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MEDICAL OXYGEN IN HEALTHCARE FACILITIES

All you need to know about **supply sources for medical gas pipeline systems**

April 2025

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ABSTRACT

This White Paper on medicinal oxygen provides a comprehensive overview of the use of oxygen, its properties, historical significance, and its various applications, specifically in the medical field. Its prime purpose is to consider the different medical oxygen supply sources used for Medical Gas Pipeline Systems (MGPS) in Healthcare Facilities (HF), but to also include information about the development of oxygen as a medicinal product and an overview of its physical properties.

These include:

- Medical Liquid Oxygen (MLO), produced by cryogenic distillation of ambient air and supplied as a cryogenic liquid to the HF, where it is stored on site in cryogenic tanks and converted to a gas to supply the MGPS, using air heated vapourisers.
- Compressed Medical Oxygen (CMO), produced by compressing MLO, vapourising it to produce a high-pressure gas supply, which is filled into high pressure cylinders and supplied to the HF for connection to a changeover manifold system connected to the MGPS.
- Oxygen produced using a Pressure Swing Adsorption (PSA) plant on site, where the gas is produced by removing the nitrogen from ambient air, using molecular sieves and fed directly into the MGPS. This relies on the HF having a reliable energy supplies and suitably trained personnel.

There are different regulatory requirements for medical oxygen supply sources. Where Medical Oxygen is obtained from a third party (MLO and CMO), these include the supplier obtaining a manufacturing license to produce the gas, complying with Good Manufacturing Practices (GMP), and obtaining a Marketing Authorization (MA) for placing the Medical Oxygen on the market as a medicinal product. Where Medical Oxygen is manufactured on site (using a PSA plant), the full responsibility for the quality of the oxygen lies with the HF pharmacist, to ensure that it complies with their own monographs and the requirements of manufacturing a pharmaceutical preparations[1]. In Europe, there is no clear regulatory status for Oxygen from a PSA plant.

The **HF Pharmacist** must ensure adherence to these regulations and maintain a Quality Management System (QMS) to ensure the quality and safety of the oxygen supplied meets the appropriate pharmacopeia specification.

When choosing a supply source, factors such as the size of the HF, the maximum flowrates and demand of the facility, the HF location, and the national regulatory requirement must be considered. The responsibilities of the Marketing Authorization Holder (MAH) and the HF are also outlined for the three sources of supply, emphasising the importance of maintaining adequate stocks and ensuring the quality of the gas supplied for patient use.

Each supply system has its own features:

- MLO is suitable where the demand for the gas is high, offering high purity product and efficient storage system with minimal HF input and maintenance;
- CMO is more suitable for lower demand HFs, but requires regular HF input to changeover cylinders on the manifolds supplying the MGPS;
- PSA plants provide an on-site production system, especially where other supply sources are not readily available, but depends on a reliable electricity supply being available and requires comprehensive maintenance to maintain the supply.

Overall, this White Paper highlights the critical role of medical Oxygen in medicinal treatments and the importance of ensuring the availability of a reliable and high-quality supply source for the HF's MGPS.

A useful comparison table, describing the key features of the three sources of supply, is given at the end of the document.

OVERVIEW OF MEDICAL OXYGEN SUPPLY SOURCES FOR MEDICAL GAS PIPELINE SYSTEMS

Supply Systems

Medical Oxygen, used for the treatment of patients in HFs can be supplied either directly from a MGPS or from individual high-pressure gas cylinders. Where the HF has an MGPS, cylinders are only directly used for supplying Medical Oxygen to the patients when being moved within the hospital (or transferred by ambulance to another facility) or where there are no MGPS terminal outlets available.

This document only considers the supply of Medical Oxygen from the pipeline system and compares the three potential sources of Medical Oxygen that can be used to feed directly into the MGPS as a supply source.

The three products used as supply sources for the MGPS include:

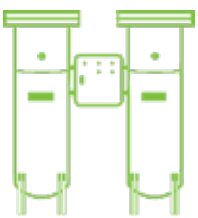
1 Medical Liquid Oxygen (MLO)

MLO is supplied to the HF as a cryogenic liquid by a tanker and stored on the HF site in a cryogenic storage tank and converting to a gas using an air heated vapouriser, as required to supply the MGPS.

2 Compressed Medical Oxygen (MLO)

CMO is supplied to the HF in large high-pressure cylinders, which are connected to a changeover manifold system to maintain the supply of Medical Oxygen to the MGPS;

3 PSA Oxygen



PSA Oxygen is manufactured on the HF site using a Pressure Swing Absorption (PSA) plant and continuously quality controlled before being fed directly to the MGPS, via buffer vessels.

