



The Importance of Vacuum and the Control of Pressure in Freeze-Drying

Kevin R. Ward, Ph.D. FRSC

Director of Research & Development, BTL, Winchester SO23 0LD

Synopsis of Presentation

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- ▶ What is Freeze-Drying?
 - ▶ What can we freeze-dry?
 - ▶ Fundamentals of freeze-dryer design
 - ▶ Vacuum systems in freeze-dryers
 - ▶ Pumps
 - ▶ Valves
 - ▶ Gauges
 - ▶ How important is pressure during...
 - ▶ Freezing?
 - ▶ The Sublimation Process ("Primary drying")?
 - ▶ Desorption ("Secondary drying")?

What is Freeze-Drying?

- ▶ The term “Freeze-drying” is quite descriptive, implying a process where a product is initially frozen, and then dried from the frozen state.
- ▶ Lyophilisation (lyophilization in USA) means “*to make solvent-loving*”, which is one of the principal features of the freeze-drying process (Louis Rey)
- ▶ Although we could argue these are different, the terms Freeze Drying and Lyophilisation are used interchangeably to describe the same process

Examples of freeze-dried products



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- ▶ Early freeze drying was used to preserve food by utilising cold and dry weather conditions often found at high altitudes.
 - ▶ The ancient Incas and South Americans would preserve their potatoes high in the Andes.
 - ▶ The Vikings would preserve cod fish in the cold dry arctic conditions.

- ▶ Towards end of the 19th c. an increasing need to preserve biological specimens
- ▶ 1890 Altman dried tissue at sub atmospheric pressure at temperature of -20°C (pressure and equipment used not known)
- ▶ 1905 Benedict and Manning dried animal tissue by using a chemical pump
- ▶ 1910 Shackell published "An improved Method of Desiccation" using mechanical vacuum pump and concentrated sulphuric acid to act as a condenser.
- ▶ 1936 Greaves and Adair at Cambridge study the thermodynamics of freeze drying and promote sound scientific principles to it.

- ▶ 1938 Nestlé in Switzerland freeze dry an abundant coffee crop for Brazil
- ▶ 1944 Blood plasma and penicillin produced on a commercial scale for 2nd world war effort
- ▶ 1950s Pharmaceutical freeze drying
- ▶ 1960s Explosion in the number of foods being freeze dried including freeze dried ice cream for Apollo missions
- ▶ 1970s Uses expand into taxidermy, museum artefacts etc
- ▶ 1980 Freeze dried flowers
- ▶ 1990 Freeze dried pets (already dead ones)
- ▶ 2000 Freeze dried fruit for breakfast cereals

What Do We Freeze Dry

- ▶ Non Biological Products
 - ▶ Heat labile chemicals
- ▶ Non living bio products
 - ▶ enzymes, hormones, antibiotics, vitamins, blood products, antibodies, vaccines, pharmaceuticals
 - ▶ bone and body tissues for surgical/medical use
 - ▶ foodstuffs
- ▶ Living Organisms
 - ▶ Live viruses, bacteria
- ▶ Non Pharma
 - ▶ Foods, flowers, small animals, flood damaged books, museum artefacts

- ▶ A method of preservation by drying whilst maintaining original structure and activity
- ▶ Provides for a long shelf life
- ▶ A “reversible” process giving a product that easily reconstitutes back to its original state
- ▶ Enables more accurate dosing than powder filling
- ▶ Allows for manufacturing under sterile conditions

- ▶ Cost
 - ▶ Capital cost of equipment
 - ▶ Costs of running
 - ▶ Energy costs
 - ▶ Manufacturing under sterile conditions
- ▶ Batch Process
 - ▶ Whilst a batch process is favourable for pharmaceutical products, it is less so for other materials
- ▶ Time
 - ▶ Many processes can take days
 - ▶ Increased risk the longer a cycle

- ▶ To determine and control the final moisture content
- ▶ To influence the appearance of the final dried material
- ▶ To use constituents that are acceptable for both the target market and any regulatory requirement
- ▶ To provide for a long shelf life and storage preferably at room temperature
- ▶ To retain activity throughout given shelf life

- ▶ Freeze drying involves energy transfers and balancing of energy equations
- ▶ From the 1st Law of Thermodynamics, energy can neither be created nor destroyed
- ▶ It can however exist in many forms – mass, light, chemical, gravity, electrical, mechanical etc.
- ▶ In freeze drying we are most interested in heat energy
- ▶ Mainly, we are moving energy into or out of a system by controlling heat energy flow and hence temperature
- ▶ The main part (sublimation) is about balancing heat and mass transfer

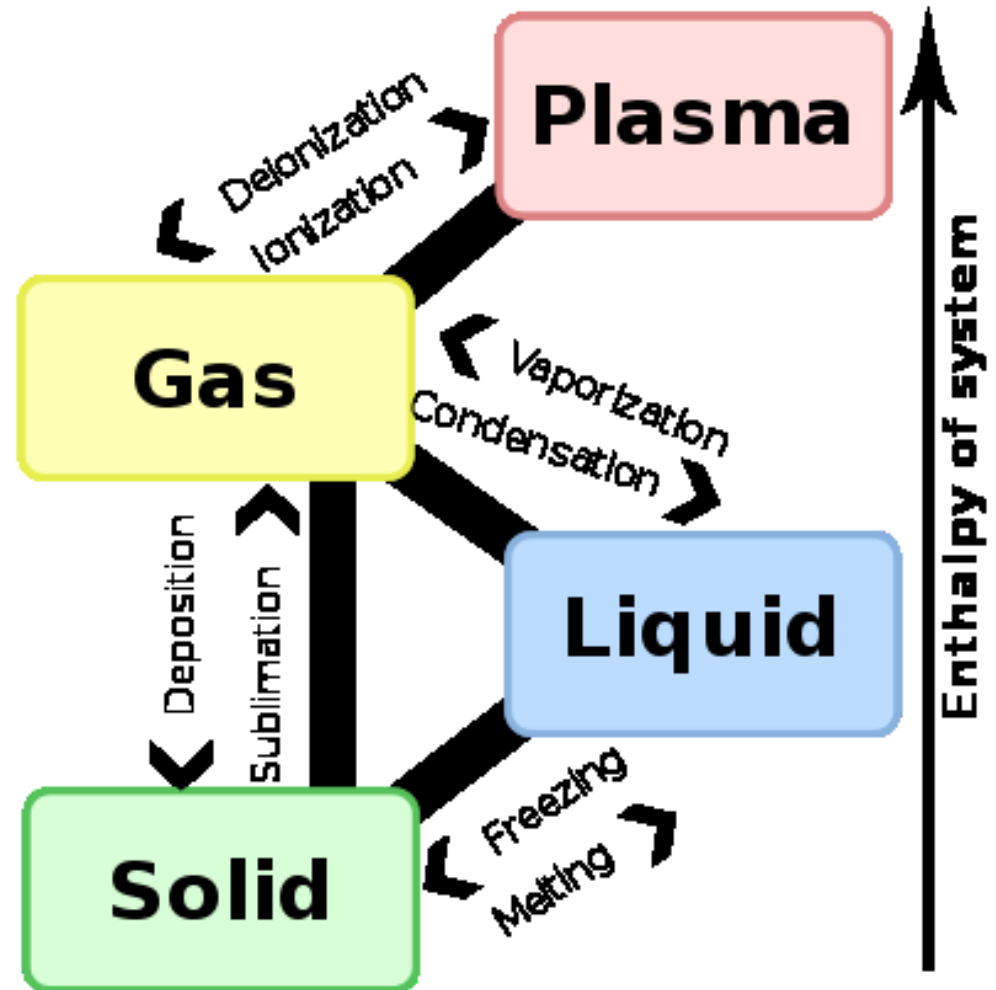
Phases of Matter

The phases of matter

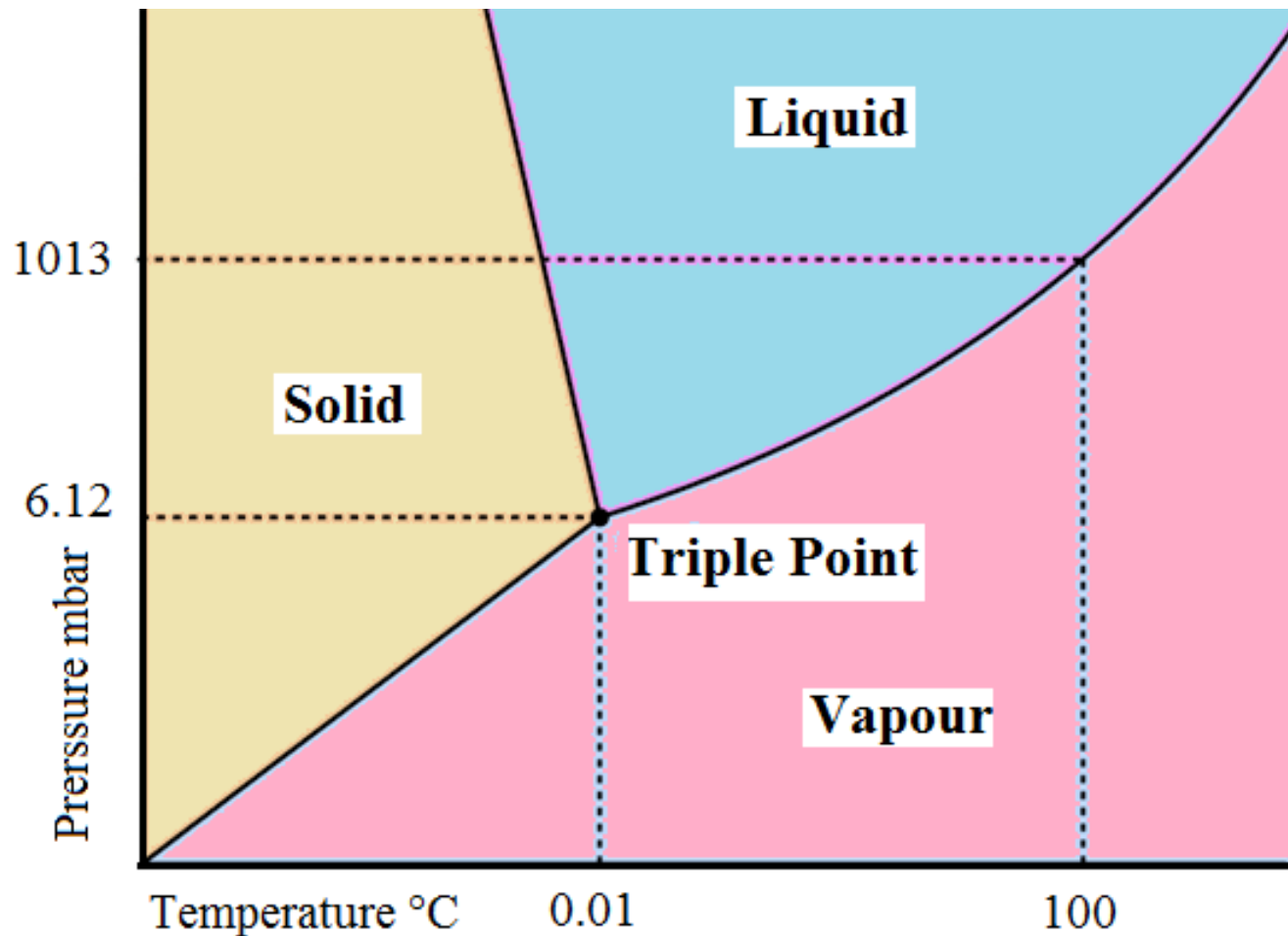
The terminology used to describe the changes from one phase to another

The energy flow (heat input) to change from the solid phase to the plasma phase

The process of going direct from the solid to the gaseous phase is a process known as **SUBLIMATION**



Phase Diagram of Water



To drive the sublimation process, we need to be below the triple point of water.

This shows we need to be in the 'vacuum' region of the graph

*As this is a calculated point and not a measured point, strictly the scales should be in thermodynamic units of **Kelvin** (273.16 K) and **Pascal** (612 Pa)*

▶ **Freezing**

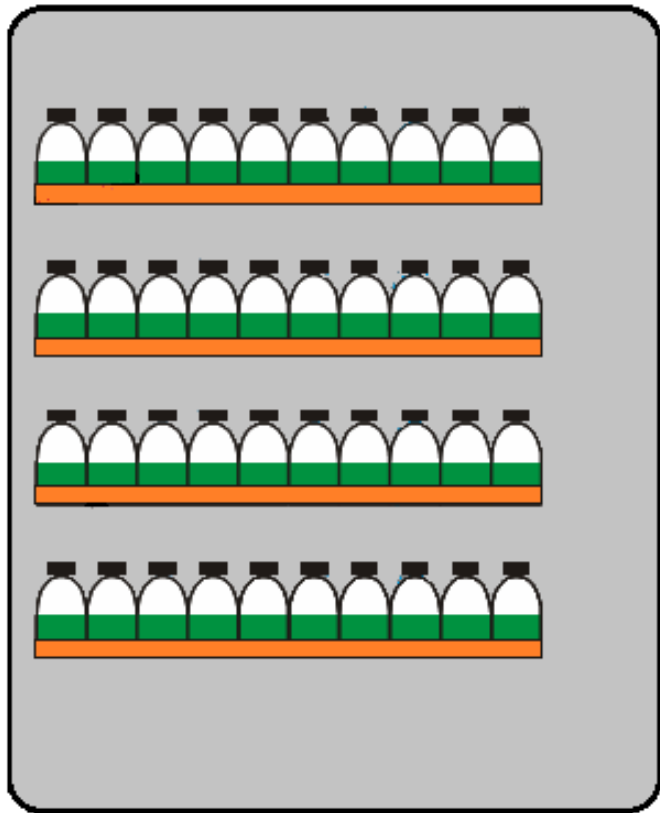
- ▶ Freezes both the solvent and the solute
- ▶ Immobilises the material
- ▶ Defines the structure ready for drying

▶ **Primary Drying**

- ▶ The removal of the frozen free moisture by a process of sublimation – the conversion of ice to vapour without passing through the liquid phase

▶ **Secondary Drying**

- ▶ The process of further drying by desorption



A chamber

Contains a shelf or a number of shelves upon which the product sits.

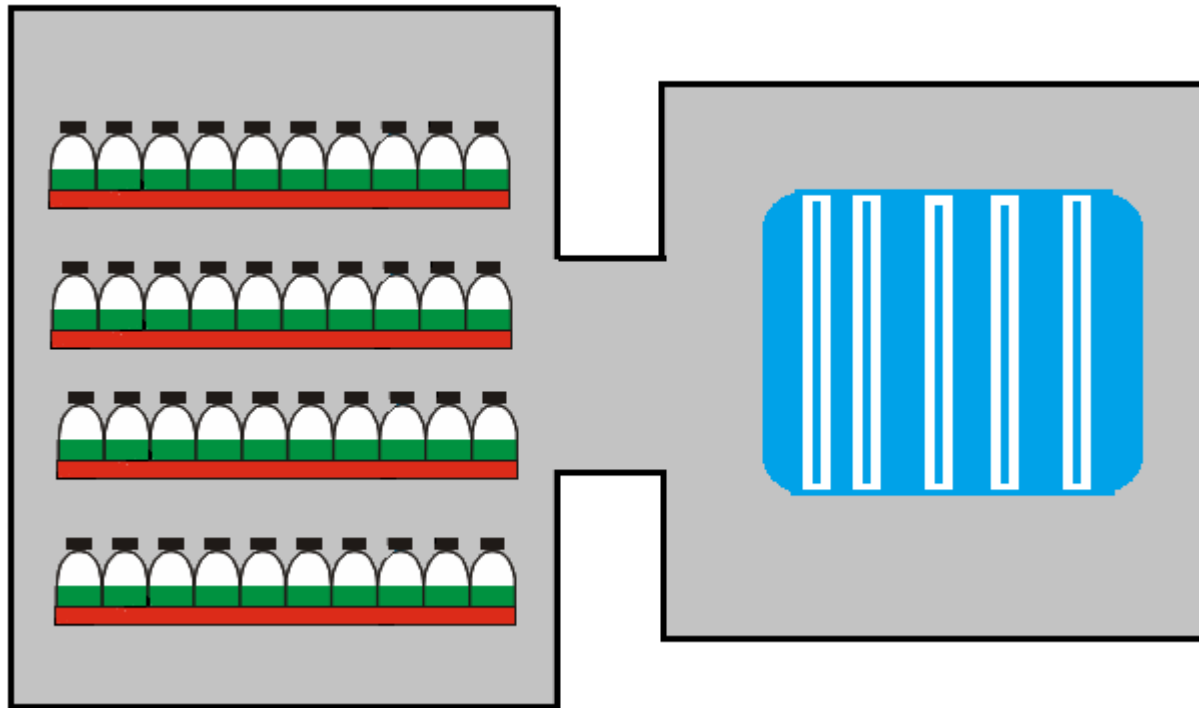
The product will be held in a container – usually glassware or trays for bulk processing but other forms are used.

