cascade Refrigeration**
Isolation Valve	**Ø 25cm**	**Ø 25cm**
Power Requirements	**3ph 415v**	**3ph 415v**

1.3. System performance expectations

The **HS-5** when in good working order and within normal running conditions should perform within the following limits.

- Shelf cool down 20°C to -50°C .... within 2 hours
- Condenser cool down 20°C to -50°C .... within 30 mins
- Vacuum evacuation down to 1mbar .... within 30 mins
- Vacuum evacuation down to 0.06mbar.............................. within 1 hour
- Vacuum evacuation down to 0.03mbar............................... within 3 hours
- Shelf heating rate approximately.. 1°C/min

The **HSL-5** when in good working order and within normal running conditions should perform within the following limits.

- Shelf cool down 20°C to -70°C .... within 2 hours
- Condenser cool down 20°C to -80°C .... within 30 mins
- Vacuum evacuation down to 1mbar.................................... within 30 mins
- Vacuum evacuation down to 0.06mbar.............................. within 1 hour
- Vacuum evacuation down to 0.03mbar............................... within 3 hours
- Shelf heating rate approximately.. 1°C/min

1.4 Safety instructions

1.3.1. Removing panels

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

1.3.2. Solvents

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

1.3.3. Protective clothing/Danger of freezing skin

Operators should wear appropriate clothing and take precautions that would prevent bare skin from coming into contact with freezing surfaces i.e. gloves and long sleeves. Skin that does adhere to frozen surfaces can only be detached from the surface by applying heat. Do not use liquid.

1.3.4. Transporting the Freeze Dryer

The **HS-5 & HSL-5** have lifting lugs and can be moved from one location to another if necessary by a crane or by forklift. The machine weighs 2000 Kg.

1.4. When the HS-5 or HSL-5 should not be used:

1. It is not properly installed by a qualified technician.
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 material safety data.

2. Installation and commissioning of the unit

2.1. Site of installation

The **HS-5 or HSL-5** can be designed to be placed in a clean room environment. The front, product chamber and controls all being accessible from the clean room and installed flush with its surrounding. The rear of the machine can be located in a separate room giving access to all serviceable parts and supply connections.

2.2. Mains power

The operating voltage indicated on the rear specification plate must correspond to the local supply voltage. Frozen in Time freeze dryers are units of safety class I. The **HS-5 & HSL-5** require a three-phase power supply of 380 to 415 Volts. The **HS-5** must be on a circuit protected by a fuse or circuit breaker with a maximum 32 Amp. The **HSL-5** will require a circuit protected by a fuse or circuit breaker with a maximum 40 Amp. A separate electrical supply will be required for the chiller if it not an air cooled model.

2.3. Air/inert gas 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 as a standalone gas cylinder. Vials can be sealed only with a vacuum or with partial inert gas fill, depending on the product. If *inert gas for stoppering* fill is selected on the freeze drier's *engineering* page of the automated screen, the valve (V003) will open, filling the main chamber with gas via needle/bleed valve (V002). Connect the desired gas type to this valve's feed.
During freeze drying the minimum vacuum level can be maintained by introducing filtered air or inert gas through needle/bleed valve (V002) and control solenoid (V003). This supply hose can be connected to the appropriate gas bottle or air supply.

2.5. Drainage pipe for condensate

The condenser chamber drain valve will require a flexible pipe to be fitted and lead to a floor drain or collecting vessel. Water from the freeze drying cycle drains away from the condenser through this valve.

2.5. Venting vacuum pump exhaust gases

Exhaust gas from the vacuum pump contains oil mist. This oil mist is trapped by exhaust filter (N103). Remaining exhaust gases then pass through the filter and are piped outside or into a vent duct. If no exhaust filter is used it is essential that the exhaust is vented outside as it will be oil mist.

3. The Freeze Drying Process

3.1. General Information on Freeze Drying with the HS-5 or HSL-5

The freeze drier uses the process of sublimation for drying. Sublimation is the direct conversion from a solid to vapour state. Under vacuum, energy (heat) is supplied to the product via the heated shelves, this starts the sublimation process. The frozen product is dried under vacuum without thawing.
Primary drying removes the majority of liquid from the product. Secondary drying removes the last traces of moisture by means of deep vacuum. The vacuum pump is only intended to remove the air from the product chamber, not vapour. The condenser chamber works as a cryogenic pump as it takes large volumes of vapour from the product chamber and deposits it as a small amount of ice.

The main components of the freeze dryer are:

- Vacuum drying chamber (product chamber) with heated shelves and a vial closing device.
- Condenser chamber with temperatures of -85°C for deposition of vapour to ice.
- Vacuum pump to evacuate air.

Sublimation

The principle of sublimation is briefly explained using **Fig. 3.1a** Phase diagram for 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 phases 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 second diagram: sublimation curve **Fig. 3.1b** shows the vapour pressure of ice as affected by temperature and pressure.

Fig. 3.1a Phase diagram for solid, liquid and vapour

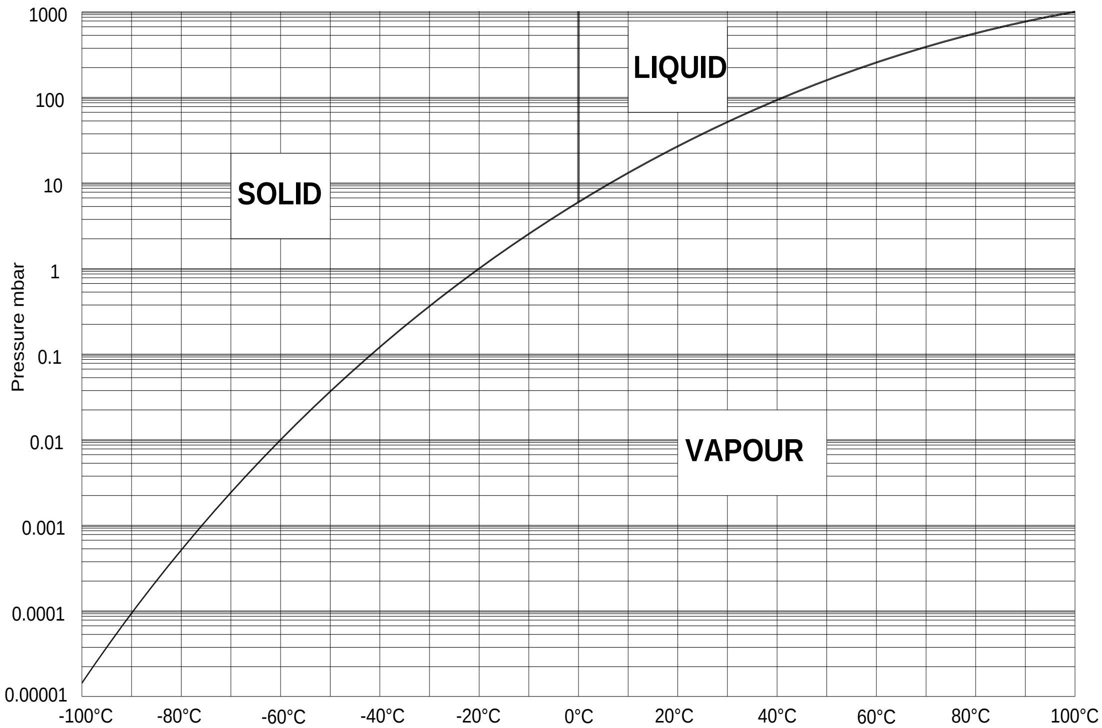


Fig. 3.1b Vapour pressure of ice

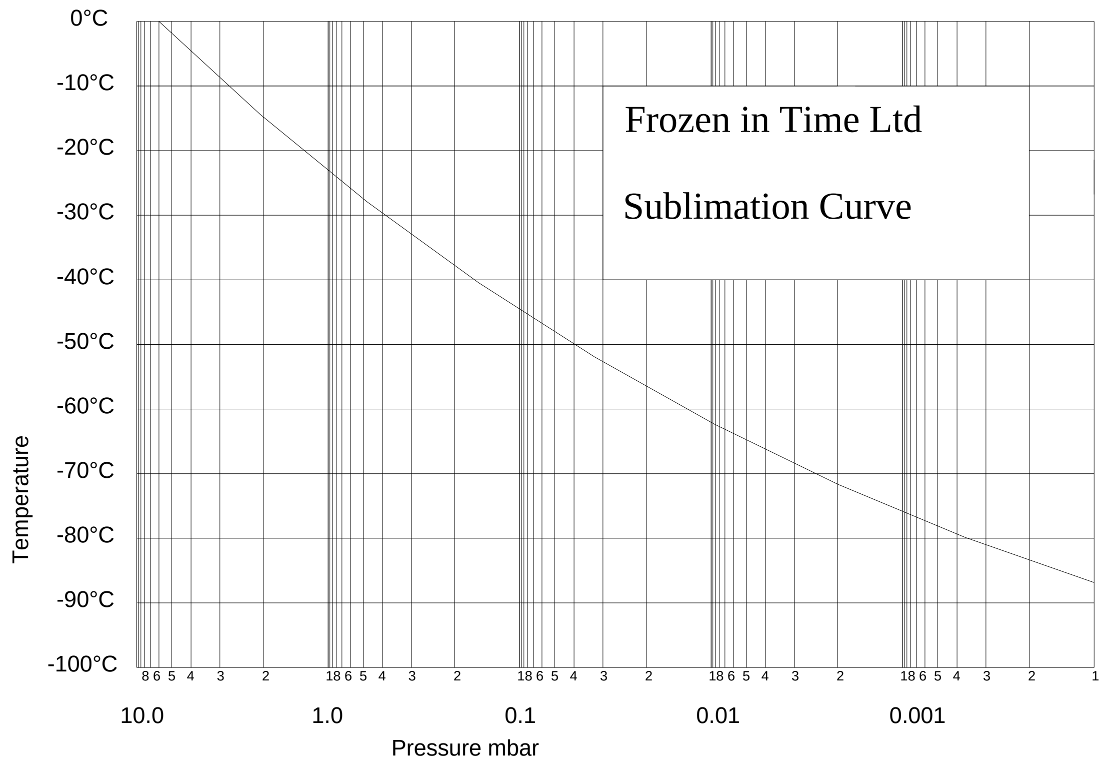
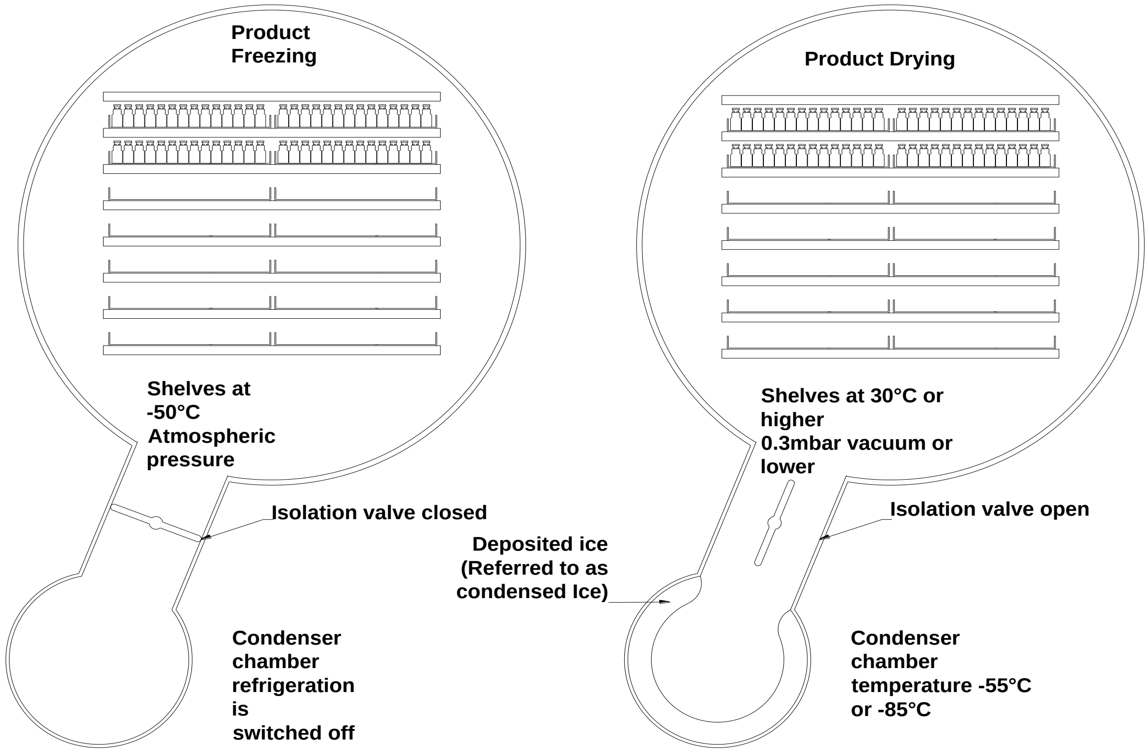


Fig. 3.1c Cross sectional diagram of the freeze drier chambers during Product freezing and Product drying.