To be compliant with the requirements of the ISO standard for the design and installation of a MGPS system (ISO 7396 - Part 1: Pipeline systems for compressed medical gases and vacuum), the MGPS is required to have:

- three separate sources of supply (primary, secondary and emergency) to protect the MGPS against a single fault condition of any key components of the supply system and controls.
- each supply source (irrespective of the type) sized correctly to ensure that it can meet the HF's predicted maximum demand (for a defined period whilst any faults are rectified). This impacts on the choice and the size of the reserve and emergency sources of supply to maintain control under single fault conditions.

There are a number of supply sources that can be used for supplying Medical Oxygen to a MGPS that have not been included in this White Paper as they are minor variants of the three main sources of supply. These include:

- large liquid oxygen dewars used for storing the MLO and either supplied to the HF as a portable container or installed as a permanent installation and filled by a small liquid oxygen tanker. These large dewars are filled from the same source of MLO, producing a Medical Oxygen gas supply by vapourising the liquid, using an integral vapouriser and considered as an MLO variant.
- cylinder bundles containing multiple large high-pressure cylinders manifolded together, which are connected to a changeover manifold (as used by CMO systems). They provide a method of supplying a large amount of compressed gas in a single unit, making it easier to maintain supplies. These cylinder bundles require a manual handling device (such as a fork lift truck) to maneuver them into position. The cylinders are filled in the same manner as those described in the CMO section and are considered as a CMO variant
- cylinders filled using the excess gas produced by the PSA plant and not used by the MGPS but stored on site as a compressed gas for use as a secondary or emergency supply source. The cylinders need to be connected to a changeover manifold system to be used. The controls and procedures to safely fill high pressure cylinders requires specific training and is not covered within the White Paper.

Regulatory Requirements

For the MLO and CMO options, where the Medical Oxygen is supplied from an external source, the manufacturer of the gas needs to hold an appropriate manufacturing licence. Within Europe this is referred to as the Manufacturing and Importation Authorisation (MIA), issued by the national Regulatory Authority. The licenced manufacturer must operate a QMS that is compliant with the principles detailed in Annex 6 of the EU GMP Guide, which specifically covers the manufacture and distribution of medicinal gases. The licenced manufacturing sites are routinely audited by the national Regulatory Authority Inspectors to ensure that their QMS remains compliant with the relevant GMP guidelines.

Dependent on the regional or national requirements, the supplier of the Medical Oxygen is normally required to hold a Marketing Authorisation (MA) to place the medicinal gas on the market. The HF Pharmacist should check with the national Regulatory Authorities whether there is a requirement to have an MA to supply MLO or CMO.

When applying for the MA, the supplier is required to detail the manufacturing and quality control testing requirements for the product, including the reference to the relevant pharmacopoeia specification. In addition, the Marketing Authorisation Holder (MAH) is required to prepare a Summary of Product Characteristics (SmPC), which provides the Healthcare Professional (HP) with information about the approved indications and contra-indications for the medicinal gas, as well as the precautions for its use. The SmPC also provides the relevant information about how to safely handle and store the medicinal gas and the type of supply packages (cylinders or cryogenic storage tanks) used.

The MA also details the various analytical test methods to determine both the assay of the gas as well as the specification limits for impurities. The MA also specifies the batch testing frequency and the relevant acceptance criteria.

The HF, where the PSA plant is installed, is responsible for the QMS that covers the use of the PSA plant. As the PSA Oxygen is manufactured on-site, it is required in Europe by the European Directorate for the Quality of Medicines and HealthCare (EDQM) to be classified as a pharmaceutical preparation[1], and needs to be manufactured following the basic principles of Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (see the Pharmaceutical Inspection Convention Co-Operation Scheme (PIC/S) PE 010-4), requiring the quality of the PSA Oxygen to be continuously monitored to ensure that it is suitable for patient treatment, following the relevant pharmacopoeia procedures.

When choosing the most suitable supply source for the HF's Medical Oxygen MGPS, several factors need to be considered by the HF, including:

- the size (number of beds) of the HF, the types of treatments it provides
- the maximum daily consumption, the variability of the demand and the maximum flowrate for the supply of Medical Oxygen used to treat patients,
- the location/proximity of the HF site to the available external sources of Medical Oxygen,
- the national Regulatory Authority requirements for:
  - the manufacture and supply of Medical Oxygen from an external supplier to the HF
  - the specific QMS requirements to be used by the HF where they are manufacturing the PSA Oxygen as a pharmaceutical preparation on site,
- the status of the MGPS (where defined as a medical device) and the requirements for its design to be compliant with requirements of the ISO standard (ISO 7396- 1, Medical gas pipeline systems — Part 1: Pipeline systems for compressed medical gases and vacuum) or the equivalent approved national standard,
- where on-site manufacture is being considered, the availability within the HF of:
  - a reliable energy supply system
  - facilities to operate any on-site equipment, including the operation of PSA plant(s), where used.
  - suitably trained operatives to manage the manufacture of the gas on site and the control of the quality of the gas delivered to the patient via the MGPS.
  - a pharmacist / responsible person to formally release the product for patient use.