Chamber Shelves

A typical example of partially stoppered glass vials sat directly on the shelf in liquid form.



The Basic Machine

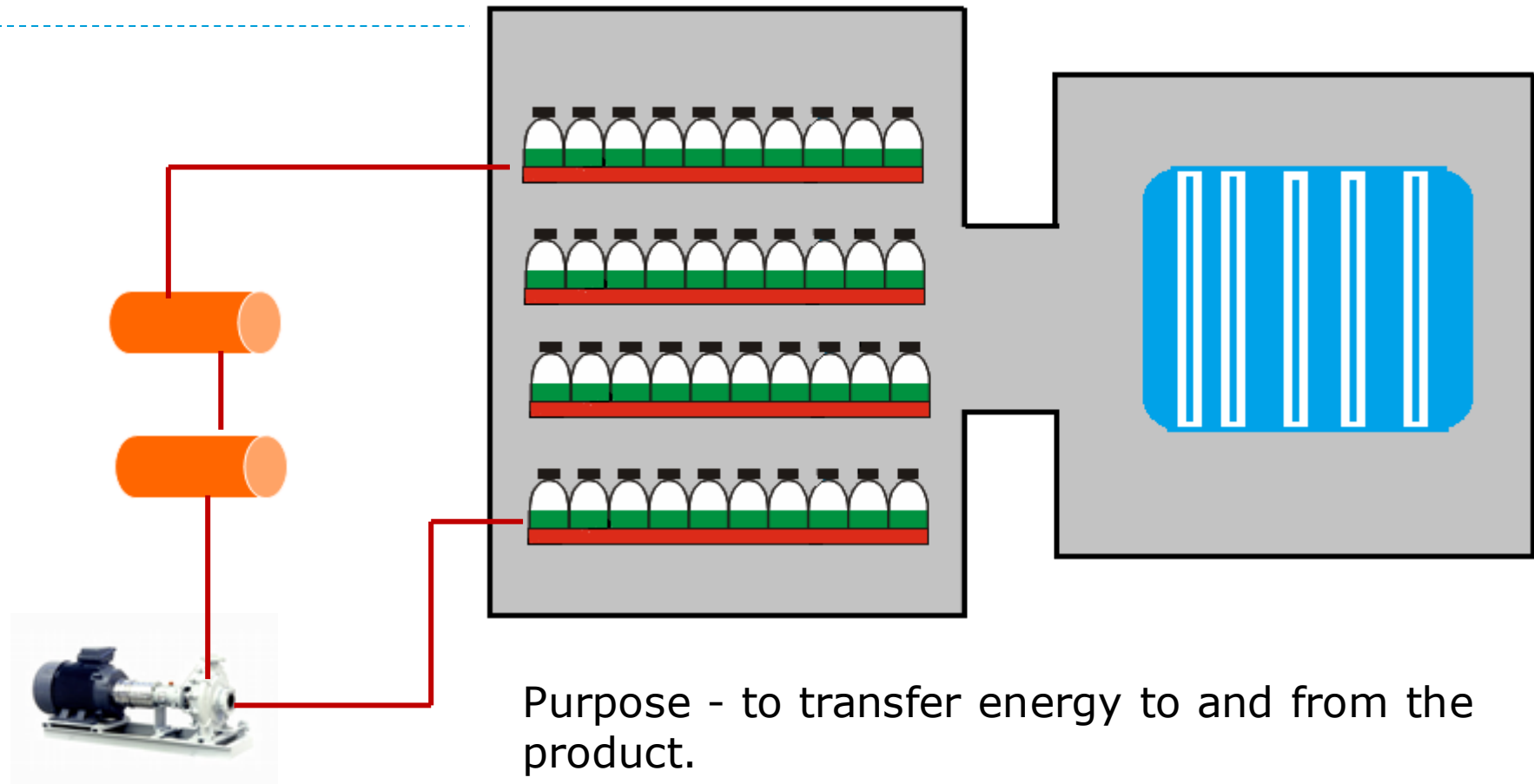


**Process
Condenser**

Acts as a “Cold Trap” to condense the vapour by a process of deposition (vapour to solid) coming from the drying product onto a cold surface within the system. This prevents having to remove the vapour from the system



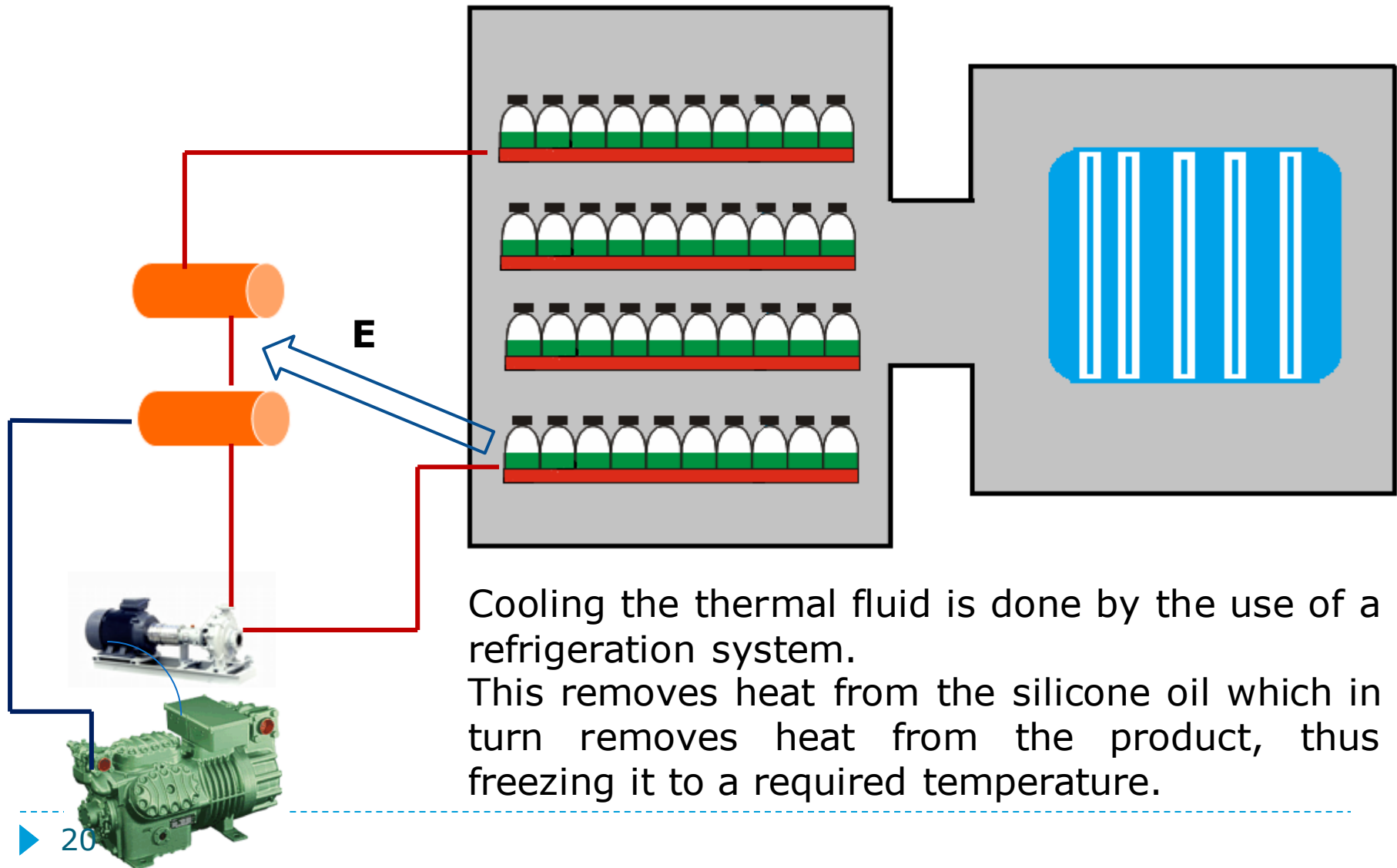
The Systems – Thermal Fluid



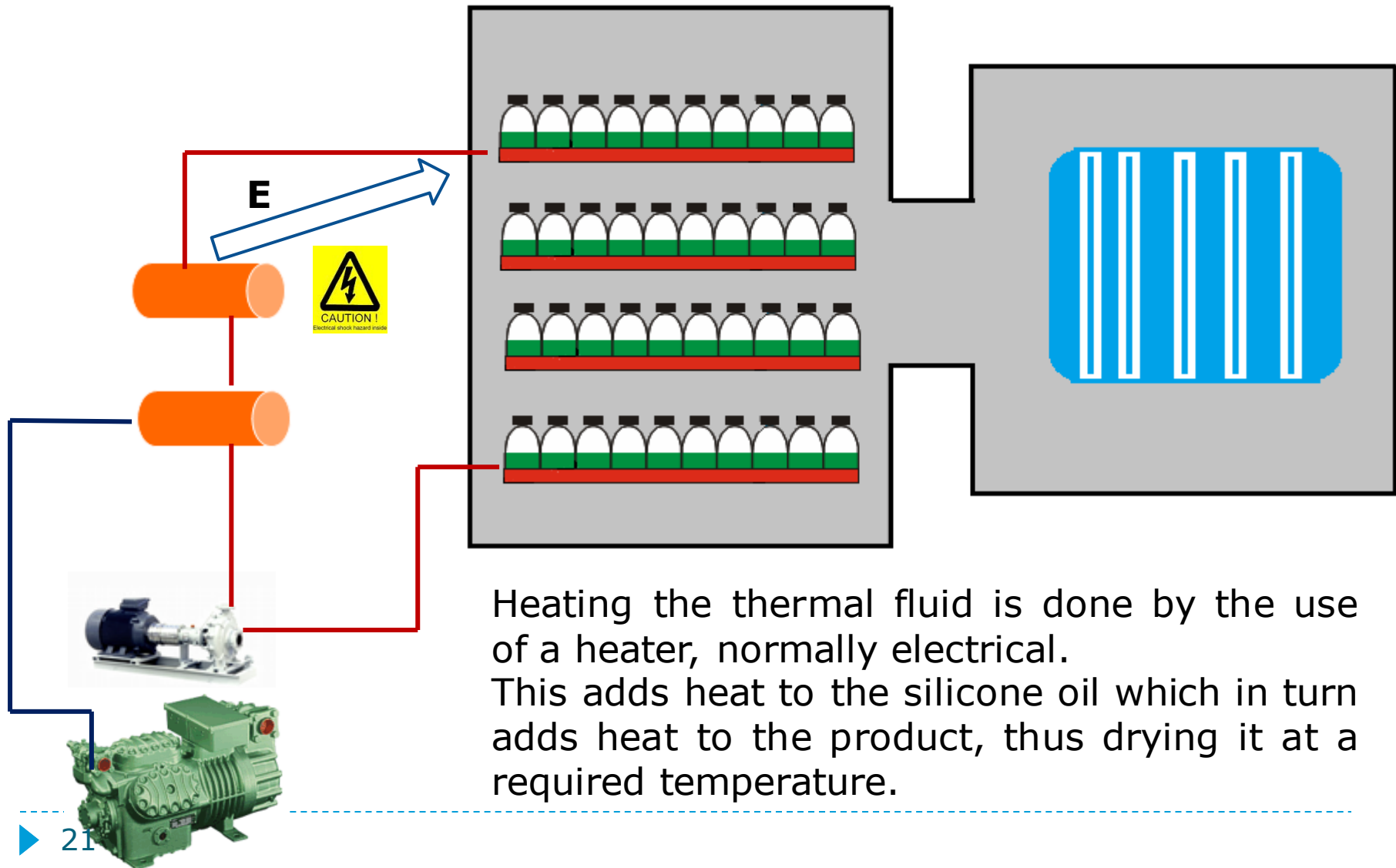
Purpose - to transfer energy to and from the product.

A thermal fluid, typically silicone oil, is pumped around the shelves. The fluid is also pumped through heat exchangers where its temperature is controlled.