Product Freezing

The Isolation valve is closed and the product is frozen by lowering the temperature of the shelves.

Product drying

The condenser chamber temperature is lowered to its minimum. When temperature goes below -30ºC approximately, the vacuum pump can be switched on. The isolation valve must be opened and a vacuum is created in both chambers. When the vacuum is sufficient, heating can be applied to the product shelves. Sublimation will take place, dehydrating the product. Deposition will occur in the condenser chamber where the vapour turns solid (ice).

3.2. Freezing the product.

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

3.3. Primary and secondary drying

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

The duration of the primary drying phase mainly depends on:

- The layer thickness of the product,
- The moisture 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.

During primary drying the unbound moisture is removed by sublimation. Shelf temperatures can be raised in stages, at a controlled rate 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.

With increased 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 vapour 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 vapour 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.

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 being approximately 3 to 5ºC). Once the primary drying is completed the secondary drying will begin.

Secondary Drying
Secondary drying takes place enabling any remaining bound or sorbed water to be sublimed from the product. The last traces of water vapour are removed and the product becomes sufficiently dry and stable.

The residual moisture of the finished dried product depends mainly on:

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

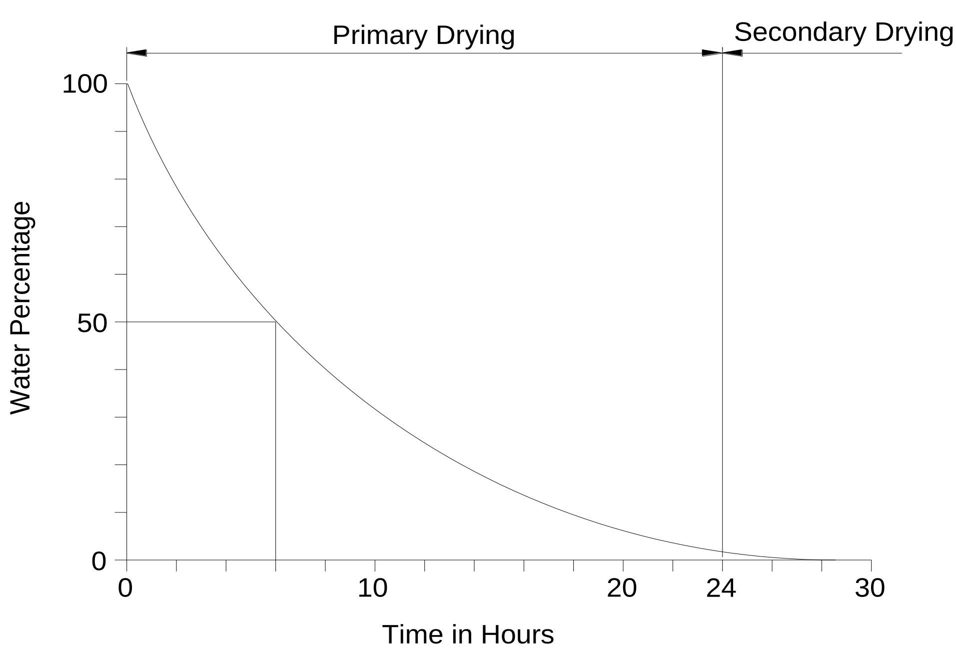
The final pressure in the drying chamber depends on the ice condenser temperature according to the vapour pressure curve above ice. **Fig. 3.1b**

e. g. 1.030 mbar corresponds to -20°C
0.370 mbar corresponds to -30°C
0.120 mbar corresponds to -40°C
0.040 mbar corresponds to -50°C
0.01 mbar corresponds to -60°C

The unit is in operating condition for secondary drying 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.

The following diagram **Fig. 3.3b** shows the drying process for a product containing approximately 10% solid matter. During the first quarter of the primary drying phase approximately 50% of the water content is removed. During the next quarter of the primary drying phase approximately 50% of the remaining water content is removed. This continues until the drying curve approaches the time axis asymptotically. This typical drying curve is created 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.

Fig. 3.3b Freeze Drying Curve



Facts regarding ice in a vacuum:

1.0 gram of ice at the following pressures will produce vapour in the quantities listed:

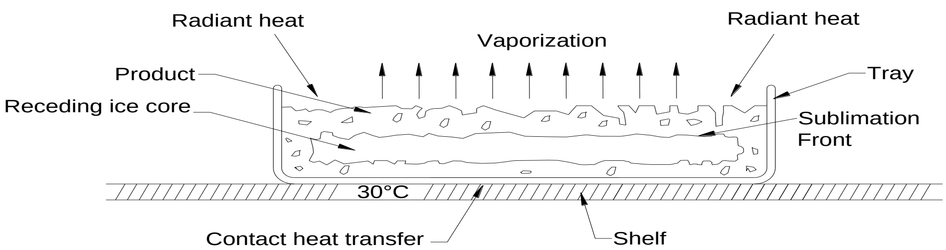
- 1.0 mbar assumes a volume of 1 m^3 vapour
- 0.1 mbar assumes a volume of 10 m^3 vapour
- 0.01 mbar assumes a volume of 100 m^3 vapour

Heat supply during drying

The required heat for the product to be dried is supply to by:

- Conduction through contact with shelves 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 greater layer thicknesses. During this drying phase it is important to regulate the heat supply and control temperature and pressure precisely.

3.4. Pressure rise test

The pressure rise test is a good way to confirm that there is no more vaporizing ice in the product. In the automatic cycle, parameters set on the engineering screen of the control system will be followed. When the secondary dying stage is considered to be finished, a pressure rise test will ensure it is. The shelf temperatures and the vacuum levels will still be in secondary drying conditions. 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. The pressure rise test can also be performed manually by the operator.

3.5. Inert gas vial filling

If the vials are to be charged with an inert gas such as Nitrogen, then this gas must be admitted before the vials are closed. If not then this step is skipped and vial closing is completed.

3.6. Vial closing

The vials are closed by raising the ram until all the shelves have stopped on the spacers. The ram activation buttons can be held for a few seconds after the shelves have closed to ensure the correct pressure has been exerted on the vial stoppers.

3.7. Air/inert gas admittance

After the vials have been closed 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 several minutes.

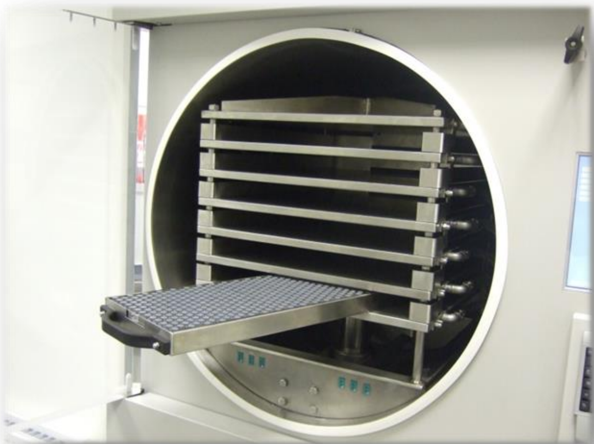
3.8. Defrosting

Defrosting of the ice condenser can be carried out manually by pressing the defrost button on the manual screen. Defrost time and temperature is adjustable on the engineering screen of the control system. The drain valve must be opened to allow the water/condensate out.

In the automatic program, defrost must be selected from the post program list. Defrost will perform automatically at the end of the process. It will follow the conditions set on the engineering screen.

4. Operating the HS-5 & HSL-5

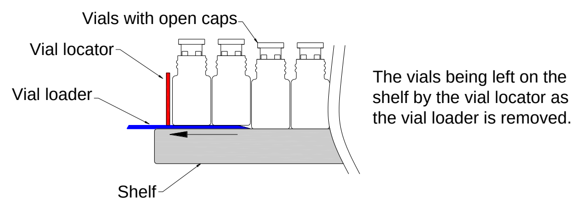
4.1. Loading Trays

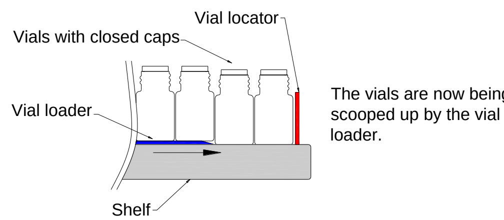


4.2.1. Vial trays

The vial trays are bottomless to allow direct thermal contact between the vials and shelves. The vials are placed onto the shelf using a vial loader and vial locator. The vial loader is slid under the locator which contains all the vials to be kept in place on the shelf.

When the product is to be unloaded, the vial loader is slid back under the vial locater, supporting the vials. And the vials, vial locator and vial loader can be removed as one unit.





There are 6 usable shelves and each shelf holds 3 vial trays. The vial locators can hold various diameters of vials. Shelf spacers can be removed and replaced with the correct sized spacer to suit any vial height. Each of the shelves can be placed at differing heights in any combinations to suit.