As the MGPS is used to deliver Medical Oxygen directly to the patient, the MGPS supply system needs to be both reliable and flexible to enable any variations in the demand to be fully met.

The basic design requirements for the Medical Oxygen supply source are covered in ISO 7396-1. A specific requirement of the standard is that there should be at least three independent supply sources to allow for a single fault condition with any part of the system. Each supply source should be capable of supplying the HF with the design demand for the MGPS. This also covers the availability of services on site (such as power and water) to enable the gas to be continually produced and stored on site.

An MGPS should be covered by a risk assessment and the maintenance programme of the HF.

MEDICAL LIQUID OXYGEN (MLO)

Section Summary:

Medical Liquid Oxygen (MLO) is a suitable supply source for a Medical Oxygen MGPS, being capable of providing large volumes of Medical Oxygen at variable flowrates, without being reliant on the HF to provide any input to maintain the supplies.

MLO is a cryogenic liquid, produced by an Air Separation Unit (ASU) by the cryogenic distillation of ambient air. The Liquid Oxygen produced by the ASU can be used for both medicinal and non-medicinal purposes. The ASU is designed so that the MLO meets the European Pharmacopoeia monograph specification for Medical Oxygen. It only becomes designated as MLO after it has been batch tested and certified for medicinal use by a Qualified Person (QP). It is supplied by road tanker to the HF and is used as a Medical Oxygen supply source for the Medical Gas Pipeline System (MGPS).

The ASU process involves separating the main constituents of atmospheric air (Oxygen, Nitrogen, and Argon) according to their boiling points. As the concentrations of these three main gases are constant in the air, the cryogenic distillation of ambient air is therefore a highly predictable process. Contaminants in the ambient air are removed before the air is cooled to cryogenic temperatures and fed into the distillation column. The Liquid Oxygen produced by the ASU is stored in cryogenic storage tanks before being certified and transported to HFs.

The supplier of the MLO is responsible for the quality of the medical Oxygen supplied to the HF. The HF Pharmacist is only responsible for the quality of the gas supplied from the MGPS, (including the potential for air ingress or cross contamination between pipeline systems). They are also responsible for ensuring that the HF has sufficient MLO available on site to meet patient demand and to ensure that the supplier provides the appropriate documentation to demonstrate that the MLO meets the relevant pharmacopeia requirements.