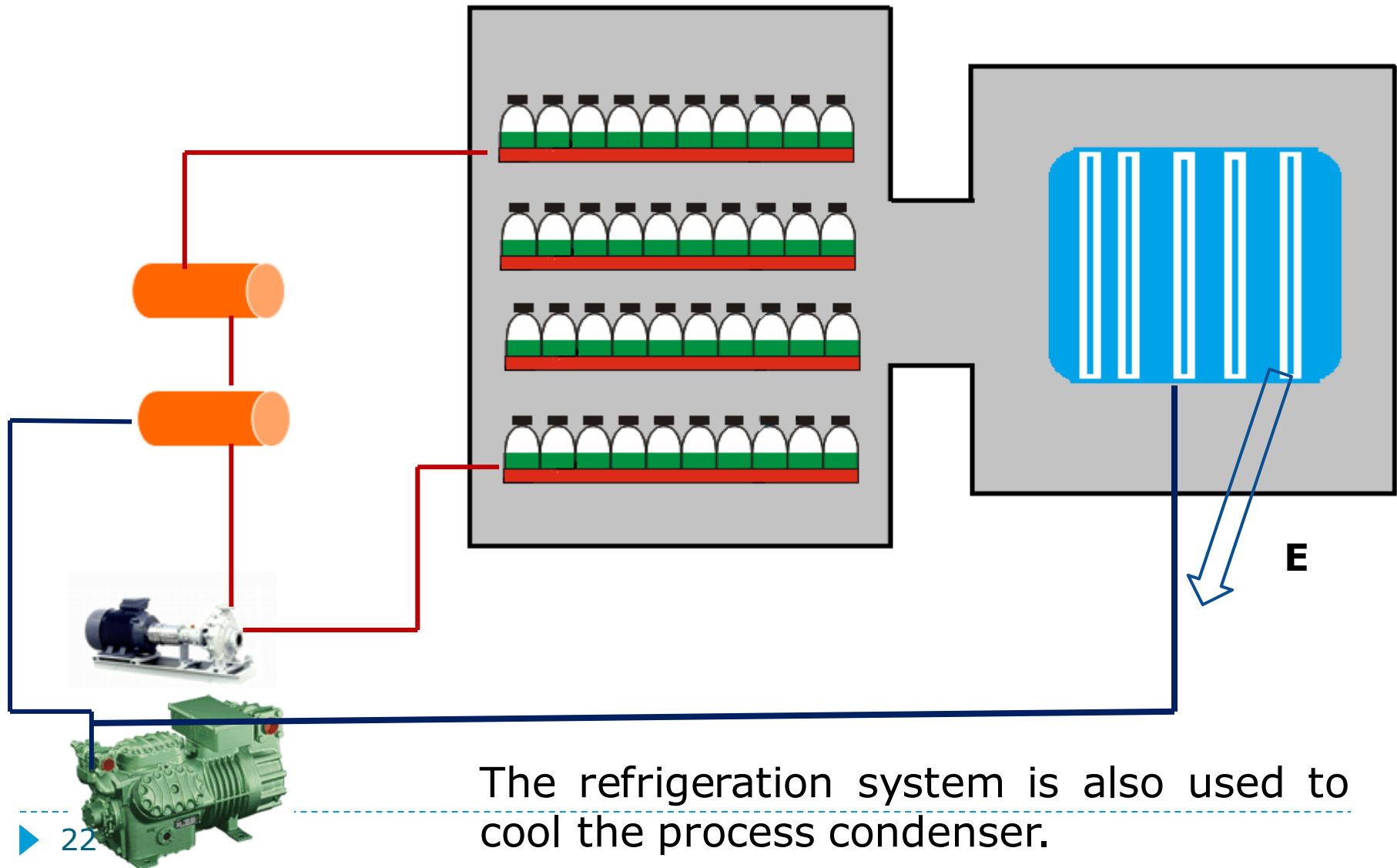
The Systems – Refrigeration



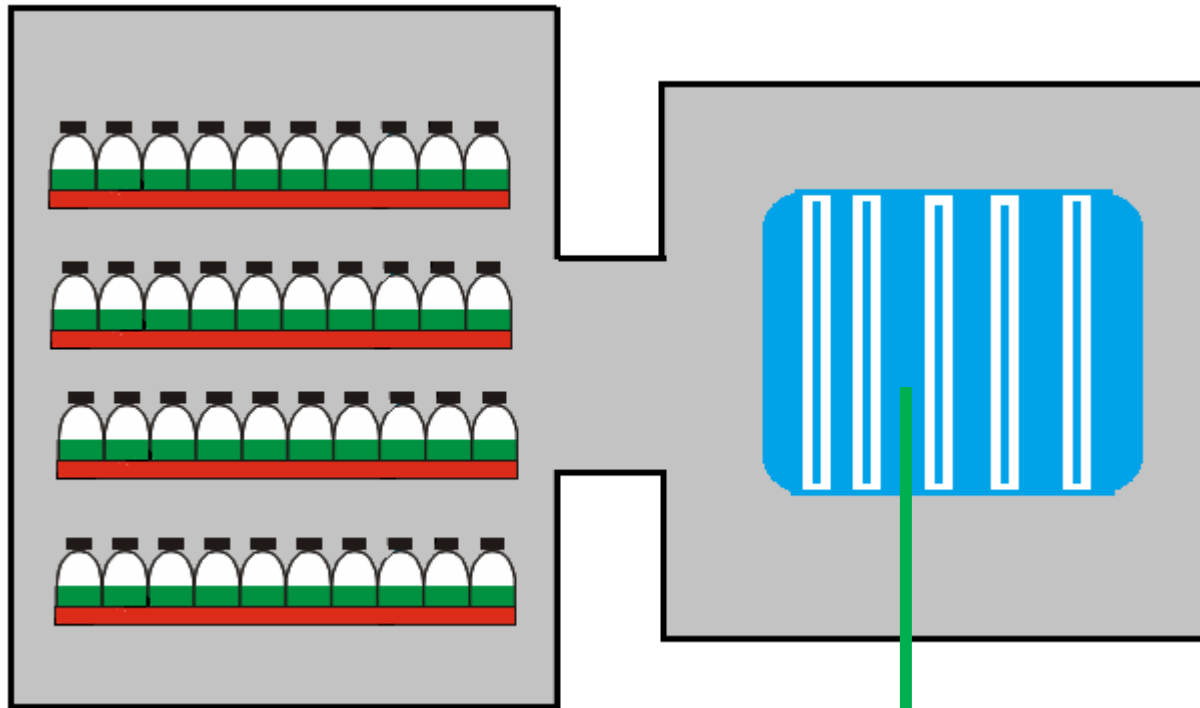
The Systems – Refrigeration



The Systems – Refrigeration



The Systems – Vacuum

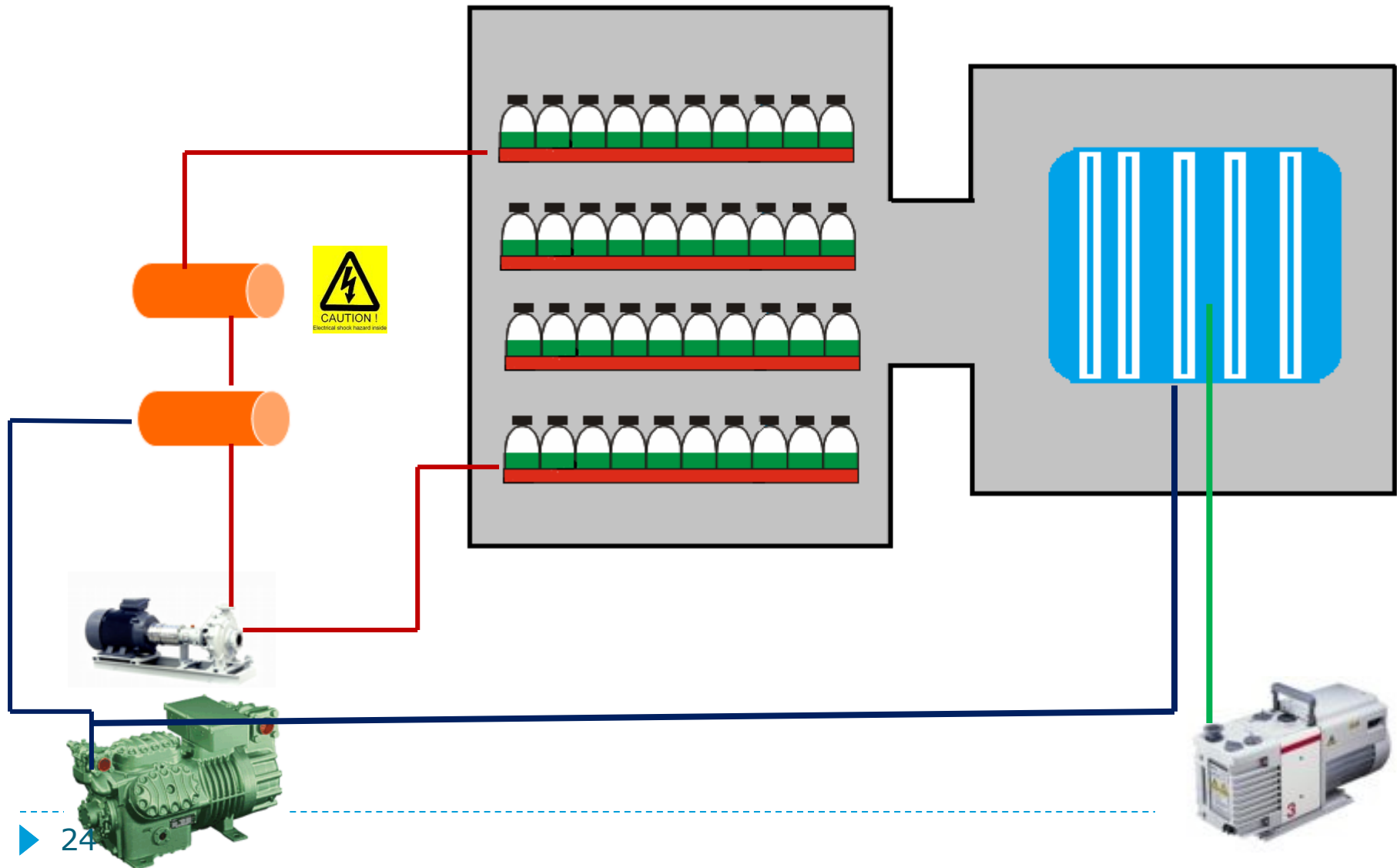


A vacuum pump evacuates the chamber and condenser down to the working pressure (vacuum).

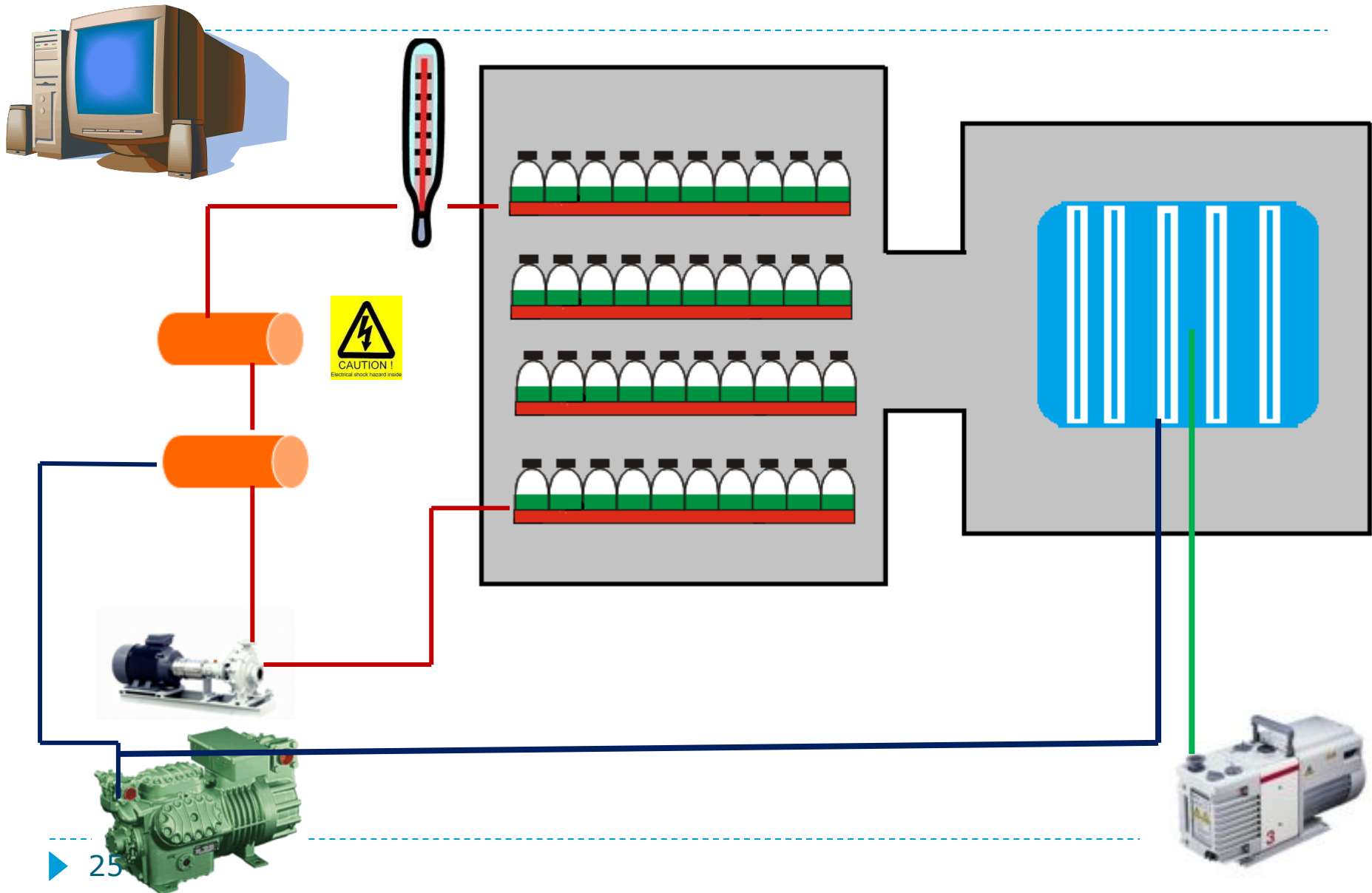
The suction is normally taken from the condenser to protect the pump from moisture



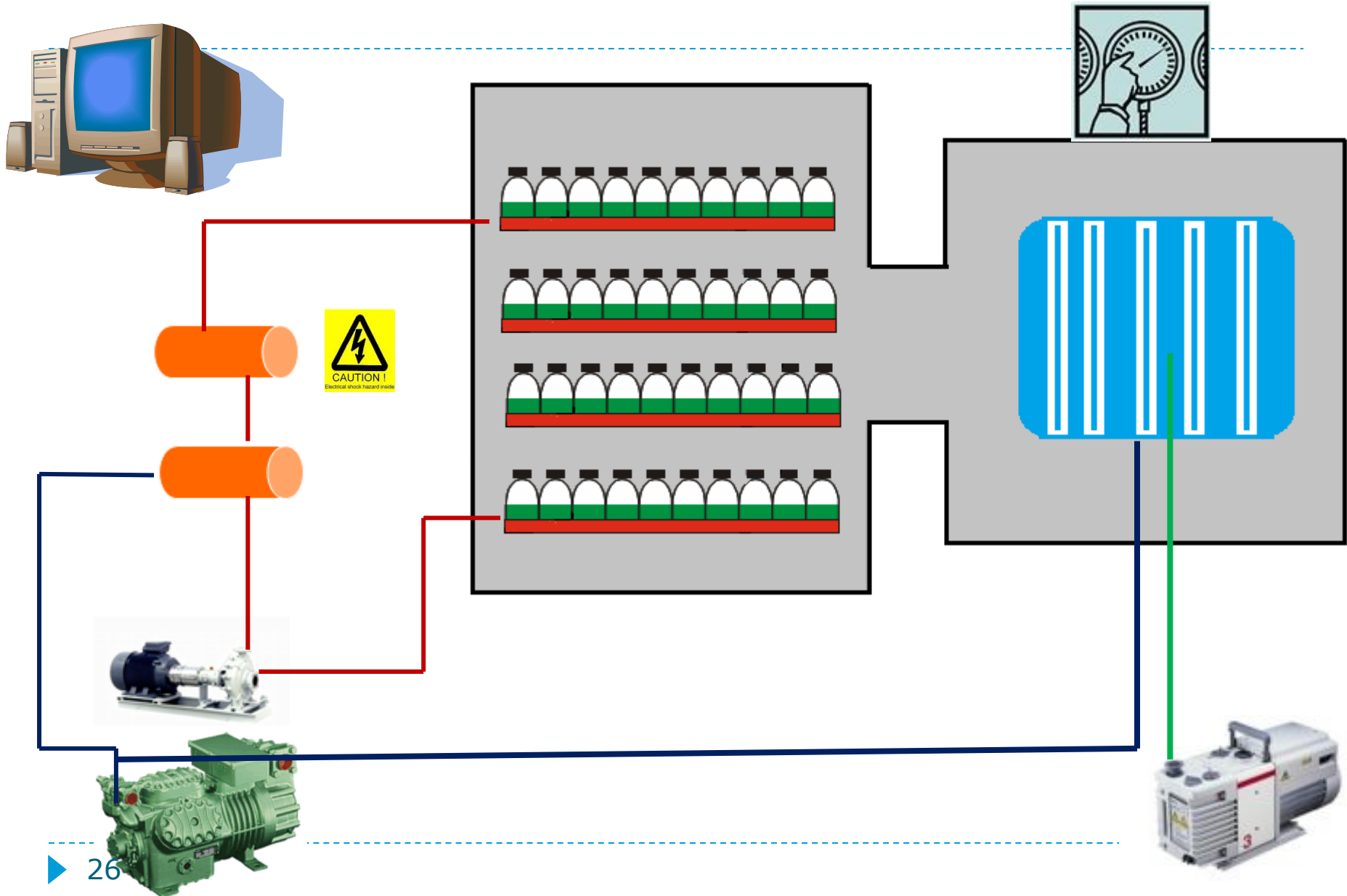
The Systems - Control



Machine Control–Shelf Temperature



Machine Control–Chamber Vacuum



Bench-top Unit

Fully programmable controller (shelf temperature and chamber pressure) for automatic cycles

Up to 3 shelves giving a shelf area of 0.3 m²

Condenser capacity of 6 litres in 24 hours



Other R&D and small production units



Large Production Machine

This photo shows the chamber of a large production freeze dryer.

All the shelves are currently in the “parked” position at the bottom of the chamber.

This aids cleaning and is useful for loading at constant height.