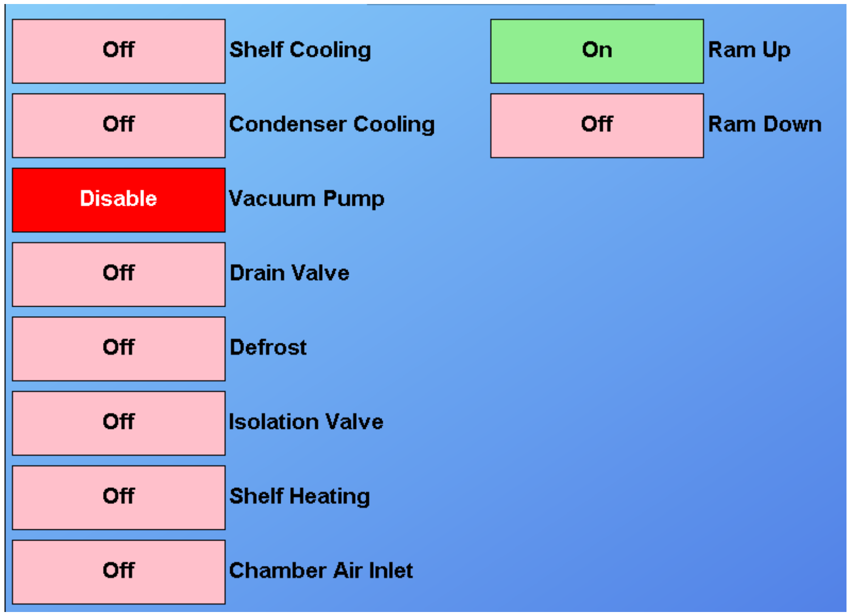
4.2.2. Bulk trays

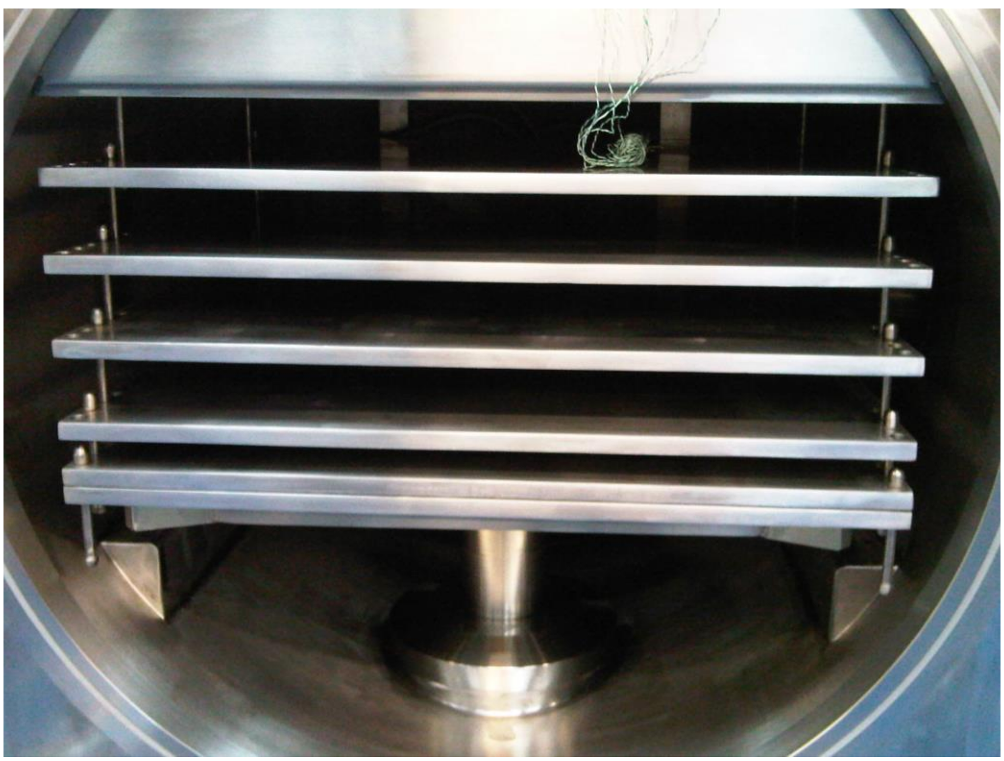
Bulk trays can simply slide onto the shelves. Trays can be supplied in various sizes to suit the application.

4.2. Raising and lowering the ram

The vial closing system is operated by raising the ram and closing the shelves.

If an automatic program is running then the ram cannot be operated in manual mode. All manual buttons are displayed in red, disabled. If the freeze drier is running in manual mode it is possible to raise and lower the shelves with the buttons on the manual screen. It is not possible to activate the ram when the door is open. There is a coded magnet on the door that requires the door to be closed for ram operation to take place.





4.3. Vacuum Pump

The vacuum pump fitted to the HS-5 & HSL-5 both have a 36 m³/h displacement

The pump can be switched on using the controls on the Manual screen. There are several interlocks that prevent the vacuum pump from starting in ways that could cause problems.
These include not allowing the pump to start when:

- There is an insufficient temperature in the condenser chamber
- The drain valve is open
- The condenser chamber defrost is switched on
- Both the Product chamber air admittance and the Isolation valve are open.

In an automatic program the vacuum pump will be controlled completely by the PLC and no user operation is needed or allowed.

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. With the -80ºC condenser chamber version it will offer better pump protection than the -55 ºC 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 corresponds to -30°C
0.370 mbar corresponds to -40°C
0.120 mbar corresponds to -50°C
0.040 mbar corresponds to -60°C
0.01 mbar corresponds to -70°C
0.003 mbar correspond sto -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.

4.4. Isolation valve

The Isolation valve can be operated by using the controls on the Manual screen. To avoid problems there are two interlocks that prevent the Isolation valve from being opened when:

- The defrost is on
- The vacuum pump is running and the Product air inlet is open.

In an automatic program the Isolation Valve will be controlled completely by the PLC and no user operation is needed or allowed

4.5. Air/inert gas admittance valve

Either filtered air or an inert gas can be admitted into the system.

4.6. Condenser drain valve

It also can be operated by the controls on the manual screen. To avoid problems there are two interlocks that prevent the condenser drain valve from being opened when:

- The condenser refrigeration is running
- The vacuum pump is running

4.7. Circuit breakers

The control box has circuit breakers that may trip out in the event of an electrical problem. If a function is not working, this is the first place to check. There are circuit breakers for the following items.

- Refrigeration compressor
- Refrigeration compressor 2 (if HSL-5)

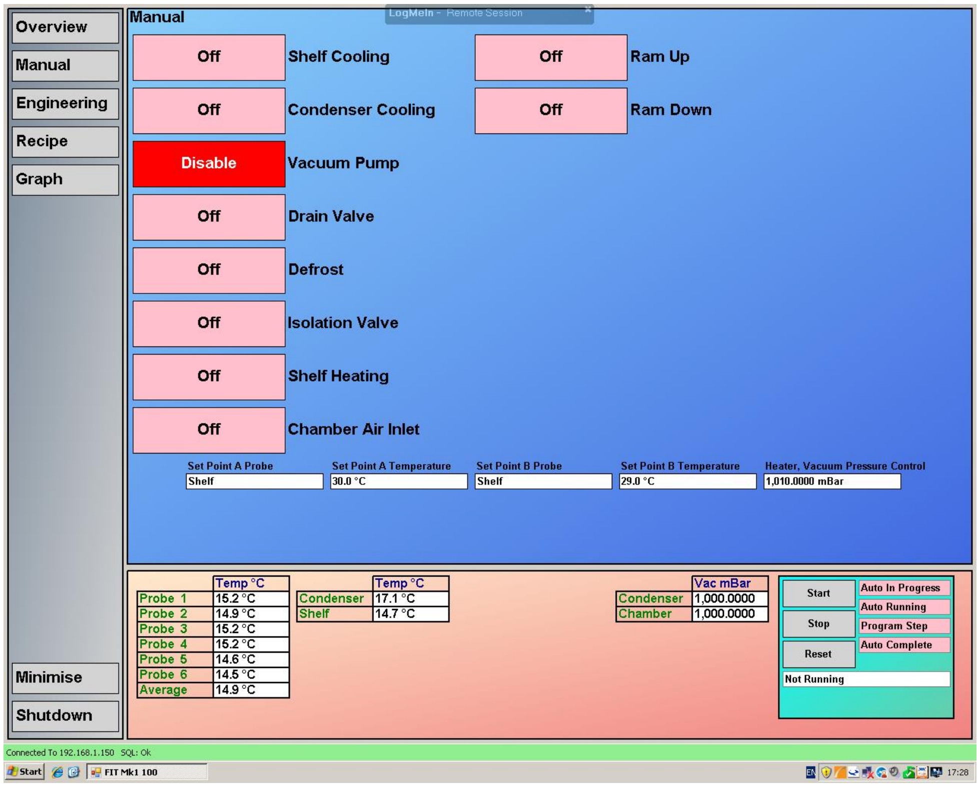
- Vacuum pump
- Air cooled condenser fan 1
- Air cooled condenser fan 2
- Defrost heater (if HSL-5)
- Immersion heaters
- Circulation pump
- Hydraulic pump
- 24VDC power supply
- 240V circuits
- UPS

Please see wiring diagrams for more detailed information.

5. The control system

The control system for the freeze drier enables the operator to run the freeze drier fully automatically or manually. All data from the drying processes can be logged, saved and printed. The automatic cycles are easily programmed by the operator and can be saved or edited for later use. Programs can be changed while the cycle is running. There is a manual screen for complete manual control. This is often used when trying out a new product before a program is confirmed. The data logging and programming are done on the PC. The running of the program is looked after completely by the PLC. If there is a power failure the computer will safely shut down with the use of a built in uninterruptable power supply.

5.1. Manual Control screen



This screen is for manual control. To change to another screen there are selection buttons the down the left hand side.

- Overview
- Manual
- Engineering
- Recipe
- Graph

Next are the function buttons that are used to operate the freeze drier. To the right of each button is the function indicator.
Pink means that the function is off but can be activated.
Green means that the function is active.
Red means that the function is off and cannot be activated due to a current lock on the function. During an automatic run all the manual function buttons are locked.
The function buttons include.

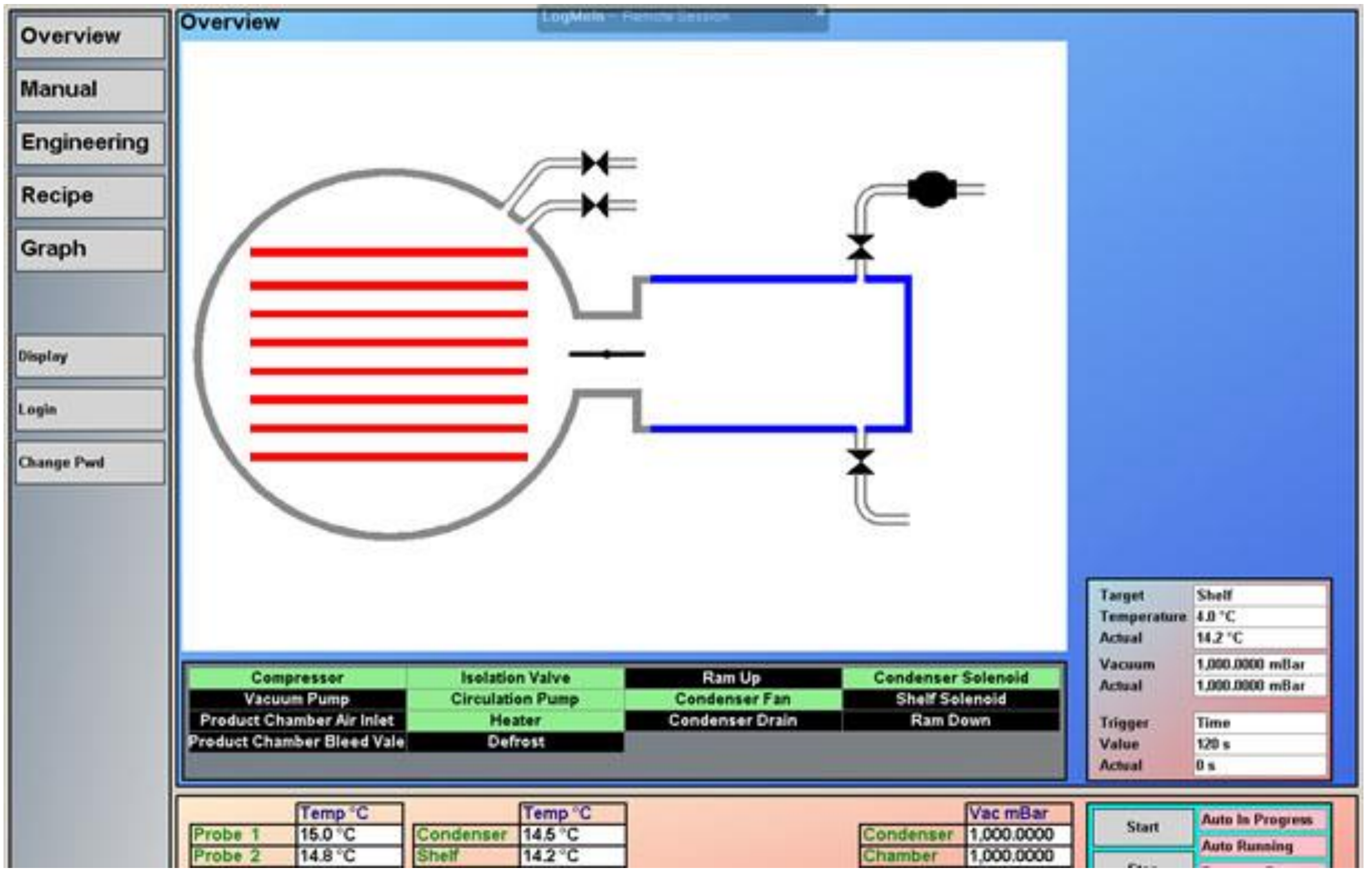
- Shelf Cooling
- Condenser Cooling
- Vacuum Pump
- Drain Valve
- Defrost
- Isolation Valve
- Shelf heating
- Chamber Air inlet
- Ram Up
- Ram Down

Below are the temperature readouts of the shelves or chamber, probes and condenser. There are also vacuum levels in millibars of each chamber.