Often, this design is used with automatic loading systems with a pizza type door

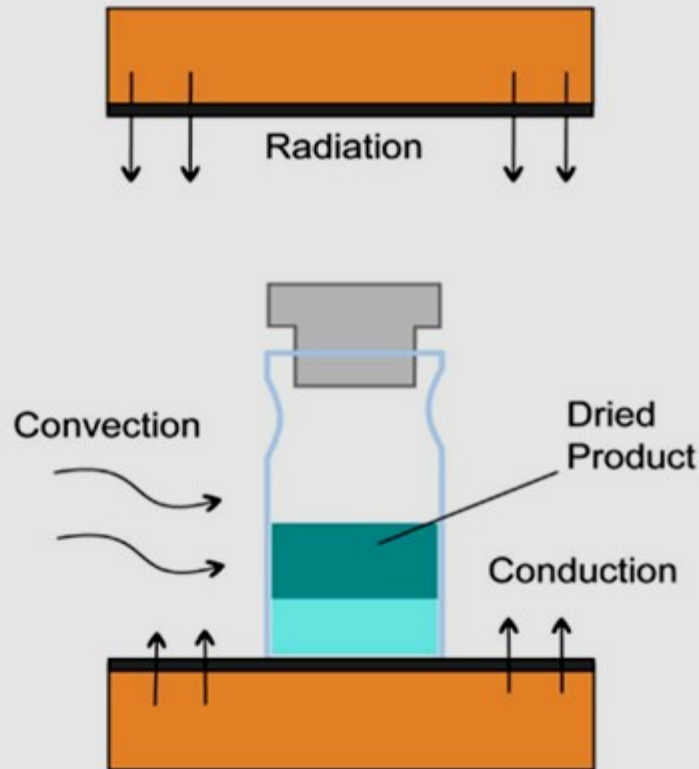


▶ Freezing

- ▶ The temperature of the product is lowered until
 - ▶ First the solution – normally aqueous - freezes
 - ▶ Then the solute freezes
 - ▶ Held for a time to equilibrate temperatures
- ▶ The rate at which this temperature is achieved is important as this can influence
 - ▶ the ice crystal structure which will determine how the product dries
 - ▶ the final porosity of the dried structure

- ▶ Primary Drying is the removal of the frozen free water by the process of sublimation.
- ▶ The temperature and pressure (vacuum) of drying will be determined by a knowledge of the product characteristics.
- ▶ Generally,
 - ▶ Temperature provides the heat energy available to be absorbed by the product in drying
 - ▶ Pressure provides the vehicle for the amount of heat energy transferred to the product

Heat Entry into Product



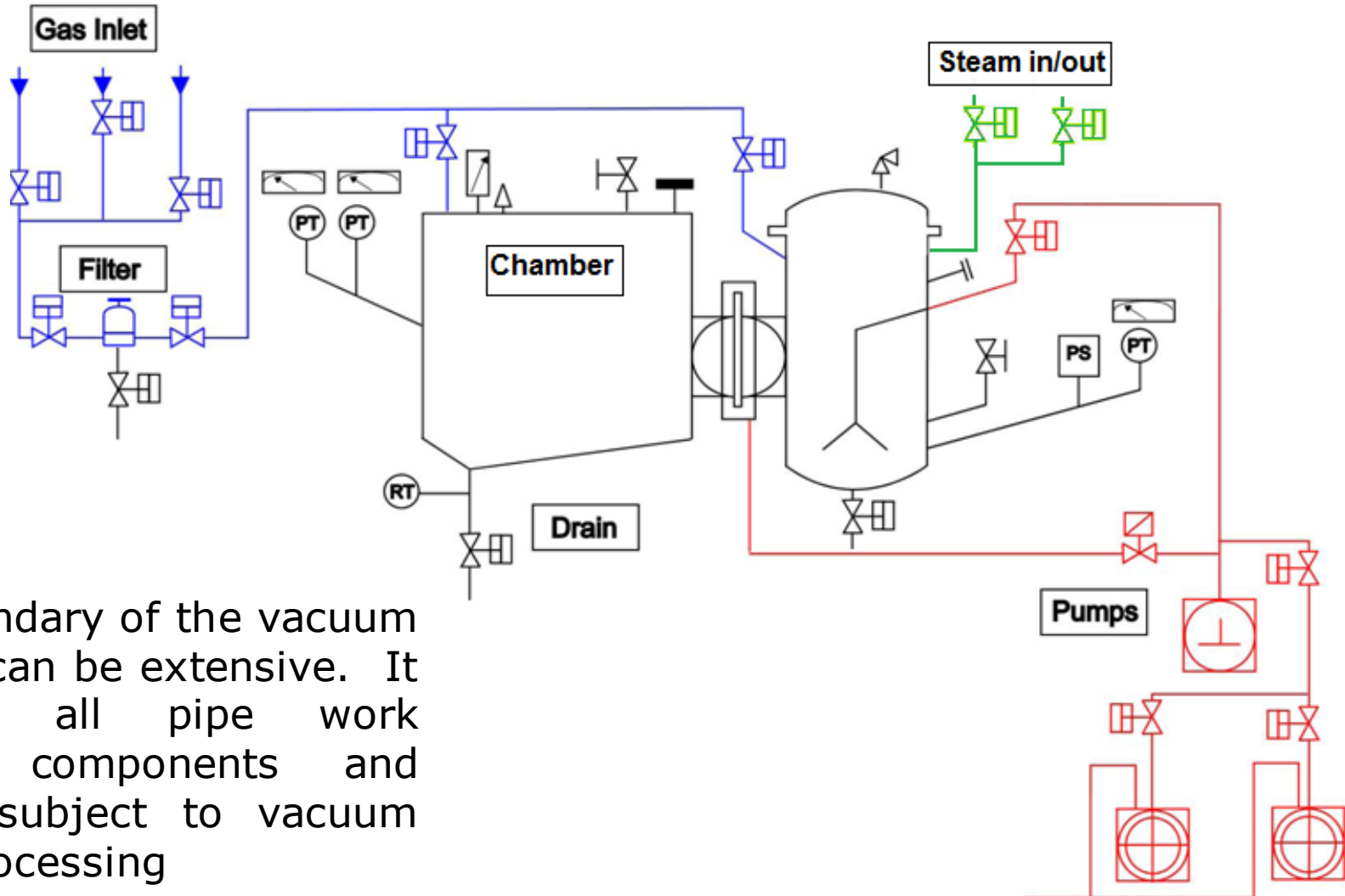
We need to put heat into the system to compensate for the energy loss that accompanies the change in state from solid to vapour...

...otherwise the product will just become colder until the system reaches an equilibrium state

- ▶ Together with the refrigeration system, the vacuum system forms the heart of the freeze dryer
- ▶ Its main purpose is to evacuate the system down to the processing working pressure
- ▶ Its secondary purpose is to then to control at this pressure and remove the non-condensable gases during the drying process
- ▶ **Note:** *It is the process condenser (or "cold trap") that is the driving force for removing vapour from the product, not the vacuum system itself.*

- ▶ The design of the vacuum system can be influenced by
 - ▶ Total volume of system to be evacuated
 - ▶ The size of the vacuum pumps fitted
 - ▶ The type and number of vacuum pumps fitted
- ▶ With modern construction methods, quality of fittings, types of pumps available and accuracy of modern instruments, ultimate chamber pressures of $<5 \mu\text{bar}$ are achievable
- ▶ A modern pharmaceutical freeze-dryer will have a leak rate in the order of $10^{-2} \text{mbar.L.s}^{-1}$, which means a 1000L chamber at $1 \mu\text{bar}$ would take >3 years to leak back to 1 bar!

Vacuum System



The boundary of the vacuum system can be extensive. It includes all pipe work valves, components and fittings subject to vacuum when processing

Vacuum System

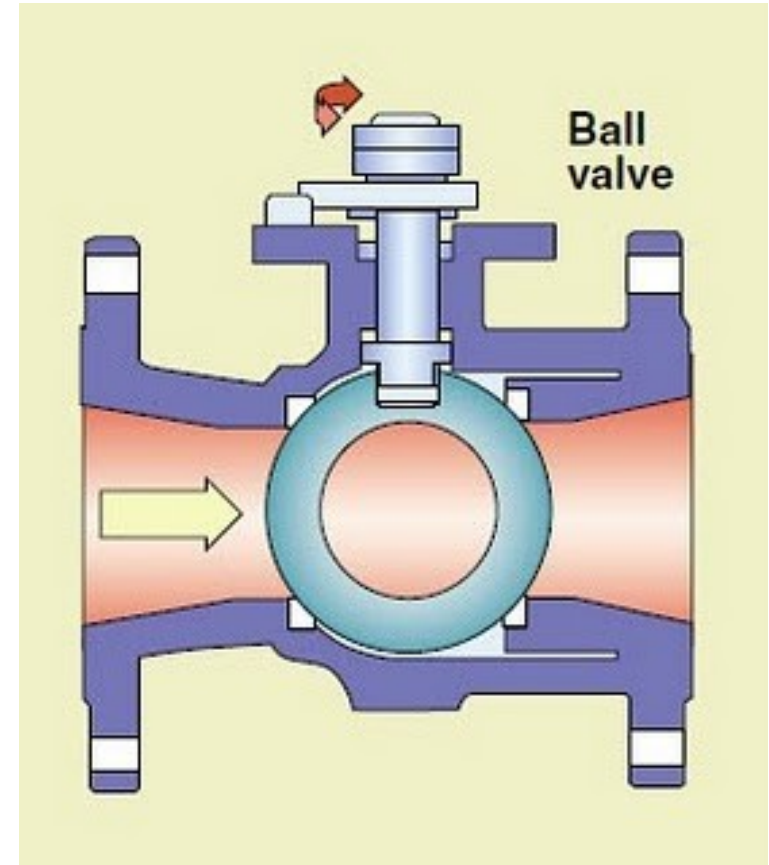
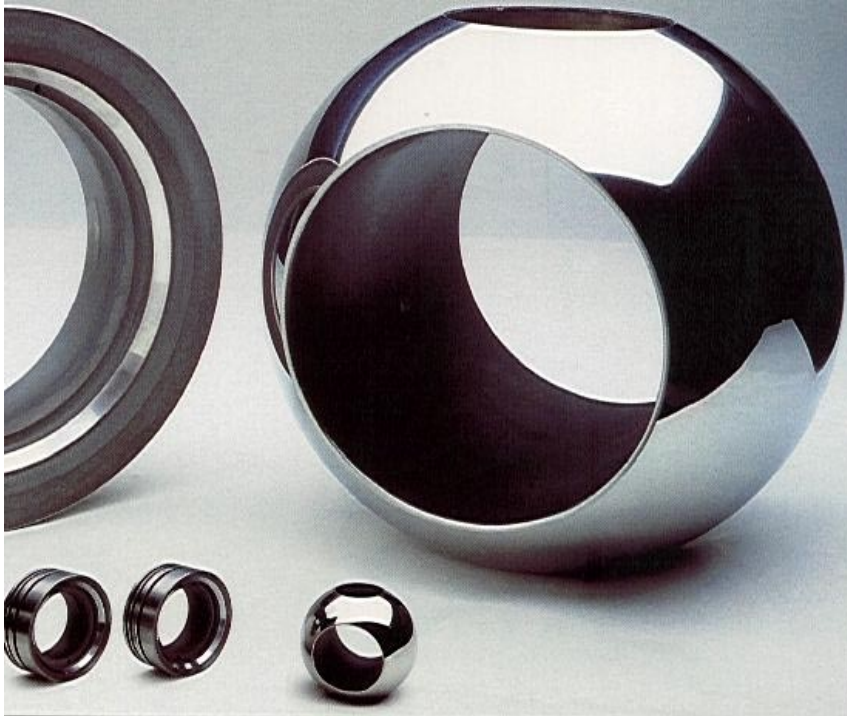
This photograph shows three large rotary vane pumps and a Roots blower forming the vacuum pumping set.

Laboratory sized machines and up to small production machines will typically have only 1 rotary vane pump sized for the volume to be evacuated.



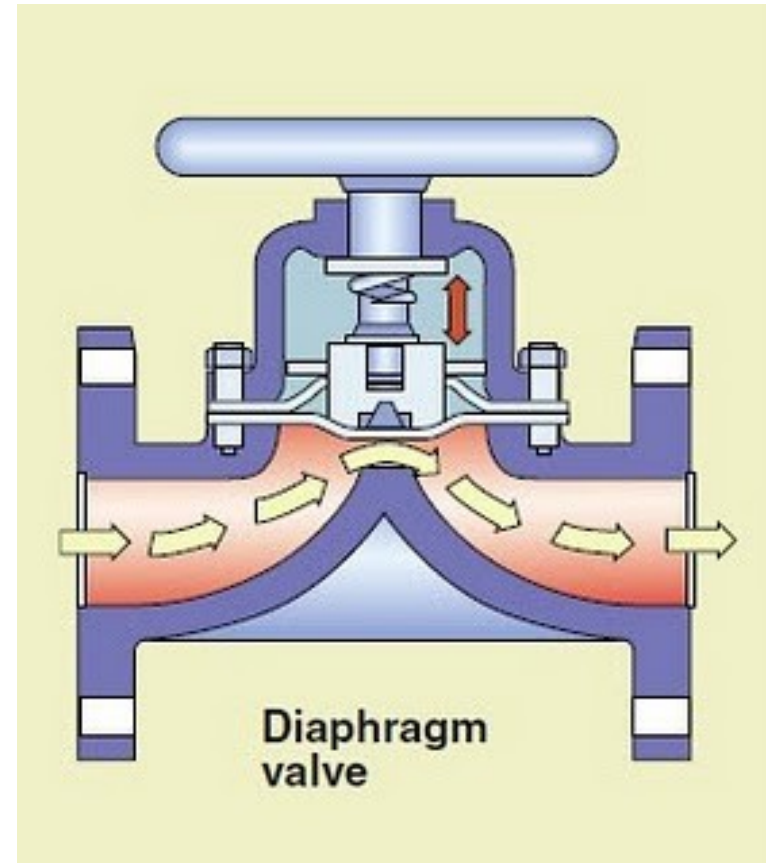
- ▶ All vacuum fittings have a tendency to leak. In maintaining the integrity of the vacuum system we need to consider the type of fittings used.
- ▶ Valves
 - ▶ The type of valves fitted to freeze dryers include
 - ▶ Ball valves
 - ▶ Diaphragm valves
 - ▶ Butterfly valves
 - ▶ Mushroom valves
 - ▶ The modern practice for GMP is to fit diaphragm valves up to the first isolating valve on the system (possible product contact parts).

Vacuum Valves - Ball



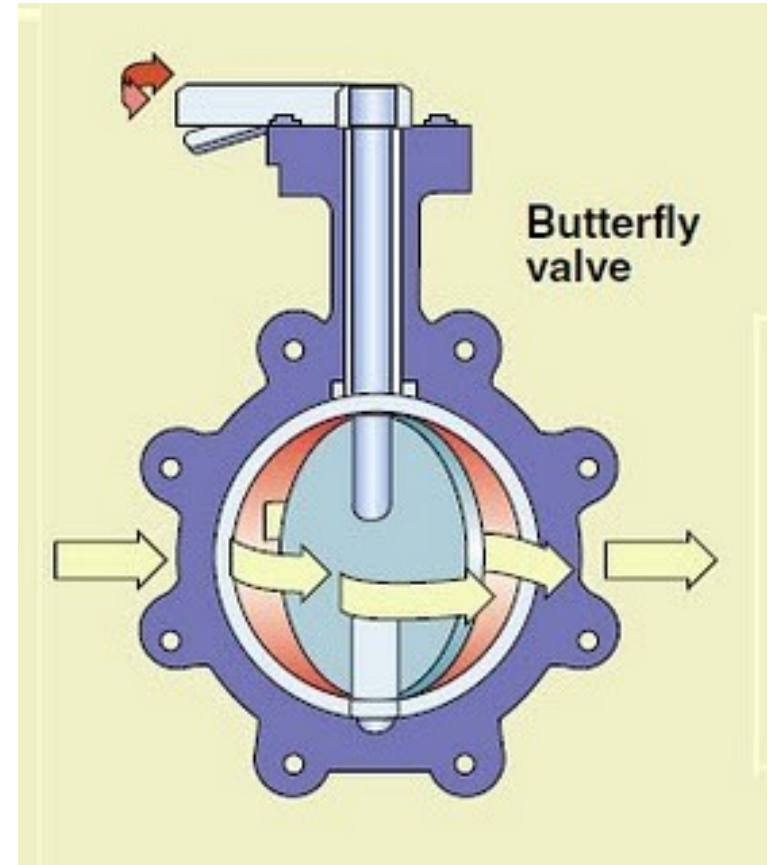
Widely used. Not ideal for sterilisable machines as one face might be deemed non sterile and this may compromise sterility

Vacuum Valves – Diaphragm



There is only 1 face the fluid sees; hence this type of valve is ideal for the isolating valves for sterilisable machines – if they are vacuum tight

Vacuum Valves – Butterfly

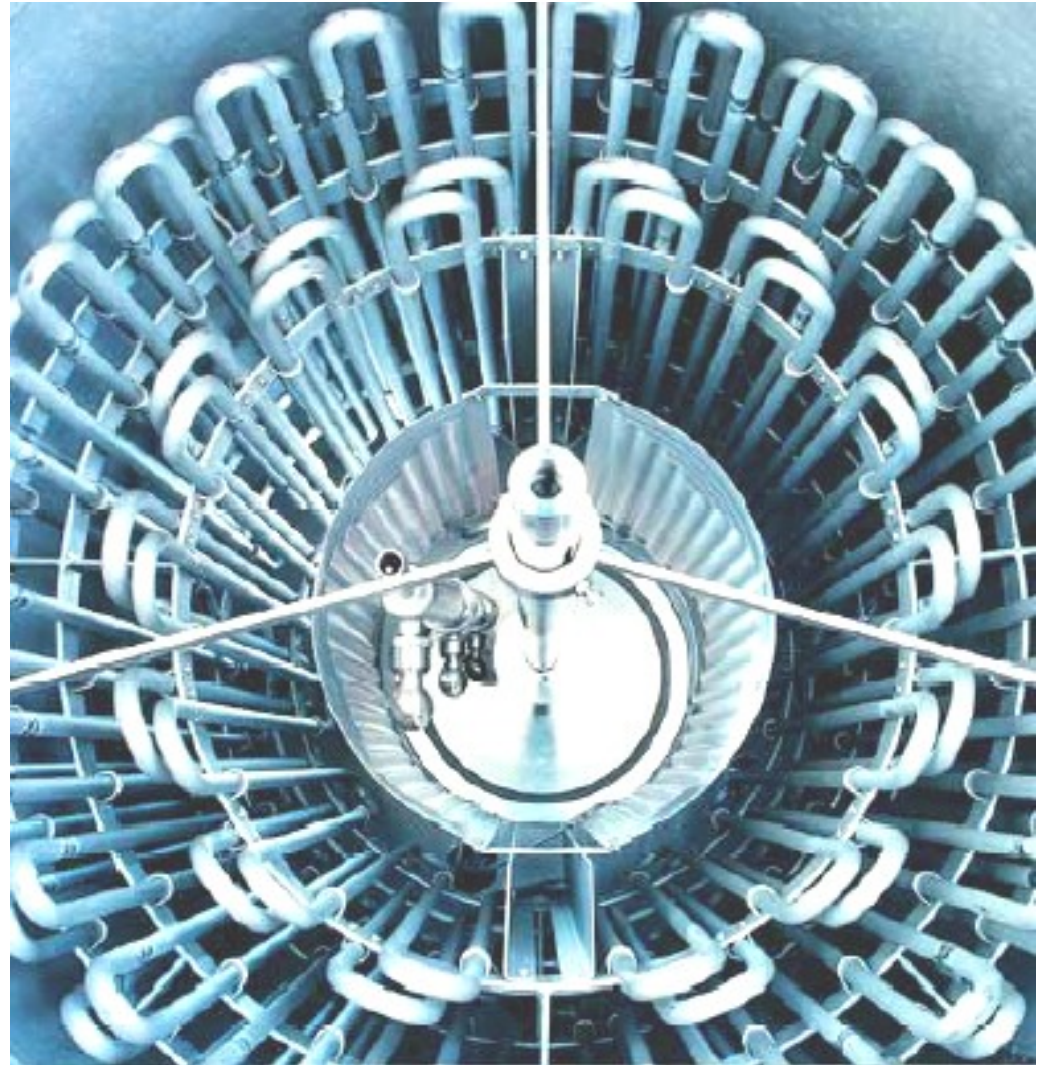


Used on large steam and vacuum systems of 150mm (6") pipes and for large separating valves up to 1 m (40") in diameter (for vacuum)

Vacuum Valves – Mushroom

Not so widely used as the butterfly valve.

Used as isolating valves between the chamber and the process condenser on horizontal and top mounted condensers.



Vacuum Fittings

- (1) Conax – Pass-through
- (2) Sanitary –Tri-clover clamps
- (3) ISO KF -Centring ring & clamp



2



3



1

Vacuum Spectrum

Atmospheric Pressure	1013 mbar
Low Vacuum	Down to 30 mbar
Medium Vacuum	30 to 1×10^{-3} mbar
High Vacuum	1×10^{-3} to 1×10^{-9} mbar
Ultra High Vacuum	1×10^{-9} mbar to 10^{-12} mbar
Extremely High Vacuum	$< 1 \times 10^{-12}$ mbar
Outer Space	1×10^{-6} to $< 3 \times 10^{-17}$ mbar
“CERN” conditions	1×10^{-18} mbar
Intergalactic Space	1×10^{-19} mbar (≈ 1000 atoms / m^3)

- Hydrostatic Gauges
 - Direct pressure measurement of the gas
- Thermal Energy Gauges
 - Measure the changes in the thermal conductivity of the gas pressure being measured
- Electrical Energy Gauges
 - Works by ionising the gas being measured and then counting the number of ions present
- Transport Phenomena Gauges
 - Measure the molecular drag between rotating surfaces and the gas being measured

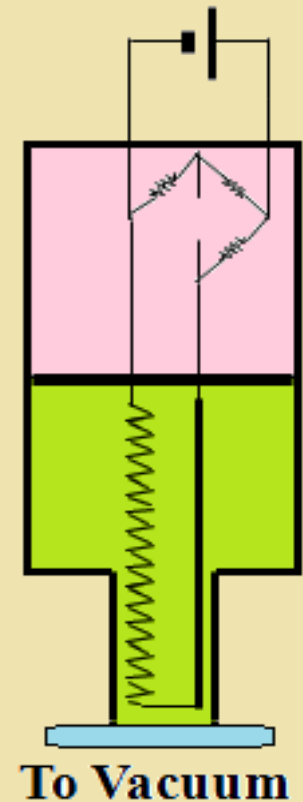
Pirani Gauge

Heated metal filament inside gas.
Loses heat to the gas molecules
surrounding it.

Reduce the number molecules and
the heat loss is reduced causing
temperature to rise.

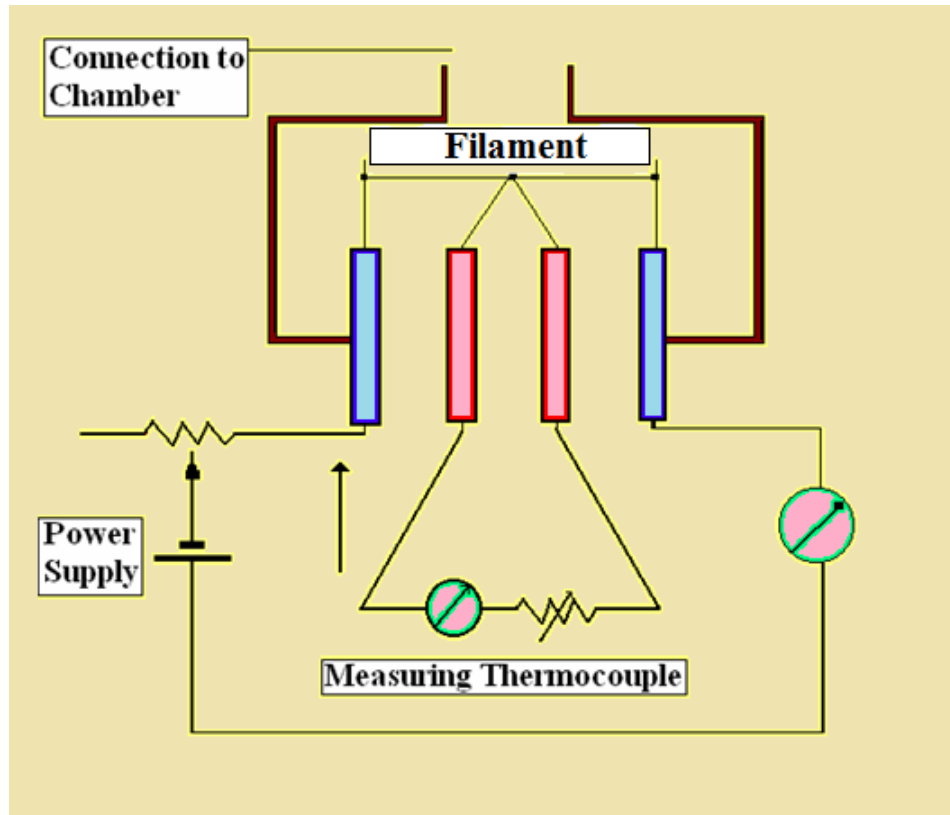
Resistance is a function of
Temperature.

Change in resistance measured



- ▶ Atmospheric pressure to 1×10^{-3} mbar a (6 decade range)
- ▶ Easily Calibrated
- ▶ Stable output
- ▶ 15% accuracy across working range (can be 2% at a fixed point)
- ▶ Different values for different gases
- ▶ Sterilisation will shorten life and stability

Thermocouple Gauge



Works on a similar principle to Pirani.
Thermocouple attached to a heating filament.
Heater supplied at constant current.

Change in pressure causes a change in heat loss.
Filament temperature changes.
Thermocouple measures temperature change.

- ▶ 2 mbar to 1×10^{-3} mbar (3 decade measuring range)
- ▶ Can only be zeroed for calibration
- ▶ Signal output drifts over time
- ▶ 10% accuracy across working range
- ▶ Different values for different gases
- ▶ Can be sterilised

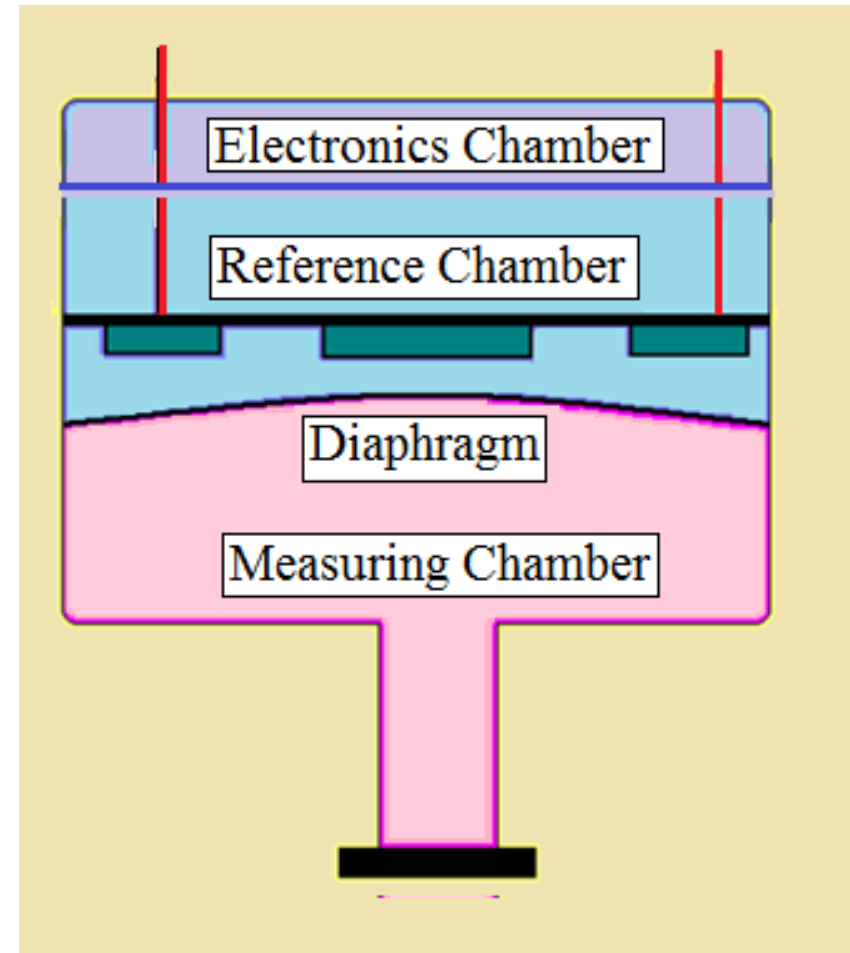
Capacitance Manometer

Works on the principal of direct pressure acting on diaphragm.

Measures change in electrical capacitance as diaphragm moves away from fixed capacitor electrodes.

Change in capacitance is converted into a change in output voltage.

The thickness of diaphragm determines measuring range



Capacitance Manometers

Non Sterilisable
one is on the left.

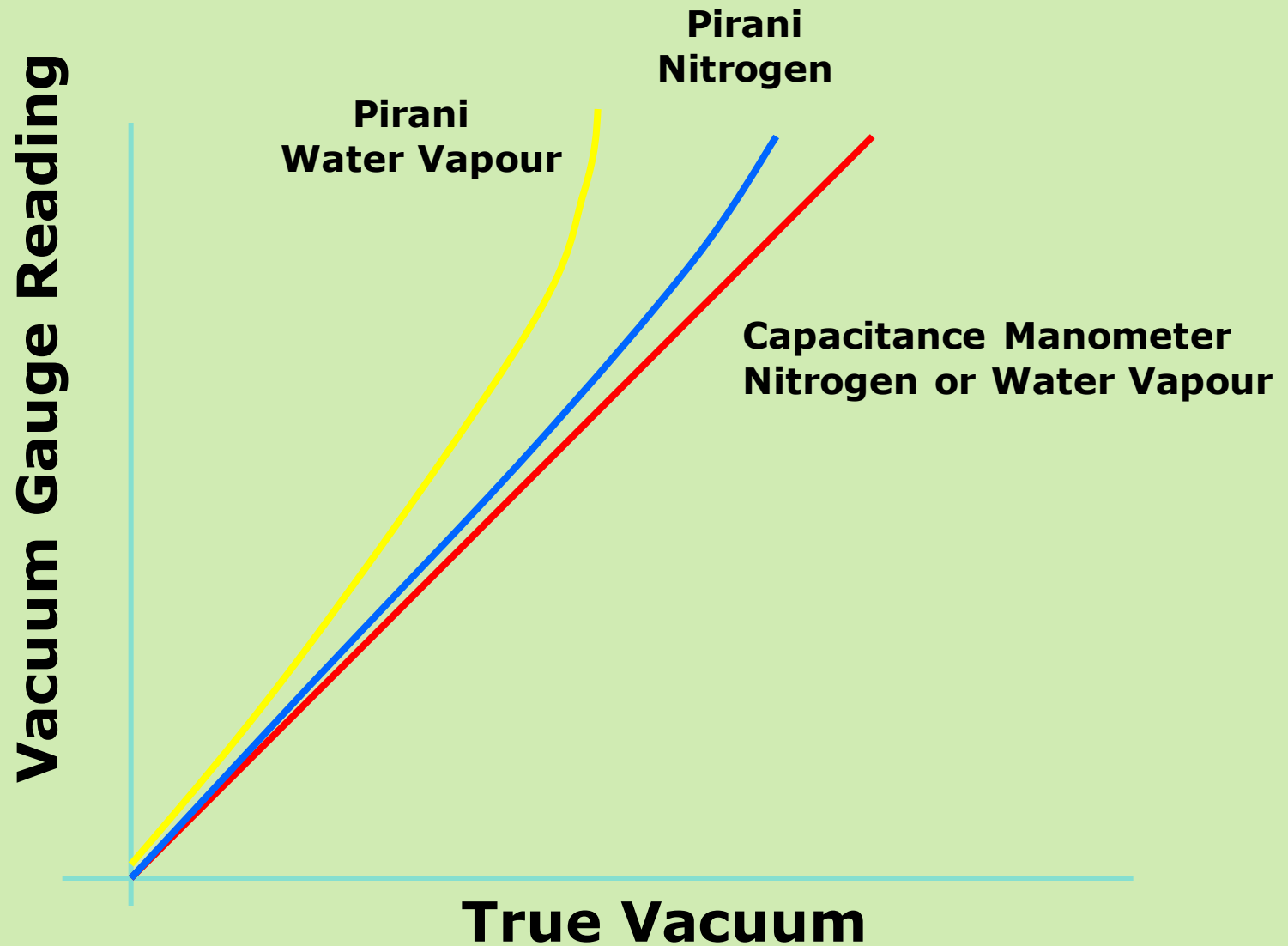
The larger one
on the right
has a heating
jacket.