Set points are required to control temperatures and vacuum levels. If the product is to be lowered in temperature then it will be cooled by the shelf/chamber. There is a thermal lag between the chamber and the product due to the speed of thermal conduction. For fast cooling set the temperature of the chamber lower than the target temperature of the product probe. Once the product probe temperature has reached its set point or the chamber temperature reaches its set point then the cooling will stop. For example;
The chamber temperature is set at -60ºC and the probe temperature is set at -40ºC.
If the chamber reaches -60ºC before the product probe reaches -40ºC then the shelf/chamber will hold at -60ºC until the product probe reaches -40ºC.
If the probe temperature reaches -40ºC before the chamber temperature reaches -60ºC the product probe will control the shelf temperature.
The same principle applies when heating. The chamber can be set higher to allow the product to heat up quicker.
A further control on chamber heating is vacuum level. If vacuum pressure rises above its set point, heating is deactivated. As sublimation slows down the vacuum level will drop below the set point and heating switches back on.

5.2. Overview screen

Display



This screen is for is an overview of the freeze drier it shows what parts of the freeze drier are running.
Vacuum and temperature set points, program step number and running status are also displayed. The diagram will change depending on what is in operation. In the current view the shelves are red because they are heating. The condenser is blue because it is cooling. The isolation valve between the two chambers is open. Below the picture are black boxes indicating the components of the machine operation. When they are green then that component it active and black indicates that it is inactive.

Login

The freeze drier control system has 3 levels of login access. These can be increased upon the customer's request.

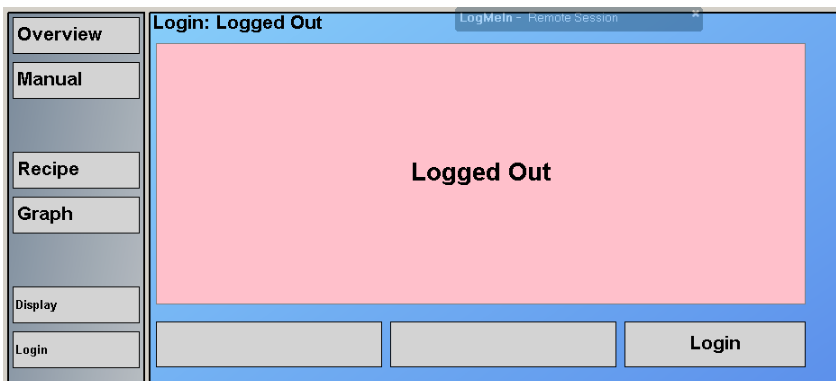
The first level has no access password, it enables the freeze drier operation in manual mode, to load a program/recipe from the list and to start/stop the automated cycle. The user can look through the screens, add and remove lines from the graph and change trace colours.

The second level also allows the programming of recipes, saving and editing. A password is required to access this level

The third level will also give the operator/engineer access to calibration settings and engineering values. A further password is required to access this level.

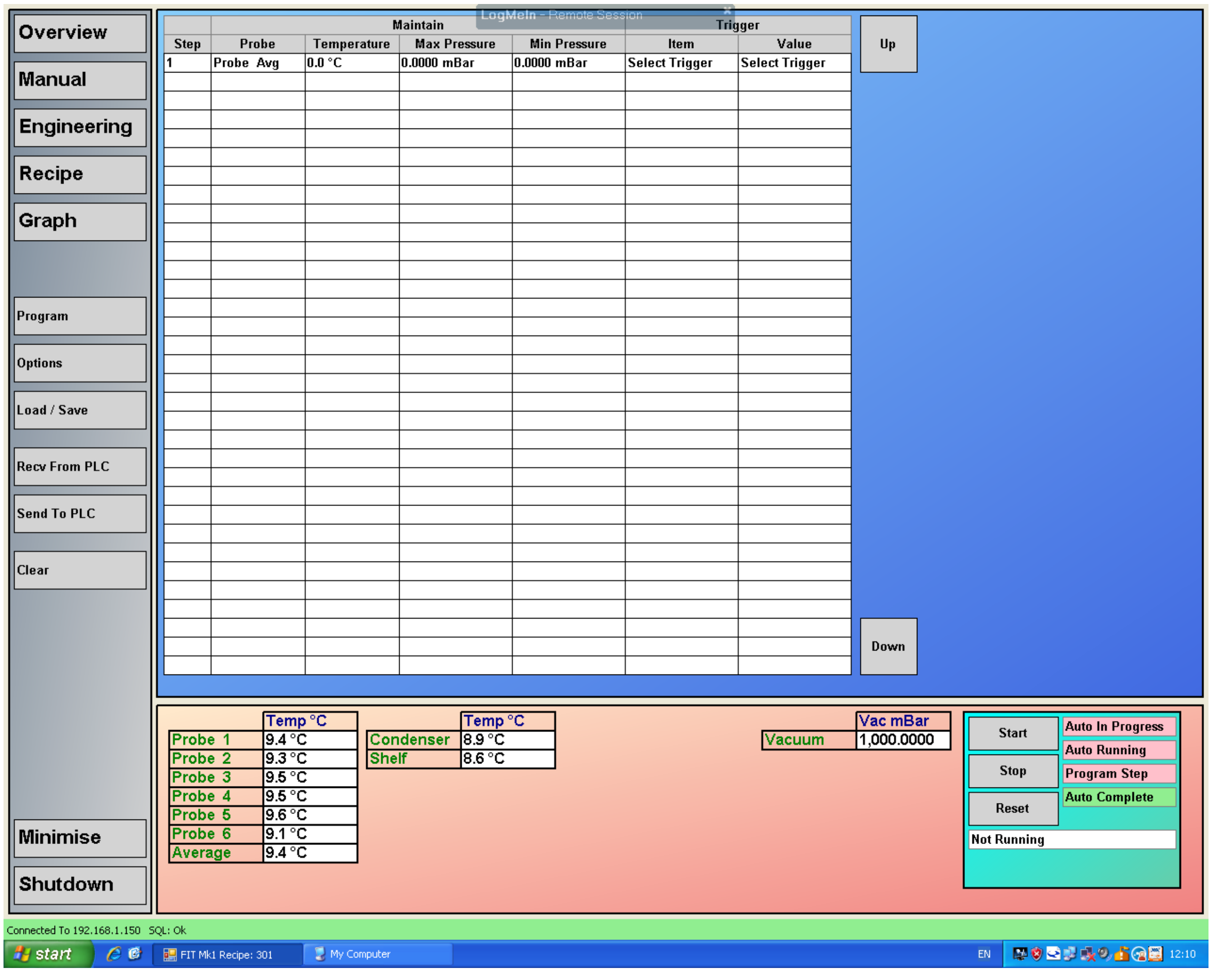
Whenever a function is not available due to current access level then selection buttons will not be visible.

To log in enter the login name in the first grey box and the login password in the second grey box and then press Login.



To log out click on the large green rectangle

5.3. Recipe screen



The Recipe screen is for programming the automatic freeze drying cycle. To change to another screen there are selection buttons down the left side as on previous pages.
There are also options for:

- **Program** - Creating a new programs
- **Options** – Preprogrammed options
- **Load/save** - Save or load a program
- **Receive from PLC** - the details of a program
- **Send to PLC** – the details of a program.
- **Clear** – Clear the programming table

Program setup

The program setup requires the input of a sequence of steps to complete a freeze drying cycle. The operator will define the running conditions within a step and an achievable value to prompt the next step. This value may be a temperature, a vacuum level or a time delay.
When a temperature is entered, the operator will need to specify which temperature probe is to be used.
On this freeze drier the shelves are not temperature controlled, only the chamber.
There are 8 mobile product probes, these are listed:
Probe 1, Probe 2…………
The following is a simplified example of programming a freeze drying cycle to explain the procedure.

Entering the first step

The Shelves are chosen as the target temperature. A triggering condition is set to initiate the next step.
To freeze the product to -40ºC the operator could do the following:

The first method
Select the required item such as Chamber temperature at -50ºC which would allow the chamber to cool down to this point. As the chamber cools down so will the product. The trigger Item would be a product probe 1 set at -40ºC. Upon reaching this the next step will be activated. Depending on the type or quantity of product, the thermal lag between the chamber may vary. In the time it takes the product to reach -40ºC the chamber may or may not reach -50ºC however they will not go below.
The disadvantage of this is:
Setting a minimum chamber temperature gives a constant temperature to absorb heat from the product. As the product temperature gets closer the temperature difference gets less. Therefore the rate of cooling is reduces. Freezing will take longer.
The advantages of this are:
The overall Product temperature will be much more even.
There is less chance of product temperature over shoot.
The chamber does have electrical fans that will operate when cooling if there is not a vacuum present. This will give a more equal temperature throughout the chamber.

The second method
Select the required item as a probe 1 temperature at -40ºC. Set the trigger item probe 1 at -40ºC. This way the chamber will cool as cold as is possible for the refrigeration system.
The disadvantages of this are:
The overall Product temperature may be much less even.
There is more chance of product temperature over shoot.
The advantage of this is:
Fastest rate of cooling due to greater temperature differences between product and shelf
(Having said this, the theory behind this bespoke machine may be proven wrong in practice!!)

Entering the second step

A time step could be used to allow the product to stabilize in temperature. The temperature of the product probe can stay the same so probe 1 is set to -40ºC. If the time step was set to one hour, the next step would be triggered after this time.

Entering the third step

The third step could be to create a vacuum on the product.
The temperature of the product would not need further cooling so probe one would remain at -40ºC. A vacuum trigger would be selected next with a value of 0.1mbar. The condenser chamber would be automatically cooled to -30 ºC and the vacuum pump would start.
Once 0.1mbar has been reached the next step would trigger.
As this is the first step that the vacuum is used a value can be put into the target vacuum box. This is the vacuum control setting. This setting will prevent the heater from activating while the vacuum level is above the value entered. As the probe 1 temperature is set at -40ºC the system would try and maintain this using heating or cooling. As the vacuum level improves the product will cool by sublimation so the heater would attempt to counter this.
Entering a value into the target vacuum box the same as the trigger value would prevent the heater from activating and allow natural vacuum cooling. The temperature will drop depending upon the level of vacuum created. If the box is left empty or a higher value is entered than the value in the target box then the heater would attempt to maintain probe 1 at the set temperature.
Due to the heat input there will be more sublimation occurring while initial vacuum is being drawn. This will increase the length of time taken to achieve the initial vacuum level.

Entering the fourth step

The fourth step would be to heat the product up to 40ºC while maintaining a vacuum level below a set point. This set point is of most importance at the beginning of the primary drying stage when the sublimation rate is at its highest. If the vacuum level rises above a set value then the ice in the product will start to melt. The vacuum control level will ensure that the ice core of the product stays frozen. To achieve the maximum rate of sublimation the vacuum level must correspond to a vapour pressure of a temperature as close to the eutectic point as is safely possible.

With regards to setting the temperatures similar methods as in the first step can be applied. Set a maximum shelf 1 temperature, reducing the chances of over shoot, but expect heat transfer to take longer. Or allow the shelves to heat up to their maximum temperature allowed (settings are in the engineering page) increasing the heat transfer rate, but also increasing the chances of product temperature overshoot.

Entering the fifth step

The fifth step could be a time step to allow the product to stabilize in temperature.
The temperature of the product probe 1 can stay at 40ºC. If the time step was set to one hour, the next step would be triggered after this time.