This permits
stability with
over pressure
from steam.



- ▶ 2 mbar to 1×10^{-4} mbar (generally 4 decades measuring range)
- ▶ Perfect linear output
- ▶ Very accurate (can be $< 0.15\%$)
- ▶ Some types can be sterilised
- ▶ Hydrostatic – independent of gas present
- ▶ Immune to contamination
- ▶ Instrument of choice for Ex(plosion)-Proof machines (when processing organic solvents)

Pirani v Capacitance



A Range of Vacuum Gauges

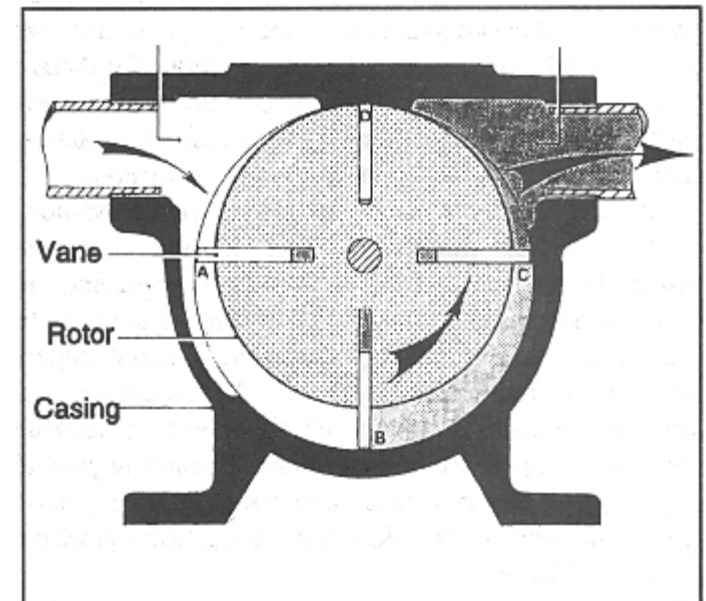


- Main Types
 - Rotary Vane
 - Roots Blower
 - Dry Pump
 - Water Ring Pump
- Other Types
 - Scroll
 - Turbo Molecular
 - Molecular Drag
 - Diffusion
 - Cryo

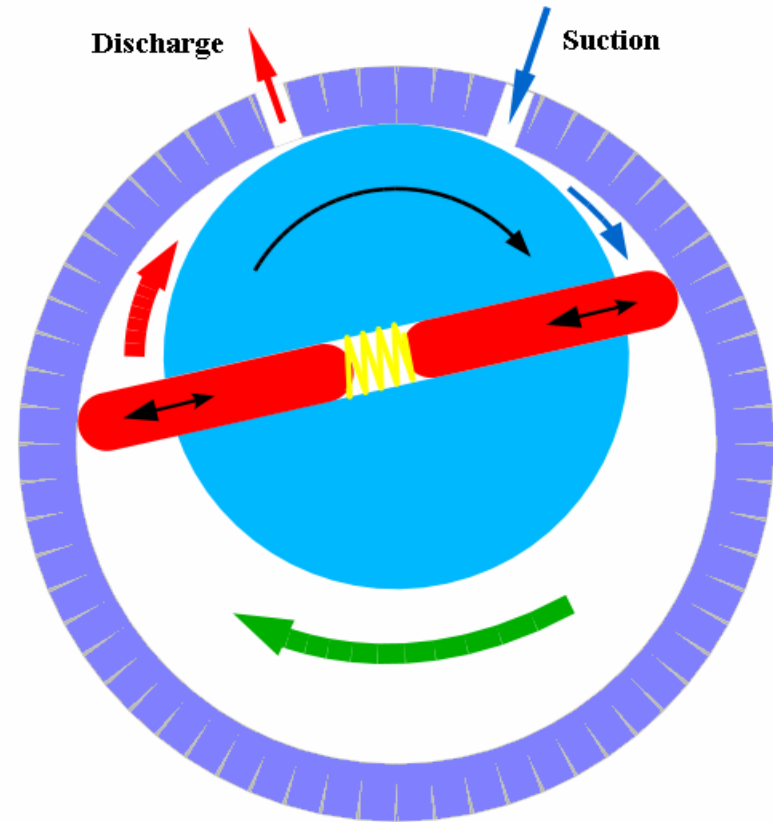
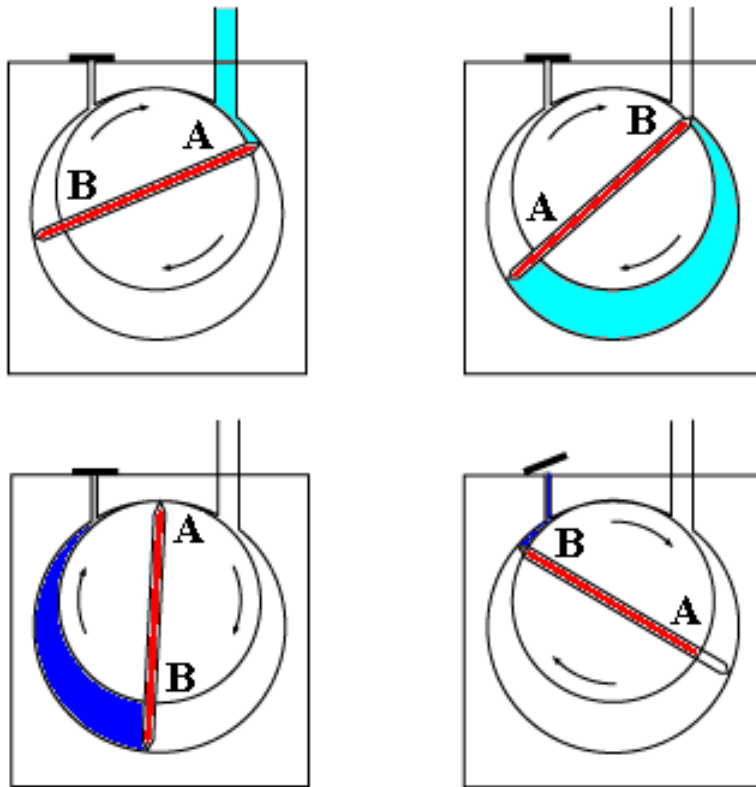


- ▶ Rotary Vane
 - ▶ Can be single or double stage
 - ▶ Pressures down to 1×10^{-4} mbar
 - ▶ Pumping speeds from 0.75 up to 275 m³/hr
 - ▶ Requires high grade oil
 - ▶ Some are water cooled

► Rotary Vane

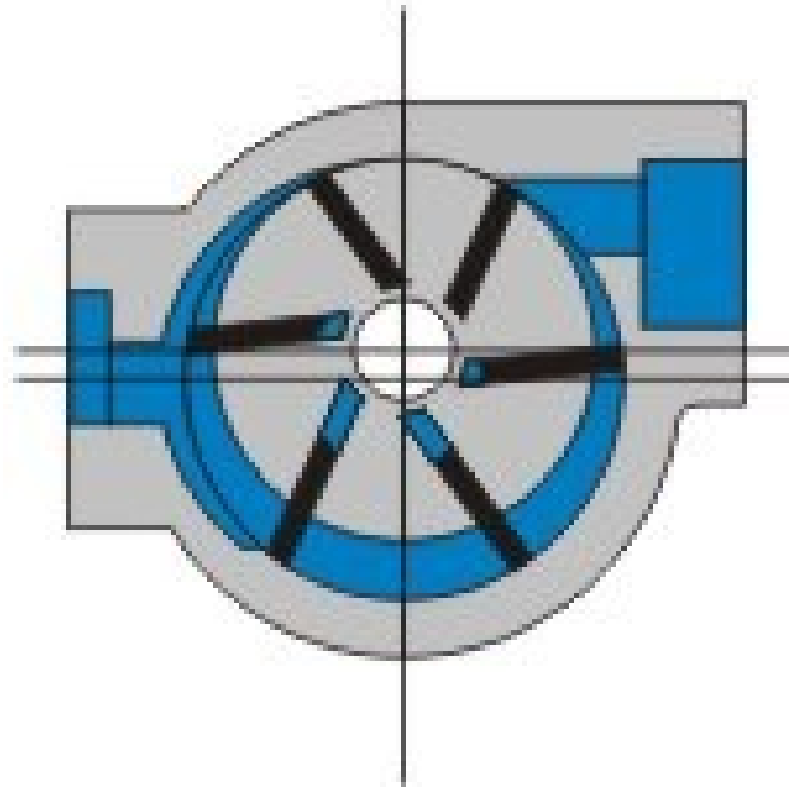
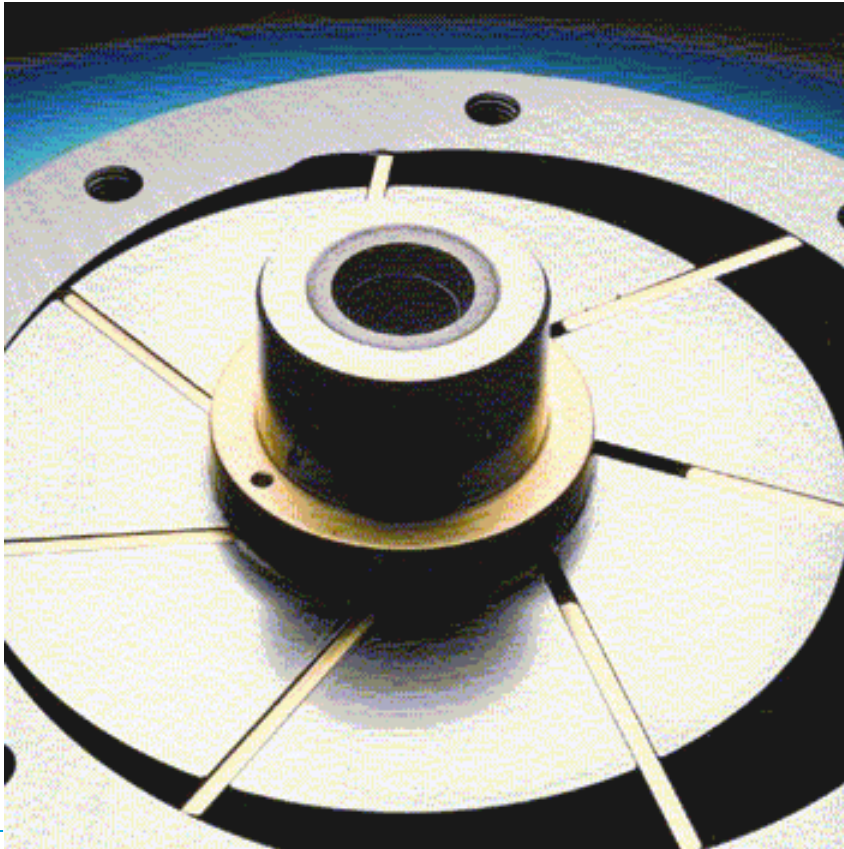


► Rotary Vane



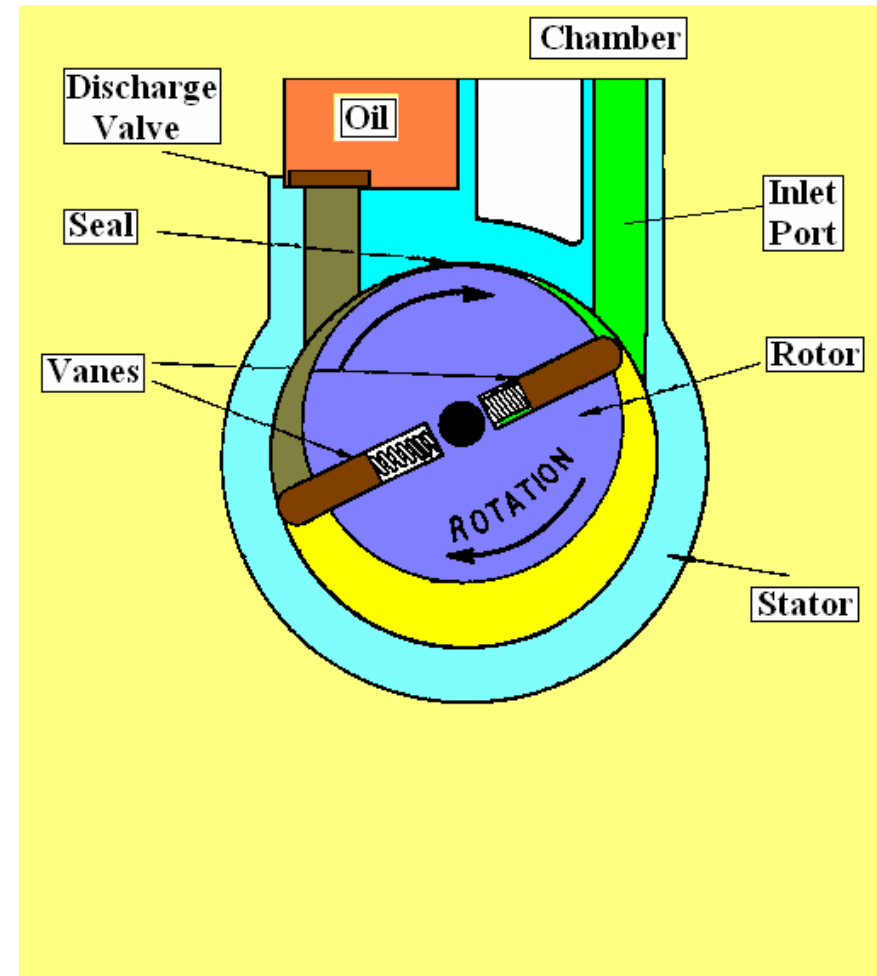
Vacuum Pumps

▶ Rotary Vane



Vacuum Pumps

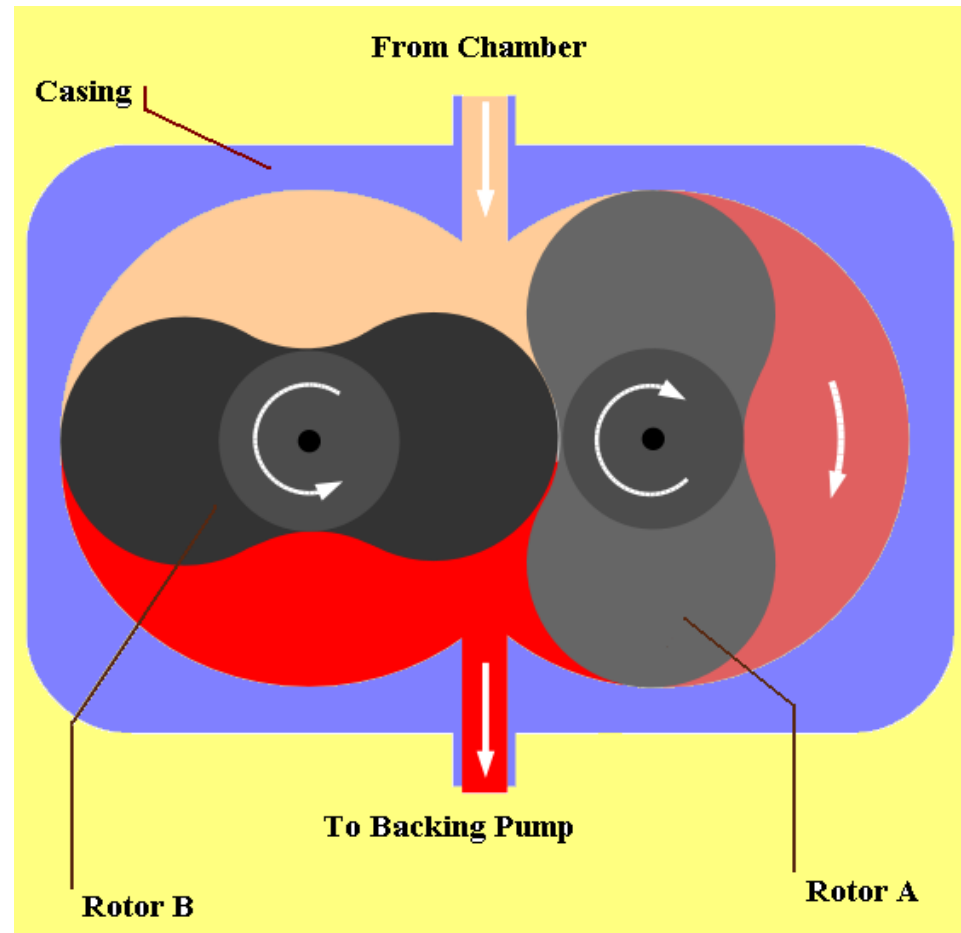
- ▶ Rotary Vane
- ▶ Oil Back-streaming



- ▶ Occurs during free molecular flow conditions. This is where the Free Mean Path of molecules is larger than the chamber size.
- ▶ Can be mitigated by using:-
 - ▶ High grade oils
 - ▶ Cooling the pump/oil
 - ▶ Limiting minimum operating pressure
 - ▶ Using a trapping device or barrier
 - ▶ Using dry pumps

-
- ▶ **Roots Blower**
 - ▶ Inertia type pump
 - ▶ High pumping speeds $> 2000 \text{ m}^3/\text{hr}$
 - ▶ Requires a backing pump

► Roots Blower



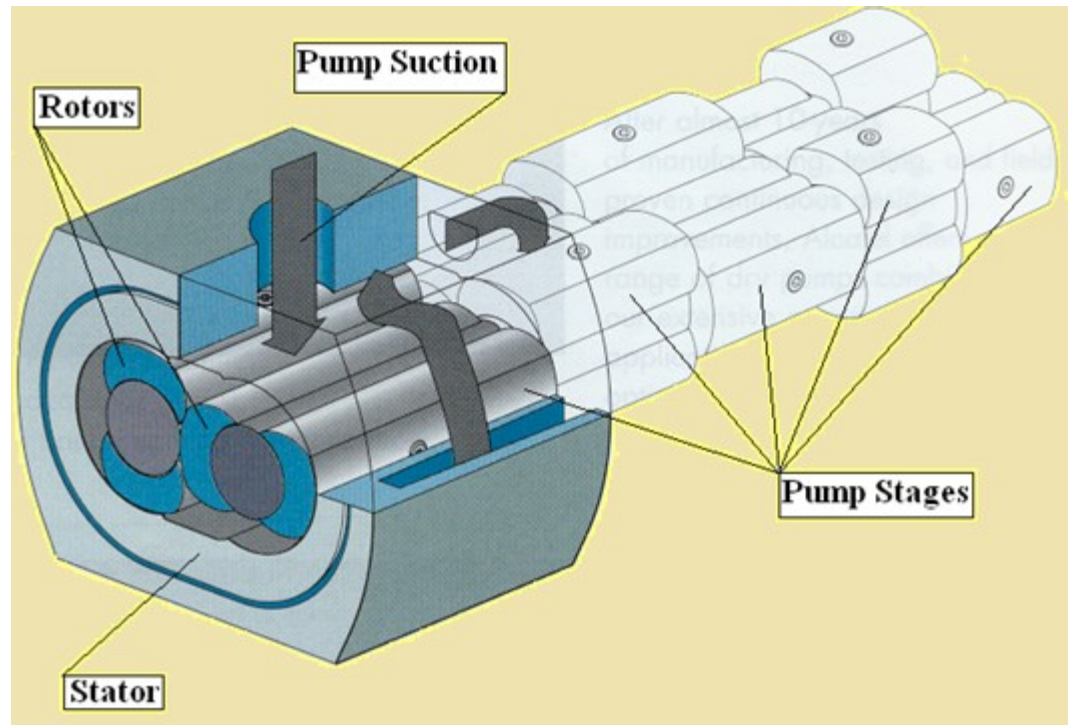
Roots and Rotary Vane



-
- ▶ Removes Oil from the pumping mechanism thus removing a source of contamination
 - ▶ Some types are able to handle moisture
 - ▶ Allows a vertical mounting geometry
 - ▶ Can be more expensive
 - ▶ Increase in noise for some designs – may require acoustic housing

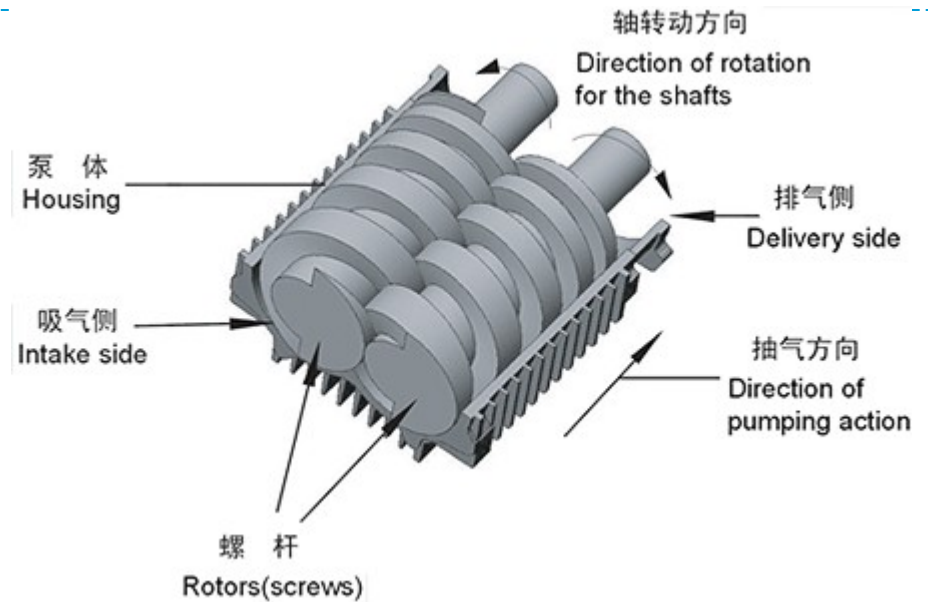
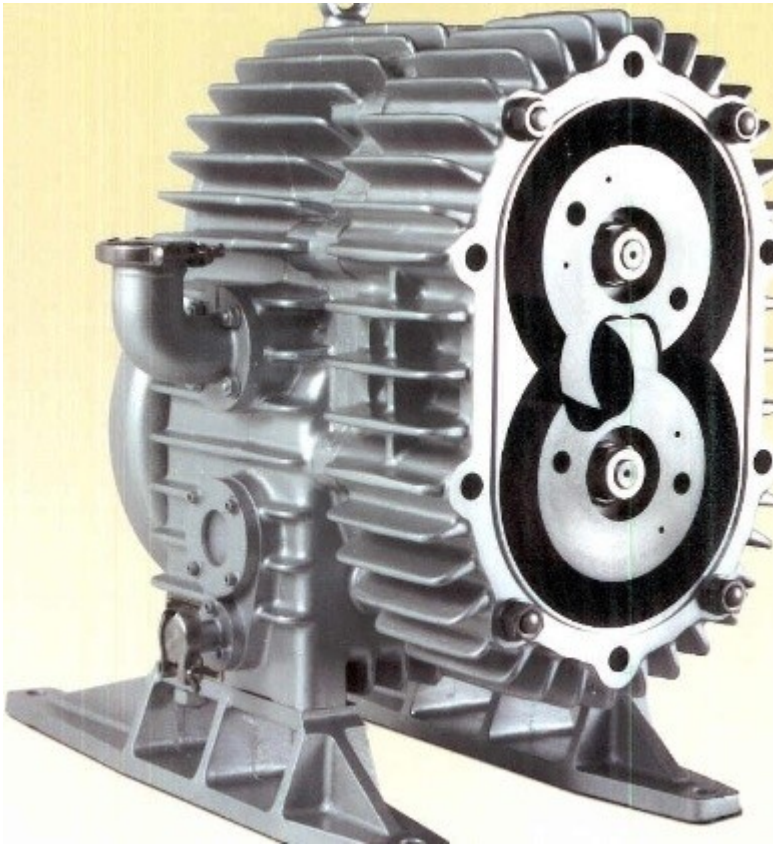
► Dry Pumps

This unit is using 5 stages to achieve low pressure required



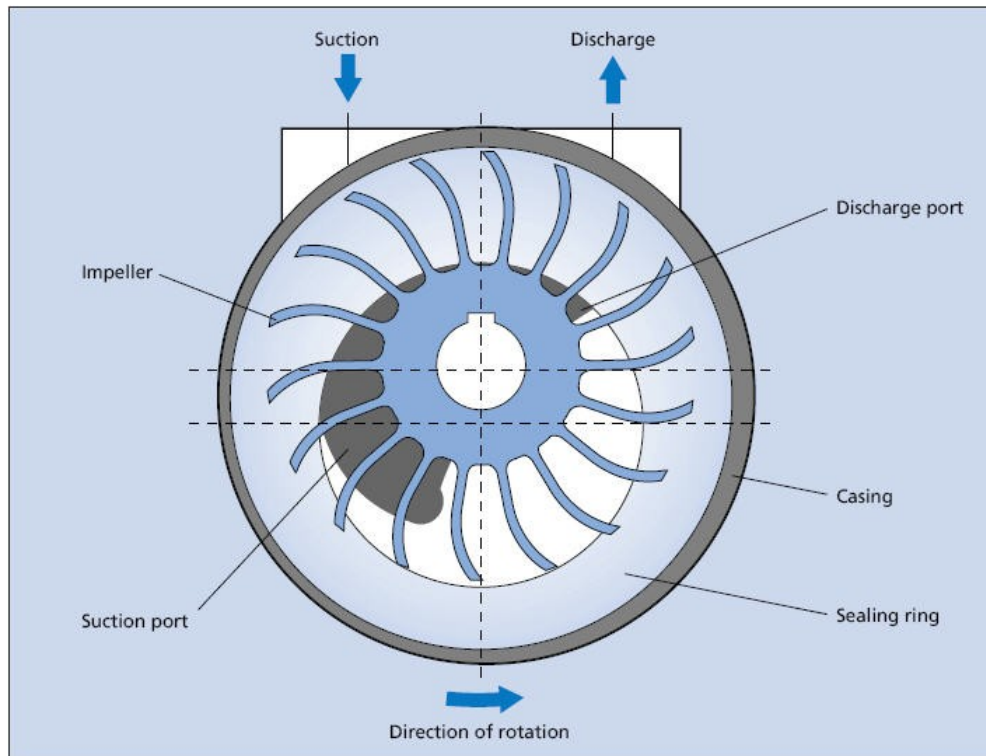
Vacuum Pumps

► Dry Pumps



Two types of dry pump

The helical Screw Pump
The Claw Pump



- ▶ **Liquid Ring (or Water Ring)**
 - ▶ Best suited for pumping vapour
 - ▶ Used for drying chamber after steam sterilisation
 - ▶ Pressures down to 20 – 30 mbar
 - ▶ Reliable and long lasting
 - ▶ Cavitation can cause erosion

▶ Freezing

- ▶ Freezes both the solvent and the solute
- ▶ Immobilises the material
- ▶ Defines the structure ready for drying

▶ Primary Drying

- ▶ The removal of the frozen primary moisture by a process of sublimation – the conversion of ice to vapour without passing through the liquid phase

▶ Secondary Drying

- ▶ The process of further drying by desorption

***Is pressure
important in
freezing?***

***Historically, the answer
has been "No". But....***

Uncontrolled vs. Controlled Nucleation:

Praxair® CONTROLyo™

- ▶ This uses “Pressurization-Depressurization” to encourage simultaneous nucleation of ice
 - ▶ The chamber isolation valve (CIV) is closed
 - ▶ The product chamber is pressurised to around 1.5bar, while the vacuum pump continues to evacuate the condenser
 - ▶ The CIV is opened very rapidly to depressurise the chamber, causing top-down nucleation



Uncontrolled nucleation: *Vials after 20 minutes at sub-zero*

September 2012

Freeze dryer manufacturer [SP Scientific](#) has broadcast a video that demonstrates how Praxair's ControlLyo™ Nucleation On-Demand Technology can be used to control the nucleation of a product during freezing, such that the entire product nucleates at the same time and in the same way – providing pharmaceutical and biotechnology companies with precise control over the freeze-drying process for drug developmental efforts. This technology is available on SP Scientific's [LyoStar 3 R&D Freeze Dryer](#).



Uncontrolled nucleation: *Vials after 43 minutes at sub-zero*

September 2012

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Tags: [controlled nucleation](#), [controllyo](#), [freeze dryer](#), [praxair](#), [process control](#), [process development](#), [SP Scientific](#), [video](#)

Controlled nucleation (vials at 0'28''):

Vials all display simultaneous nucleation

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Controlled nucleation (***still*** at 0'28''): *Vials all display simultaneous nucleation*

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- ▶ Freezing

- ▶ ***Is pressure important in sublimation?***

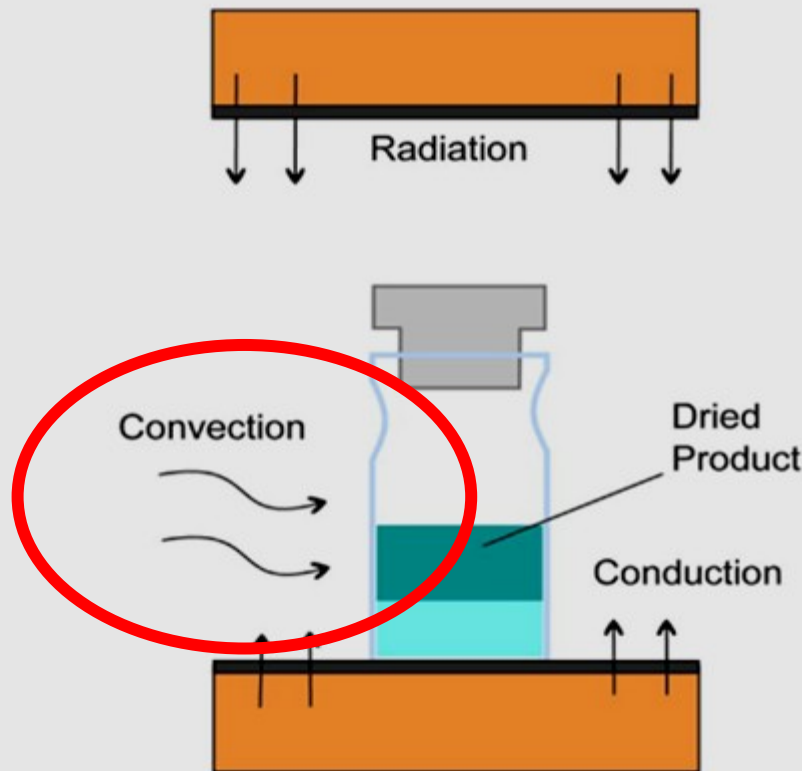
- ▶ Primary Drying

- ▶ The removal of the frozen free moisture by a process of sublimation – the conversion of ice to vapour without passing through the liquid phase

- ▶ Secondary Drying

- ▶ ***Here, the answer is almost always a resounding "Yes".***

Heat Entry into Product



We need to put heat into the system to compensate for the energy loss that accompanies the change in state from solid to vapour...