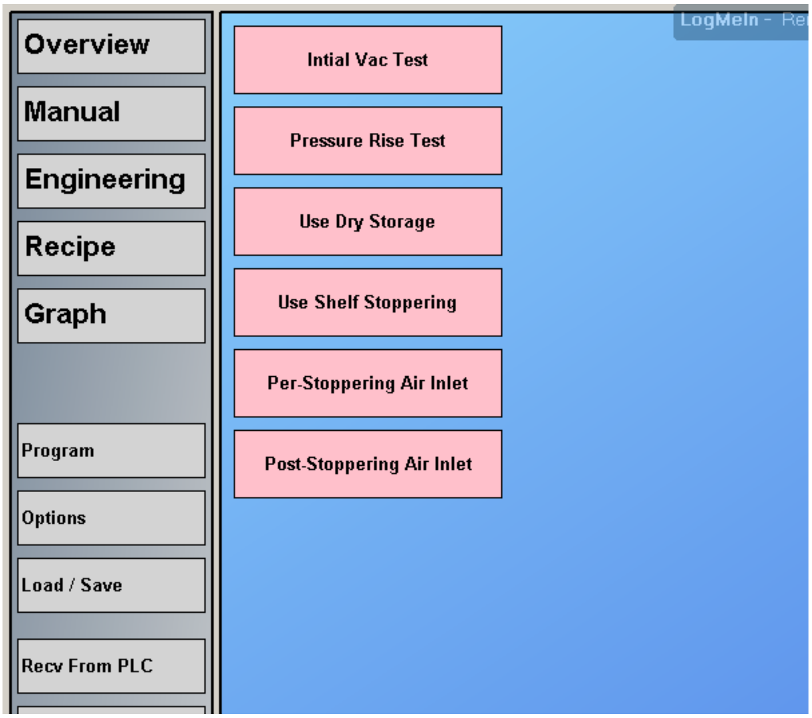
Entering the sixth and final step

The sixth step in this example would be secondary drying. This can be considered as another vacuum step.
The temperature of the product does not need further cooling. Select a trigger item as vacuum, with a value of 0.05mbar. When 0.05mbar is achieved it is the end of the programmable steps. If selected there may be some post steps to complete.

Notes:

Usually programming an automated freeze drying process will involve many more steps detailed steps. As there are several shelves it is sometimes important to repeat each temperature step for each shelf or product probe. This will ensure that every probe reaches the set points required.

Options



The operator may choose to activate the pre-programmed steps listed as

- **Initial Vacuum test**
  This ensures that the chambers are going to be vacuum tight before the process is allowed to start. Once the program has started an initial vacuum is pulled on the chambers. As long as a slight vacuum can be reached the program will know that it is safe to start, that the door has not been left open or fittings/seals are missing.
- **Pressure rise test**
  The pressure rise test if selected will occur after the last of the programmed steps has ended. The isolation valve will close. An initial vacuum reading in the product chamber will be taken. After a preset timer has lapsed another vacuum reading will be taken. If the pressure rise is within an allowable range then the next post step will activate. If the pressure rise is too high then the valve will re-open and drying will continue for a time span before retesting.
- **Dry storage**
  This is a means of storing the product within the freeze drier at a controlled temperature once the process has ended. This is useful if the product finishes its process in the middle of the night and there are no operators to unload it. If products are usually transferred to a fridge after drying then the freeze drier can match these conditions for ideal storage until unloading can take place.
- **Use Shelf Stoppering**
  If the freeze drier is required to stopper vials automatically as soon as the product is dry, then this should be selected. At the end of the program the shelves will close together pushing the stoppers into the vials.
- **Pre – Stoppering Air Inlet**
  It may advantageous to fill the vials with a charge of inert gas before stoppering. Perhaps, nitrogen or argon, this may be at a partial vacuum level. By selecting this option the chamber can be raised in pressure via the vacuum bleed valve using a chosen gas before vial stoppering takes place.
- **Post – Stoppering Air Inlet**
  This option will allow the chamber pressure to rise only after vial stoppering. This will ensure that the vials are closed with a vacuum inside.

Load / Save

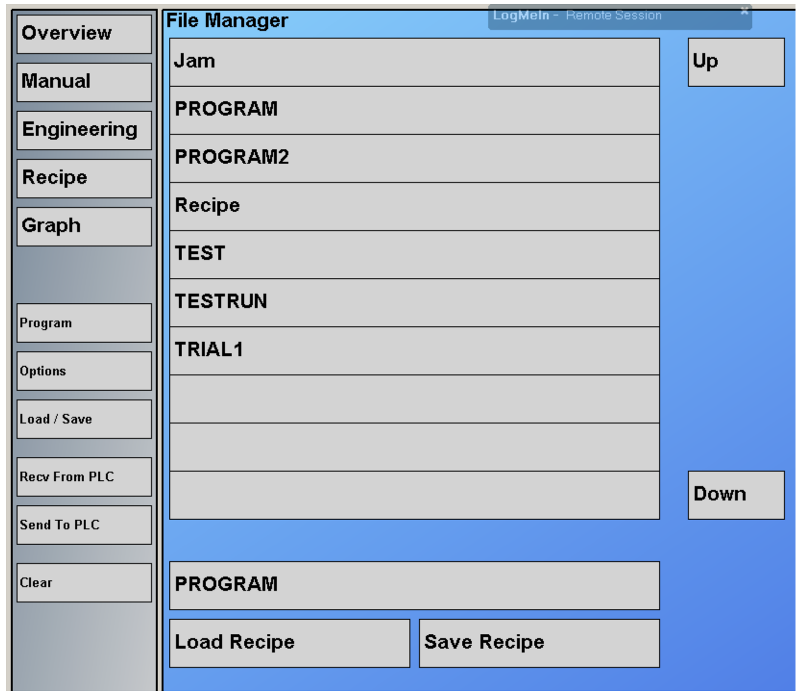
This will open up File Manager. The operator can load a saved Recipe off the list or save one that is currently programmed.

Receive from PLC

The PLC contains the recipe that the freeze drier will operate with. If the program list has been cleared or programming mistakes have been made then this button will re-populate the programming list with current values on the PLC.

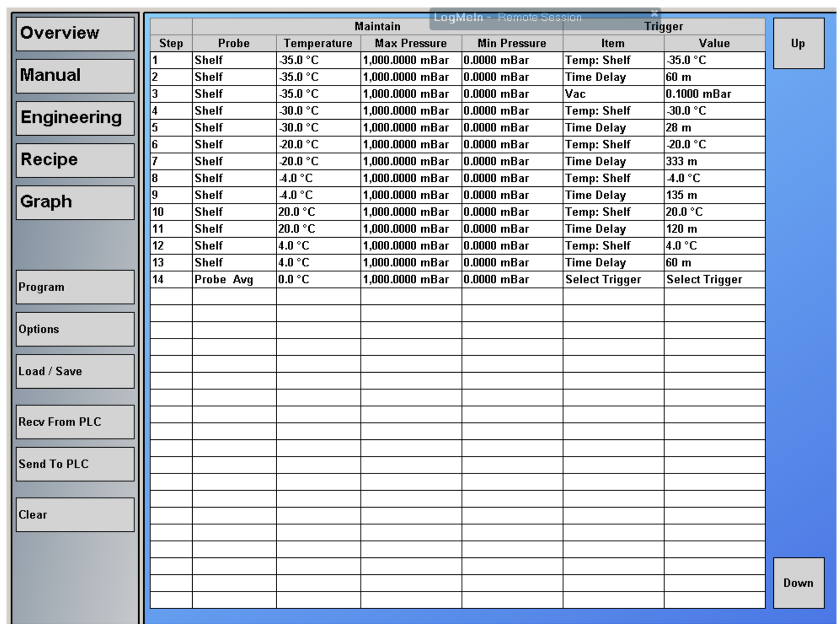
Send to PLC

Once a program has been altered, created or loaded then it must be sent to the PLC. This will enable the PLC to operate the freeze drier with the up dated program rather than the last programming it was using.



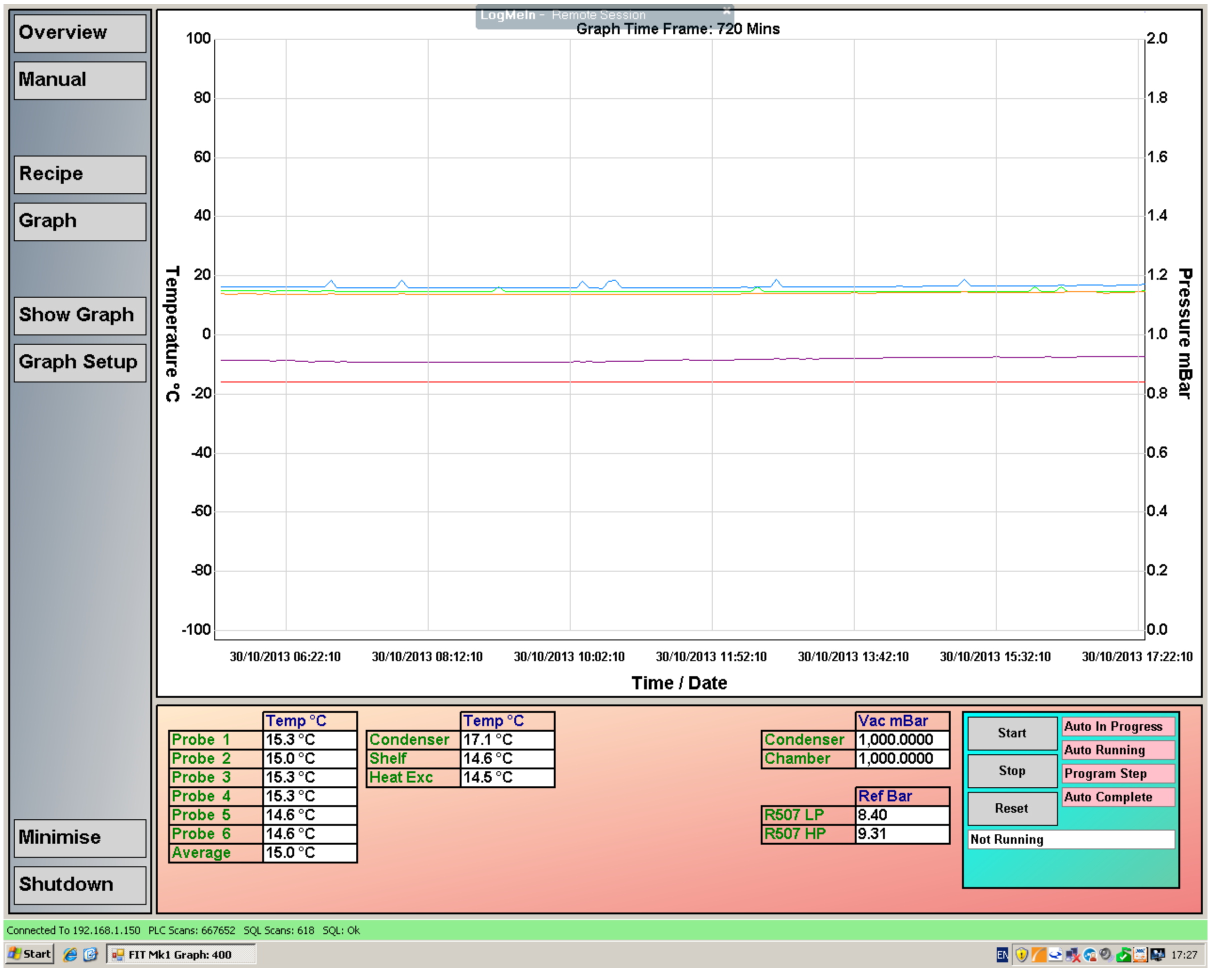
Clear

To delete all program step data off the list and return to a clean unpopulated list press Clear.



	Maintain				Trigger	
Step	Probe	Temperature	Max Pressure	Min Pressure	Item	Value
1	Shelf	-35.0 °C	1,000.0000 mBar	0.0000 mBar	Temp: Shelf	-35.0 °C
2	Shelf	-35.0 °C	1,000.0000 mBar	0.0000 mBar	Time Delay	60 m
3	Shelf	-35.0 °C	1,000.0000 mBar	0.0000 mBar	Vac	0.1000 mBar
4	Shelf	-30.0 °C	1,000.0000 mBar	0.0000 mBar	Temp: Shelf	-30.0 °C
5	Shelf	-30.0 °C	1,000.0000 mBar	0.0000 mBar	Time Delay	28 m
6	Shelf	-20.0 °C	1,000.0000 mBar	0.0000 mBar	Temp: Shelf	-20.0 °C
7	Shelf	-20.0 °C	1,000.0000 mBar	0.0000 mBar	Time Delay	333 m
8	Shelf	-4.0 °C	1,000.0000 mBar	0.0000 mBar	Temp: Shelf	-4.0 °C
9	Shelf	-4.0 °C	1,000.0000 mBar	0.0000 mBar	Time Delay	135 m
10	Shelf	20.0 °C	1,000.0000 mBar	0.0000 mBar	Temp: Shelf	20.0 °C
11	Shelf	20.0 °C	1,000.0000 mBar	0.0000 mBar	Time Delay	120 m
12	Shelf	4.0 °C	1,000.0000 mBar	0.0000 mBar	Temp: Shelf	4.0 °C
13	Shelf	4.0 °C	1,000.0000 mBar	0.0000 mBar	Time Delay	60 m
14	Probe Avg	0.0 °C	1,000.0000 mBar	0.0000 mBar	Select Trigger	Select Trigger

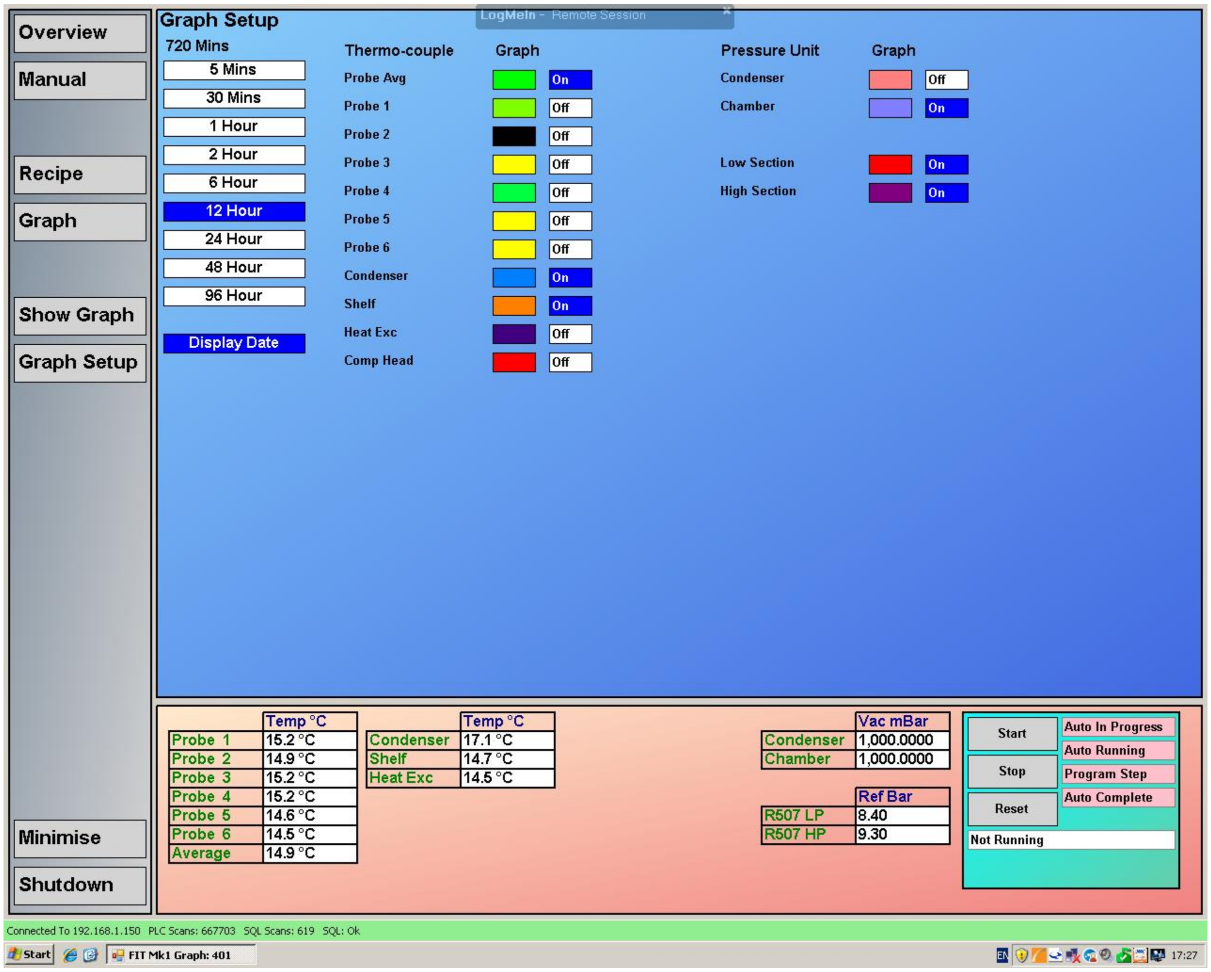
5.4. Graph



Show Graph

The data logging monitors temperatures of all mobile probes, shelves, condenser and vacuum levels. Information on temperature and vacuum changes becomes very easy to analyze on a line graph.

Graph Setup



Within Graph setup

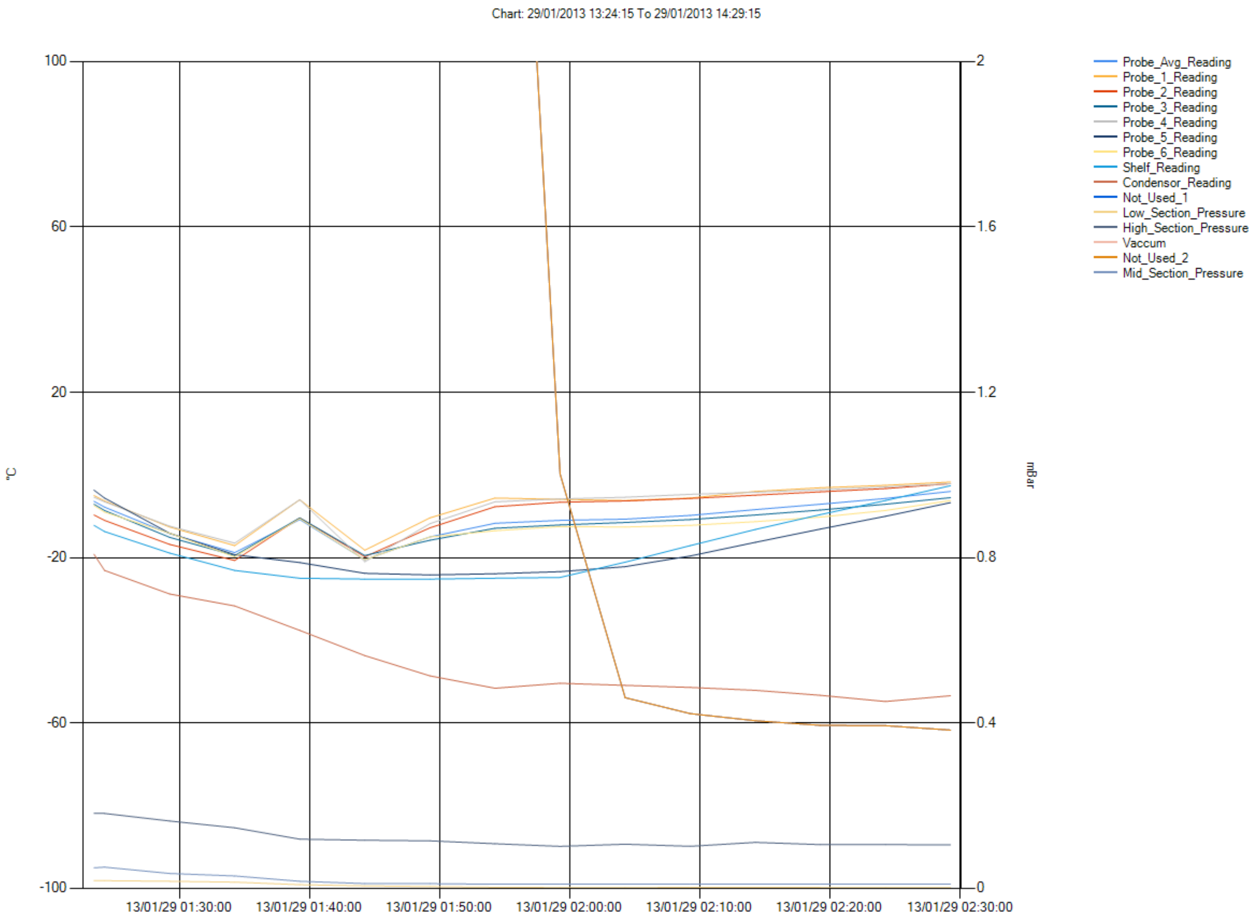
The time scale that the graph shows can be selected, 30mins to 96 hours. Blue will indicate the time scale that has been selected.

Thermocouple can be identified on the graph by changing the line colour. They can also be hidden by turning them off.

Vacuum pressures can be identified on the graph by changing the line colour. They can also be hidden by turning them off

The Graph print out

Below is an example of a cycle printout. On the left there is a key to identify graph lines. Product and Batch identification appear as the heading.

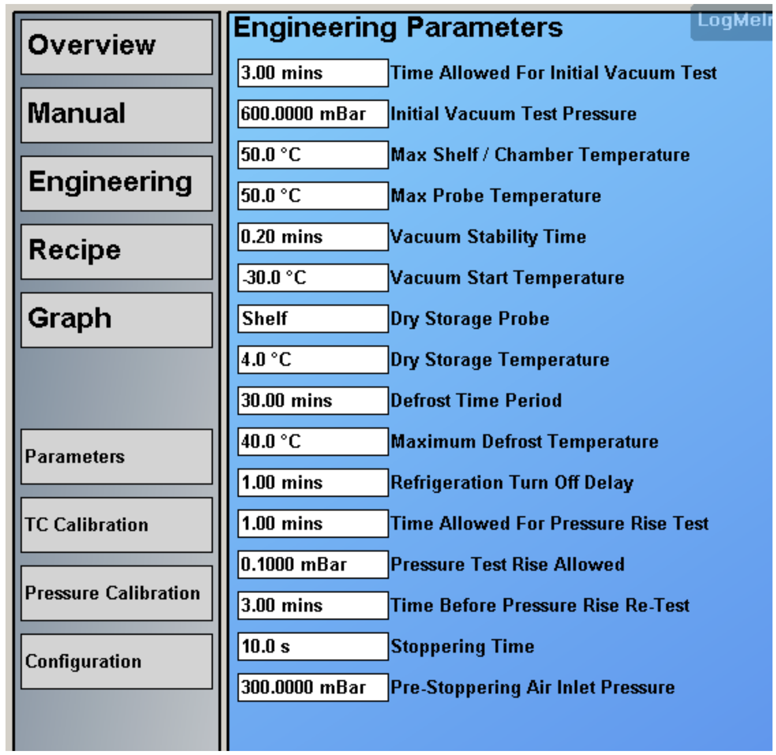


5.5. Engineering

The Engineering screen is for programming the automatic freeze drying cycle. To change to another screen there are selection buttons down the left side as on previous pages.

There are also options for:

- **Parameters** – Engineering parameters
- **TC Calibration** – Temperature Calibration
- **Pressure Calibration** – Pressure Calibration
- **Configuration** - configuration



<u>**Engineering Parameters**</u>

Time allowed For Initial Vacuum Test
This is the time that the vacuum pump will run during an initial vacuum test to confirm the chamber is leak tight before an automated program can start. A moderate vacuum level is set of approximately 600 mbar to confirm doors are closed and the vacuum pump is switched on at the motor. Depending on the volume of the chamber, a sensible time is allowed for this test. As soon as the vacuum level is achieved within the time frame, the test is complete. If the required vacuum is not achieved within the set time the program will not commence. The problem will require investigation.

Initial Vacuum Test Pressure
This is the box were the vacuum level is entered. As mentioned above a sensible setting is 600 mbar, this is only achievable with a leak tight vacuum system. This vacuum level will not adversely affect unfrozen product.

Max Shelf / Chamber Temperature
A value can be set so that if any temperature goes above it all heating will stop and a warning will be displayed. This is regardless of which sensors are used for temperature control. It is an overall safety limit incase the thermocouple used for temperature control acquires a fault or is poorly programmed or positioned.

Max Probe Temperature
A value can be set so that if any temperature goes above it all heating will stop and a warning will be displayed. This is regardless of which sensors are used for temperature control. It is an overall safety limit incase the thermocouple used for temperature control acquires a fault or is poorly programmed or positioned.