...otherwise the product will just freeze until the system reaches an equilibrium state

CONVECTION relies on the gas and vapour molecules that are present in the chamber!

Primary Drying (Sublimation):

Convection, conduction and radiation

- ▶ The relative significance of convection, conduction and radiation will vary according to:
 - ▶ Temperature and pressure being employed at any point in time (*e.g.* low pressure would lead to less convection, so conduction and radiation “become more important”)
 - ▶ Thickness (depth) of product in container
 - ▶ Thickness of ice remaining in product (insulating effect with respect to direct conduction)
 - ▶ Heat transfer characteristics of product container (*e.g.* glass vial, stainless steel tray)
 - ▶ Design of the freeze-dryer (radiative effects; location of condenser; baffles; jacketed vessel?)
 - ▶ “Edge effects” of shelf (perimeter *vs.* area)

What is important for a product undergoing sublimation?

- ▶ In order to **drive** sublimation, the partial pressure of vapour in the chamber must be below the vapour pressure of ice (VP_{ice}) at the “drying front” in the product
- ▶ BUT if the chamber pressure is far below this pressure, then convection will become less effective and the process will slow down...
- ▶ HOWEVER, if the pressure is too close to VP_{ice} , there may be too much heat transferred into the product, meaning it can collapse or melt, and/or the dryer may not cope with vapour load (a phenomenon called “choked flow”)
- ▶ Therefore, we need to strike a balance in order to have a robust yet efficient process

A commonly encountered issue on Scale-up / Technology transfer...

- ▶ Use of Pirani gauge on lab machine and CM on industrial machine, meaning that for a given pressure setpoint, there is a disparity in the absolute pressures experienced by the product in the chambers, leading to:

Less effective convection on scale-up



Slower drying rate

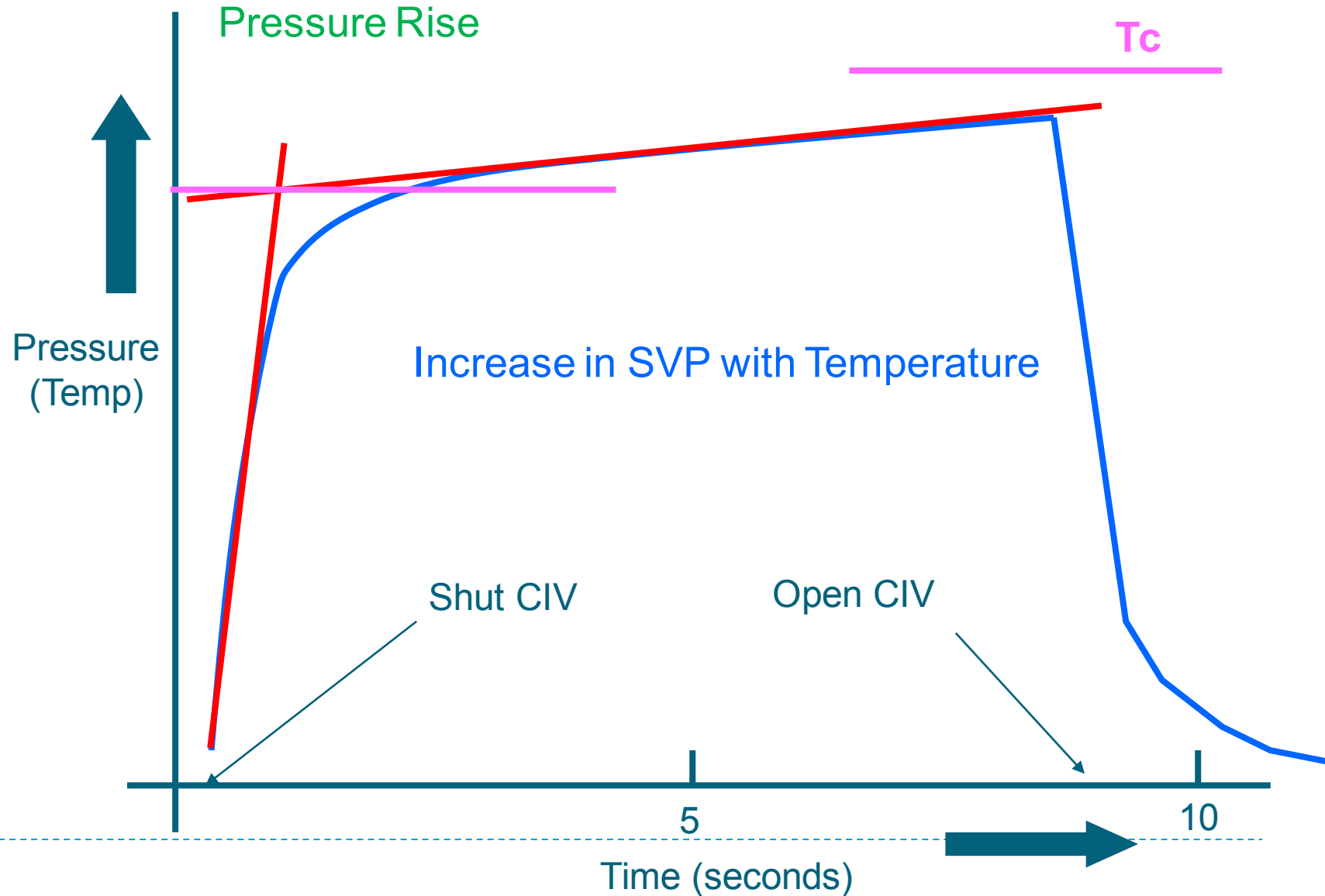


Possibility of incomplete drying in "established" cycle

Manometric temperature measurement (MTM): *using pressure rise to calculate temperature*

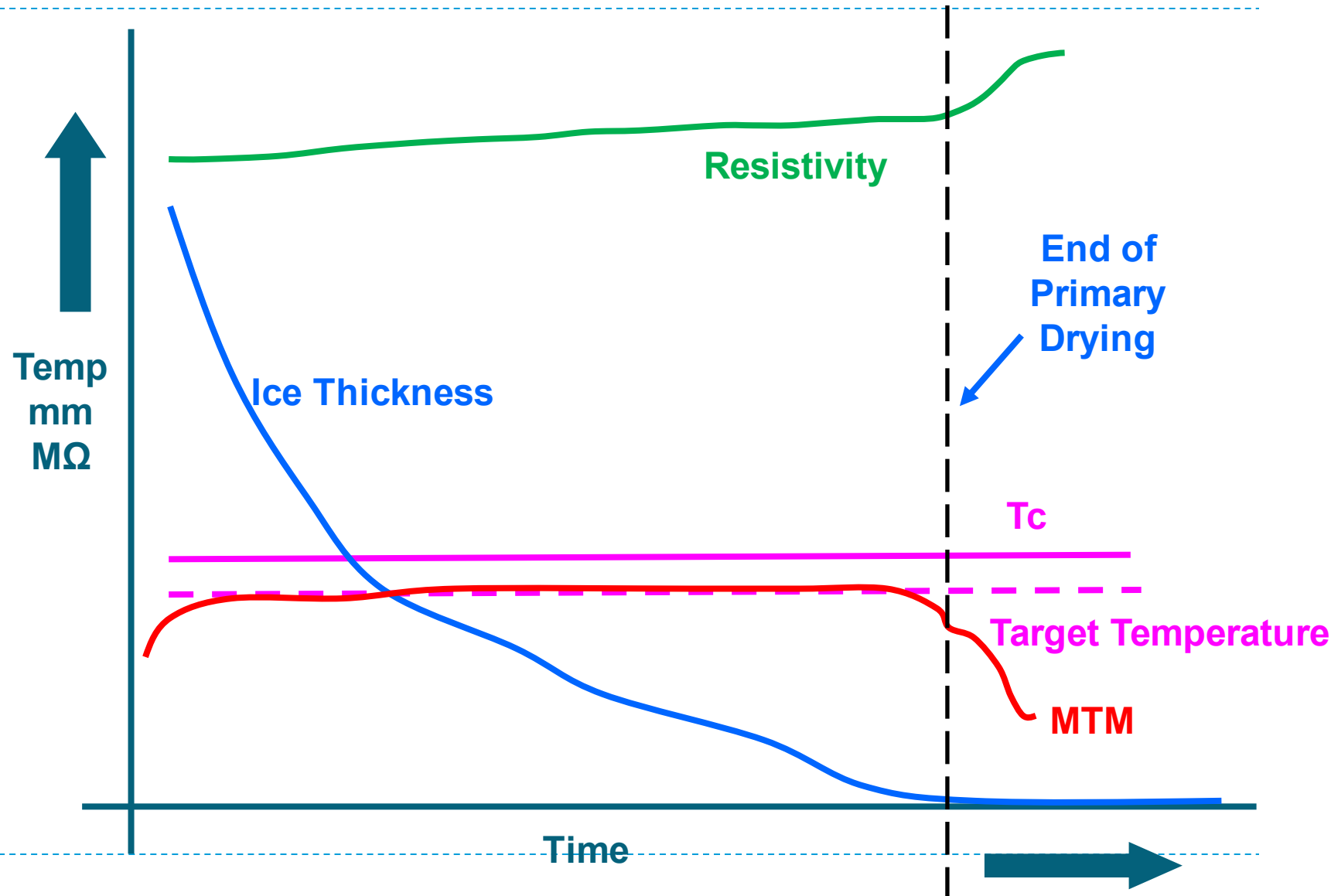
- ▶ This method is employed in FTS SMART freeze-dryer software, in order to calculate the temperature of the drying front
- ▶ Its advantage is that it is non-destructive and non-invasive compared with traditional temperature probes (thermocouples or resistance thermometers)
- ▶ The disadvantage is that the user needs to input several pieces of information about the product's physico-chemical characteristics for the software to work effectively – and even then, it makes various assumptions...

Manometric Temperature Measurement



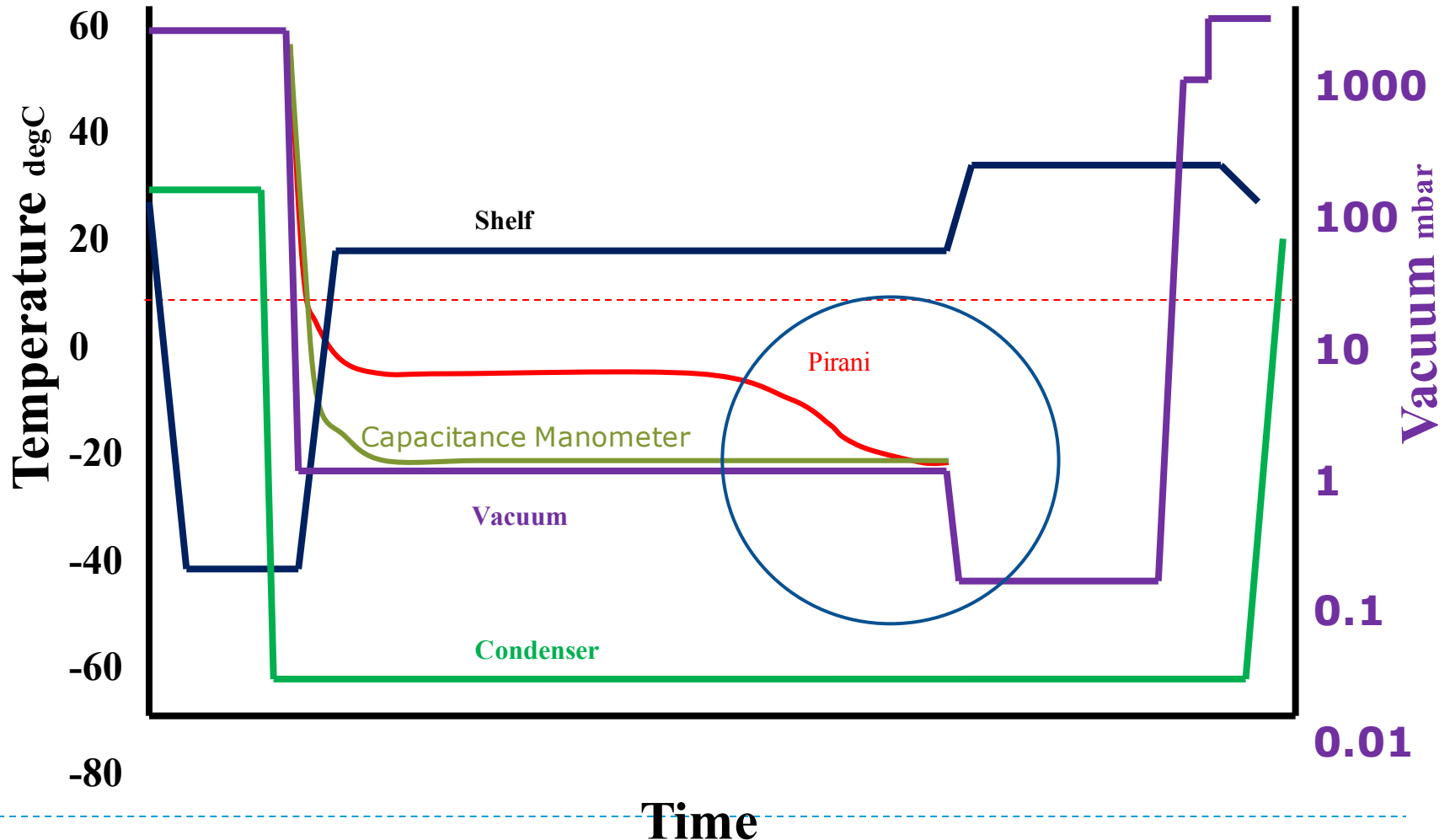
End Point Determination

Manometric Temperature Measurement



Pirani v Capacitance Manometer:

Example of how differences might be exploited to determine the endpoint of sublimation



► Freezing

- Freezes both the solvent and the solute
- Immobilises the product
- Defines the structure ready for drying

► Primary Drying

- The removal of the frozen free moisture by a process of sublimation – the conversion of ice to vapour without passing through the liquid phase

► Secondary Drying

- The process of further drying by desorption

Generally, temperature is considered more influential than pressure...

Why does pressure seem to be less important in desorption?

- ▶ The process is governed by sorption isotherms. In this case:
 - ▶ The energy required to release (desorb) the molecules of water trapped in the material compared to the decrease in free energy the molecules achieve by being adsorbed (or chemically bound, H-bonded, etc...)
 - ▶ The difference in energies above becomes much more favourable to desorption at higher temperatures, yet it is (theoretically) independent of pressure

Does pressure affect desorption in practice?

- ▶ This parameter has not been widely studied in isolation from other parameters
- ▶ In reality, there is some overlap between sublimation and desorption during the process, so any changes in pressure (and temperature) may come too late to affect desorption significantly
- ▶ One novel idea includes flushing the chamber with dry nitrogen to shift the equilibrium between adsorbed and free water, but this has not been taken up in industry

- ▶ Pressure is important in freeze-drying but in some stages more than others:
 - ▶ It can be used to control nucleation
 - ▶ It is very important in controlling heat transfer during sublimation to give the right balance between process efficiency and robustness
 - ▶ Believed to be less important in desorption (but less well studied)
- ▶ A range of vacuum pumps, gauges and valves are employed, each having an impact on system performance and process scalability



Thank You for your attention!

Any Questions?