Vacuum stability Time
The vacuum readings that initiate a change in programmed steps must remain beyond the set point threshold for this selected time. This will ignore sporadic readings on while on the edge of the vacuum sensors designed operating range.

Vacuum start temperature
This is the temperature set point that does not allow the vacuum pump to start until the condenser temperature is below it. Usually set at -30ºC. This will stop unfrozen water vapour being drawn into the vacuum pump.

Dry product storage probe
This is the product or shelf probe that is used to control the temperature when the freeze dryer is in dry storage mode. Dry storage can be selected to run after the automated freeze drying cycle has ended if the product is not unloaded straight away. If a cycle ends during the night and the operator cannot unload the freeze drier, preferred conditions such as fridge temperatures can be matched on the shelves. A product or shelf probe may be chosen for this control.

Dry product storage temperature
This is the temperature that dry product will be controlled to if dry product storage is selected.

Defrost time
This is the time that the condenser chamber will be heated for. A setting that will give enough time to melt all the condensed ice is required. This can be set by the operator to suit the application of the freeze drier.

Maximum defrost temperature
This is the maximum temperature that the condenser temperature is allowed to reach while defrosting.

Refrigeration turn off delay
The compressors of the refrigeration system will continue to run for a period of time after the refrigeration has been switched off. This will prevent liquid refrigerant being left in areas of pipe work that are exposed to high temperatures.

Time allowed for pressure rise test
The end of the automated cycle has the option a pressure rise test. This is where the product is sealed off in the product chamber to see if sublimation has finished. If the pressure rises above the set limit (pressure rise quantity) it can be considered to not be dry, as sublimation is still occurring. If the pressure rise is within limits the product is dry. For the pressure rise test there is a set time frame that the pressure rise can occur within.

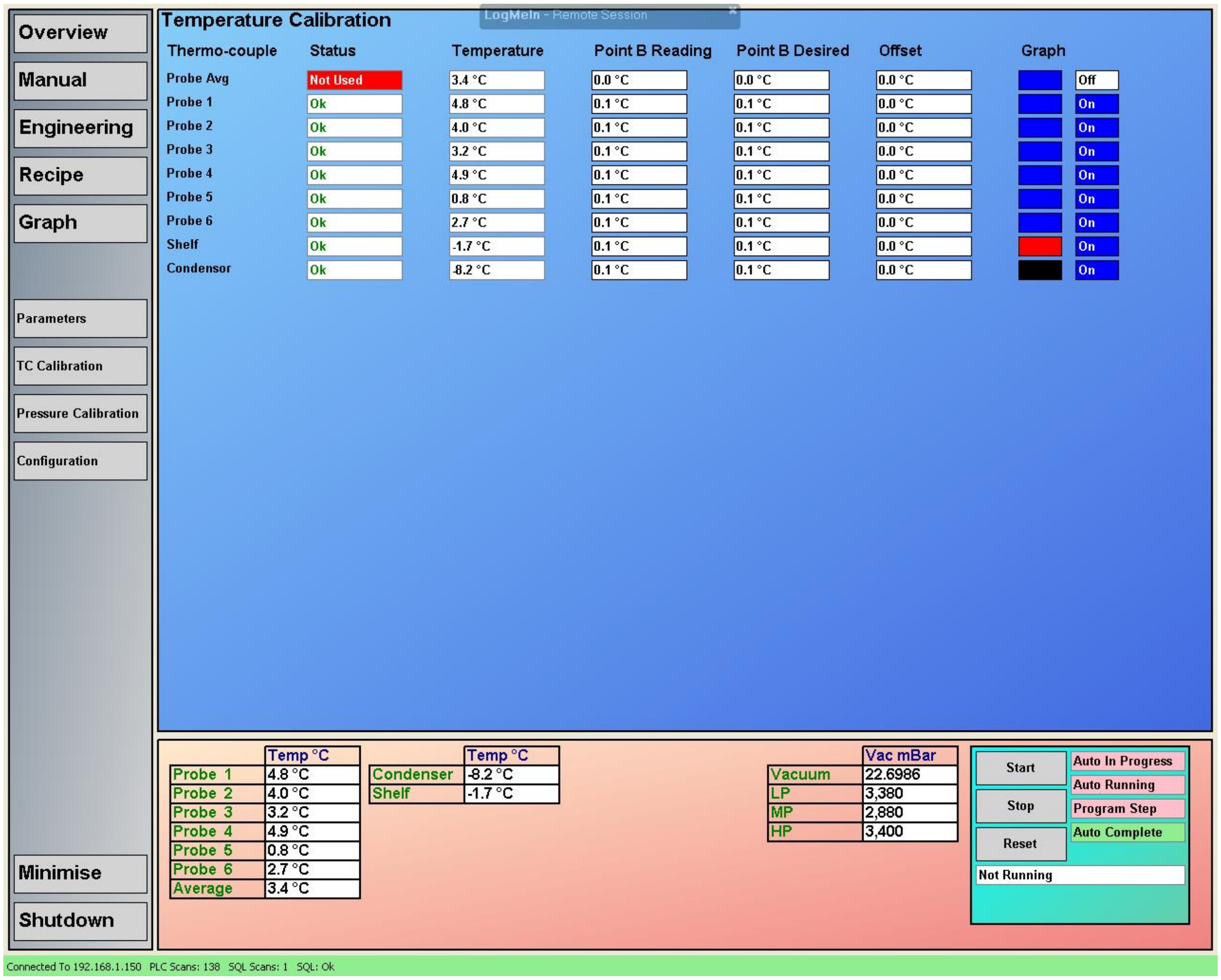
Pressure rise allowed
The end of the automated cycle has the option a pressure rise test. This is where the product is sealed off in the product chamber to see if sublimation has finished. If the pressure rises above the set limit it can be considered to not be dry as sublimation is still occurring. If the pressure rise is within limits the product is dry. For the pressure rise test there is a set vacuum level that is allowable. A rise above this pressure indicates that the product is not dry and the test has failed.

Time before pressure rise retest
A fail is if the pressure rises beyond the allowable **pressure rise quantity** within the **Time allowed for pressure rise test.** Time before retest is the time that the product will have back under drying conditions before the next test.

Stoppering time
During automatic vial closing the ram will raise up to close the shelves together and seal the vials. This is the time allowed for this procedure and is set at the factory.

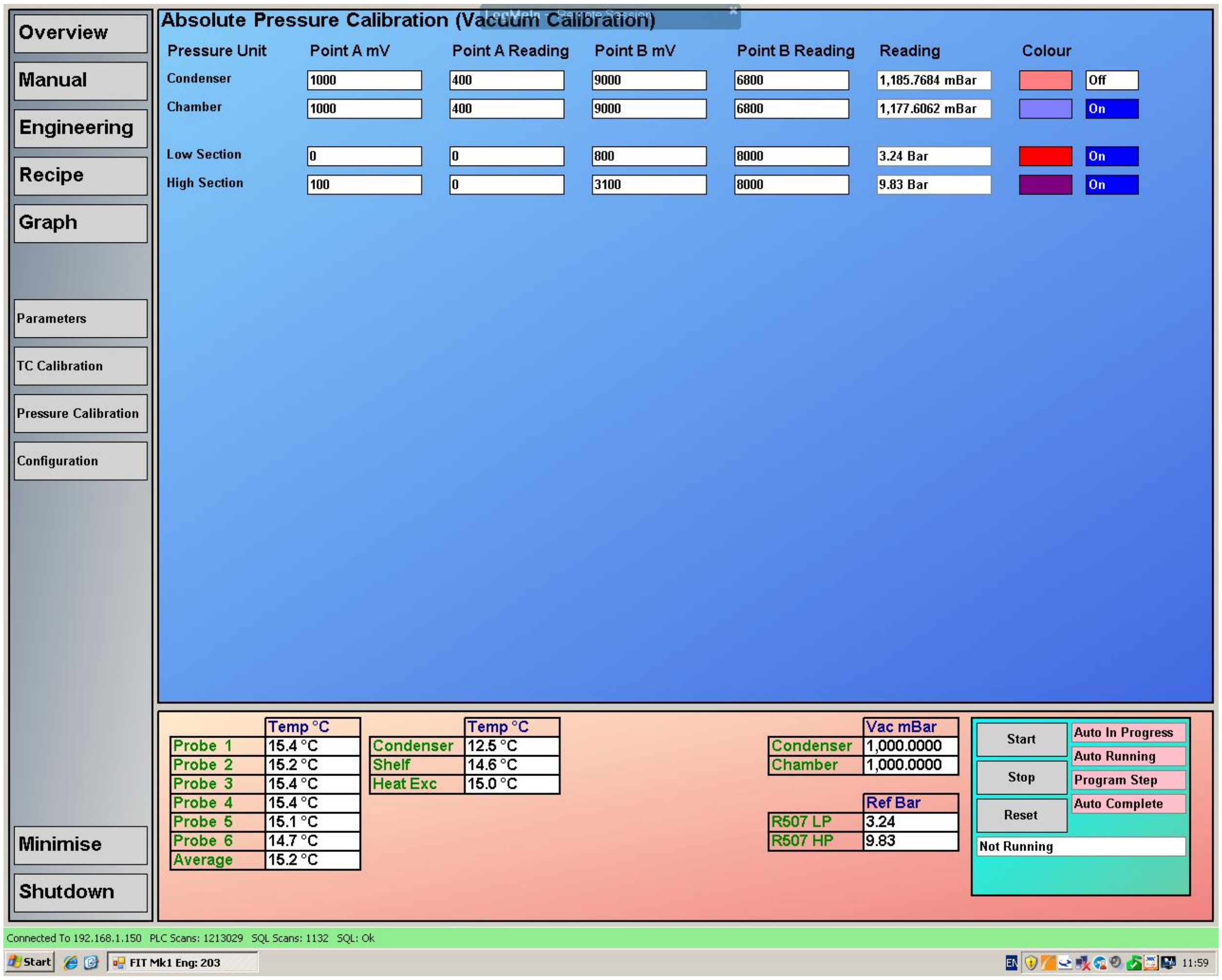
Pre – Stoppering air inlet pressure
If a pressure of inert gas is required to fill the vials before they are sealed then the level of vacuum can be entered.

Thermocouple Calibration



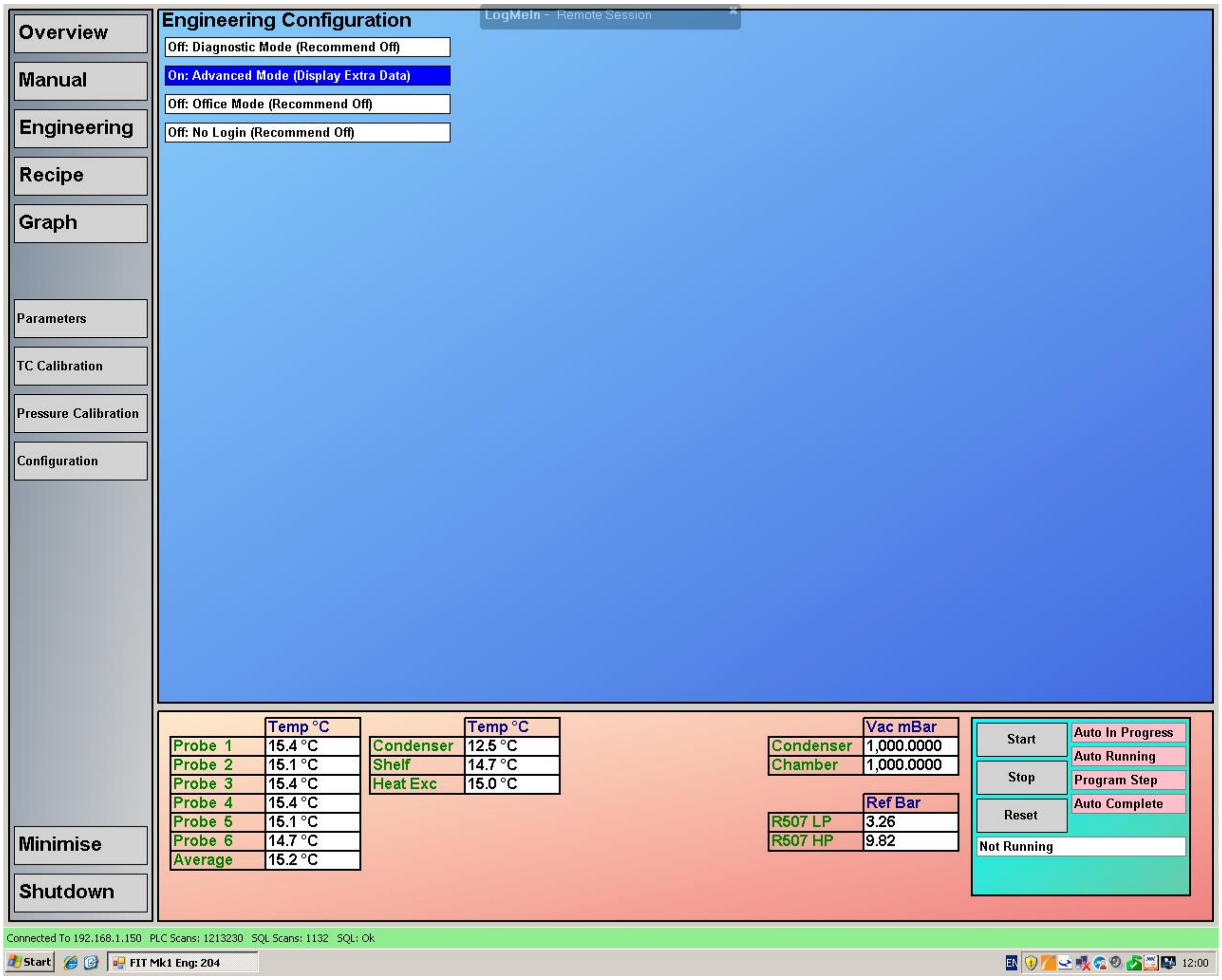
This screen is for factory setup or periodic temperature calibration. Sensor connection status, PLC temperature reading, correction scaling and offset can be set to give the correct reading.

Vacuum / Pressure Calibration



This screen is for factory setup or periodic vacuum calibration. Sensor connection status, PLC Vacuum reading, correction scaling and offset can be set to give the correct reading.

Engineering Configuration

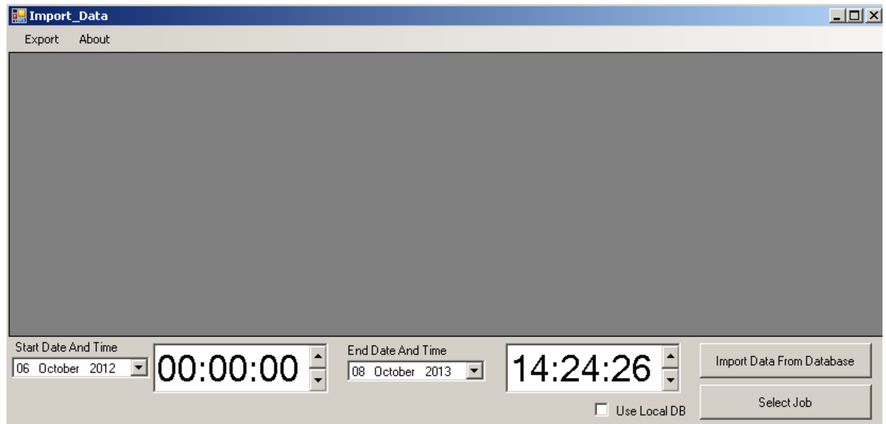


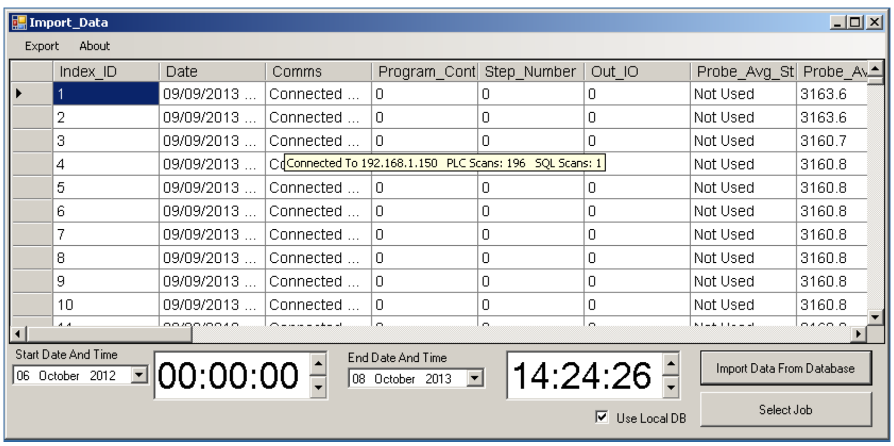
Several configurations can be selected, this is for online support of the freeze drier or the software. Extra information can be displayed that would not be needed for the everyday operator. There are several levels/layers of information that displayed. This is only accessible with the higher level of login access.

6. Reporting

There is a continual data logging process taking place whenever the freeze drier operating system is in operation. The data logging application is accessible in the windows desktop. Minimize the freeze drier application and open “Reporting”.

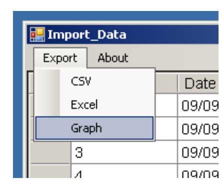
1) Enter the start date and time of the data you wish to view.
2) Enter the end date and time.
3) If unchecked select “Use Local DB”
4) Press “Import Data from Database”

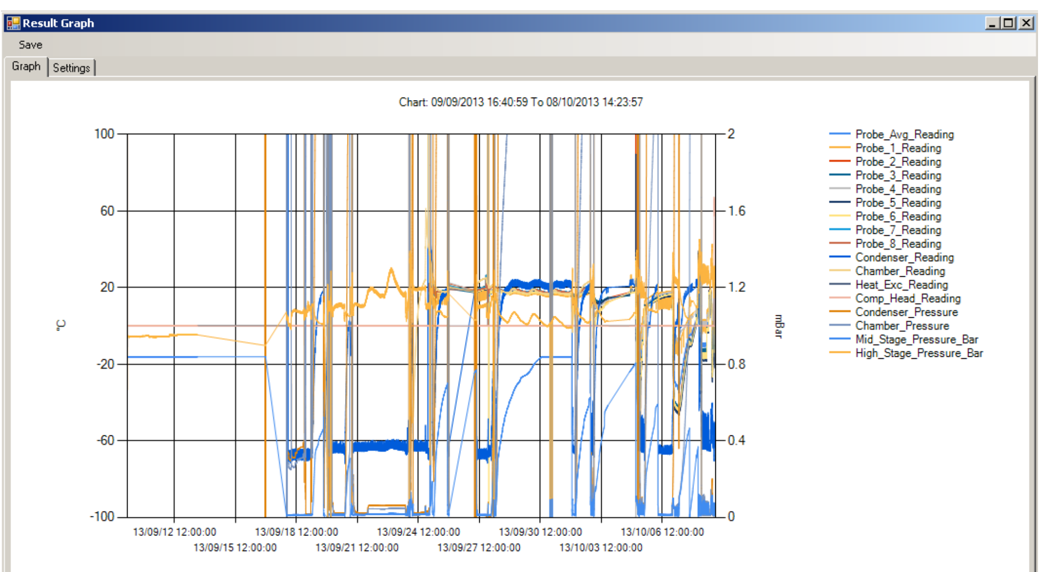




The data base can be scrolled through to find out temperatures vacuum levels and refrigeration pressures for every data logging interval. Each data logging interval is currently set at 1 minute. An extension of this data will show every active function and PLC output.

Select Export send data to CSV, Excel or Graph file.





A graph can be generated using the data selected. Trace colours can be changed or removed in the settings page to show the information that important.

7. Troubleshooting

7.1. Power failure

The freeze drier will resume its program or 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.

7.2. 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 is sufficient on the condenser chamber but significantly worse on the specimen chamber:

- Check that air admittance and inert gas valves are closed on the overview or manual screen.
- Check all vacuum connections on specimen chamber including door seal. Repair or replace.
- Check for oil leakages from the shelf thermal fluid. Oily residue may collect in the chamber.
- 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.

If the vacuum cannot be achieved in the condenser chamber with the isolation valve closed:

- Check all vacuum connections on condenser chamber including door seal. Repair or replace.
- Check the condition of the isolation valve sealing surface. Glass pieces from broken vials can slit the rubber seal. If there is a doubt about this coat in vacuum pump oil or vacuum grease and test to see if there has been an improvement in the vacuum level.
- Check that there is no suction on the condenser drain hose. This would indicate a leaking valve.
- Check the vacuum pump is pulling an adequate vacuum, test with a separate vacuum sensor.
- Check that the isolation valve is sealing by opening it and pulling a vacuum on the product chamber as well, eliminating the seal of the valve.

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

7.3. Insufficient cooling of the condenser chamber

If the condenser chamber is not reaching the relevant temperature -55ºC or -85ºC
(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 compressor 1, compressor 2 and fans.
- Check that the contactors are operating.
- Check the overview screen to ensure that refrigeration and condenser cooling are operating.

7.4. Insufficient defrosting of the condenser chamber

If defrost is not heating up.

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

7.5. Insufficient cooling of the shelves

If the shelves are not reaching low set points or relevant temperature -45ºC or -70ºC

- 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 compressor 1, compressor 2, fans and circulation pump
- Check that all the contactors are operating.
- Check the overview screen to ensure that refrigeration, shelf cooling and circulation pump are operating.
- Check that temperature control is not controlled by a sensor that is malfunctioning and reading an incorrectly low temperature.

7.6. Insufficient heating of the shelves

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

- Check the circuit breaker for heater and circulation pump.
- Check that all the contactors are operating.
- Ensure that heater and circulation pump are activated on the overview screen.
- 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 unachievable vacuum set point entered preventing the heater from being activated.
- Check that the settings in the Engineering screen are allowing its activation

7.7. Fluctuations in shelf temperatures

If the shelf fluctuations are high it could be due low levels of thermal fluid in the system. Fluid levels should be topped up when the fluid is at its maximum operating temperature. This is when the level is at its highest it will ensure that no over flowing can occur later. Be sure to reconnect the nitrogen blanketing system after the fluid has been accessed.

Shelf fluctuations occurring when the fluid is below 0ºC. This can be caused when water vapour enters the thermal fluid and when it freezes it creates a flow restriction. Please contact the manufacturer, supplier or trained maintenance department. Maintaining a positive nitrogen blanket above the fluid prevents this situation from happening.

Malfunctioning thermocouples can cause sporadic readings or solidly fixed irrelevant readings.

7.8. Defrost will not drain away

If the condenser chamber will not drain away after defrost it could be due to a blocked pipe. However first check that the drain valve is opening.

- Check the overview screen to see if the indicator shows that it is activated.
- Check the circuit breaker for the drain valve
- Check that the contactor is operating.
- Check the valve actuator and see if the indicator dial is reading open.
- Check that the manual handle is turning as the valve is activated.

7.9. Air admittance will not open

If the vacuum cannot be broken in the product chamber the air admittance valve may not be operating. If it is remove the filter or Nitrogen supply line and try again.

7.10. Isolation valve will not open

If the Isolation valve does not operate:

- Check the overview screen to see if the indicator shows that it is activated.
- Check the circuit breaker for the Isolation valve
- Check that the contactor is operating.
- Check the valve actuator and see if the indicator dial is reading open
- Check that the manual orange handle is turning as the valve is activated.

7.11. Doors will not seal under vacuum

If the doors will not seal under vacuum

- Check that the vacuum pump is running
- Close the isolation valve and check that the condenser door is sealing
- Check that the air admittance valves are closed
- Clamp the product chamber door and check that it is pushed up against its seal all around.
- Open the isolation valve and release the door clamps.
  Does the door still open?

7.12. Incorrect probe temperature

Incorrect probe temperatures can be due to

- Unplugged probes
- Broken thermocouples
- Thermocouples with loose connections
- Incorrectly calibrated thermocouples

8. Maintenance

8.1. Condenser chamber

Before each start-up, ensure that condenser chamber is drained.

8.2. 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.

8.3. 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.

8.4. 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.

8.5. 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.

8.6. 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.

8.7. 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