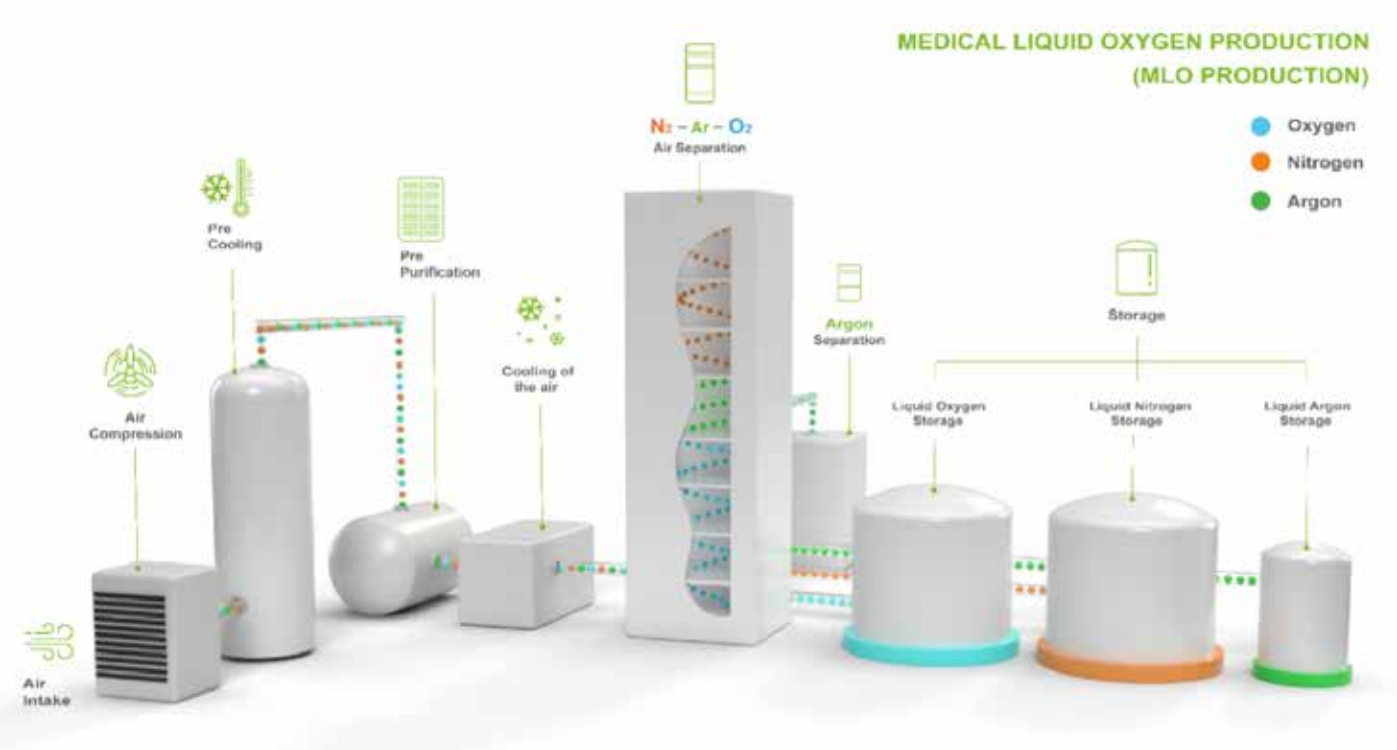
MLO Manufacturing Process

Medical Liquid Oxygen (MLO), used as the supply source for larger HFs, is exclusively manufactured by the cryogenic distillation of ambient air, using an Air Separation Unit (ASU). It is supplied by a road tanker to the HF site as a cryogenic liquid at approximately -180°C.

The ASU uses ambient air as the starting material, which consists primarily of nitrogen (78 %), oxygen (21 %) and the inert gas argon (0.9 %). The remaining 0.1 % is made up mostly of carbon dioxide, carbon monoxide, moisture and very small amounts the inert gases neon, helium, krypton and xenon.

As the concentrations of the three main gases are constant in the ambient air and the boiling points of the gases are fixed, dependent on their pressure the cryogenic distillation of ambient air is a highly predictable process. The critical process steps within the production of liquid oxygen are managed primarily by the design of the plant, ensuring that there are sufficient distillation trays within each column to ensure that the nitrogen will be removed to a sufficiently low enough level for the oxygen to meet its specification.

The following scheme shows a typical ASU with its main processing steps:



The following steps and equipment are used in the manufacturing of MLO:

AIR COMPRESSION

The air compressor draws in ambient air, which is initially filtered to remove any particulate and then compressed up to around 5 bar(g), using a multistage compression process.

PRE-COOLING OF COMPRESSED AIR

To separate air into its components, it must first be liquefied at an extremely low temperature. As a first step, the compressed air is precooled. Pre-cooling can be achieved either by using an ammonia cooling system or by direct cooling using water where the latent heat of vaporization of water is used to cool the gas.

PRE-PURIFICATION OF COMPRESSED AIR

Prior to cooling the gas down to cryogenic temperatures, it is necessary to remove any contaminants that may freeze out in the distillation column, especially moisture and carbon dioxide, causing the distillation plates to become blocked and stop the column from working efficiently.

The Pre-Purification Unit (PPU) consists of two vessels containing a mixture of molecular sieve materials and alumina to adsorb these contaminants. The plant operates with one of the vessels 'on-line', removing the contaminants from the ambient air, whilst the other vessel is being 'regenerated'. The PPU system continuously monitors the carbon dioxide levels to indicate that the gas is suitable for cooling and feeding the distillation column. The PPU is regenerated by passing heated waste nitrogen from the distillation process back through the molecular sieve beds, removing the carbon dioxide and moisture (including any other contaminants adsorbed by the molecular sieve).

Another option to remove the contaminants is to pass the gas through a reversing heat exchanger (RHE). The RHE system uses a heat exchanger with two separate passes, with the compressed air being fed through one pass and cold waste gas from the distillation column being fed through the other pass. The cooling of the ambient air causes the carbon dioxide and moisture (plus any other contaminants with a 'high' freezing point) to form as solids on the surface of the exchanger. Before the exchanger becomes blocked, the passes are changed over so that the frozen contaminants are removed with the waste gas, as it warms up by passing through the exchanger.

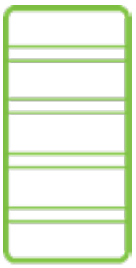
LIQUEFYING THE PURIFIED AIR

As the component gases which make up air liquefy only at very low temperatures, for the cryogenic distillation process to be efficient it is necessary to conserve as much of the 'cold' from the process before venting or using any gas from the plant. Hence any gas streams from the plant are warmed up to ambient temperature by cooling down the ambient air being fed to the distillation column.

Rapid pressure reduction of the cooled ambient air then causes it to cool further, undergoing partial liquefaction, when the air is fed to the distillation column, where the actual separation takes place.

The equipment operating at below ambient temperature is enclosed in a large cold box, which is an insulated container to minimise the heat inleak to the system.

AIR SEPARATION



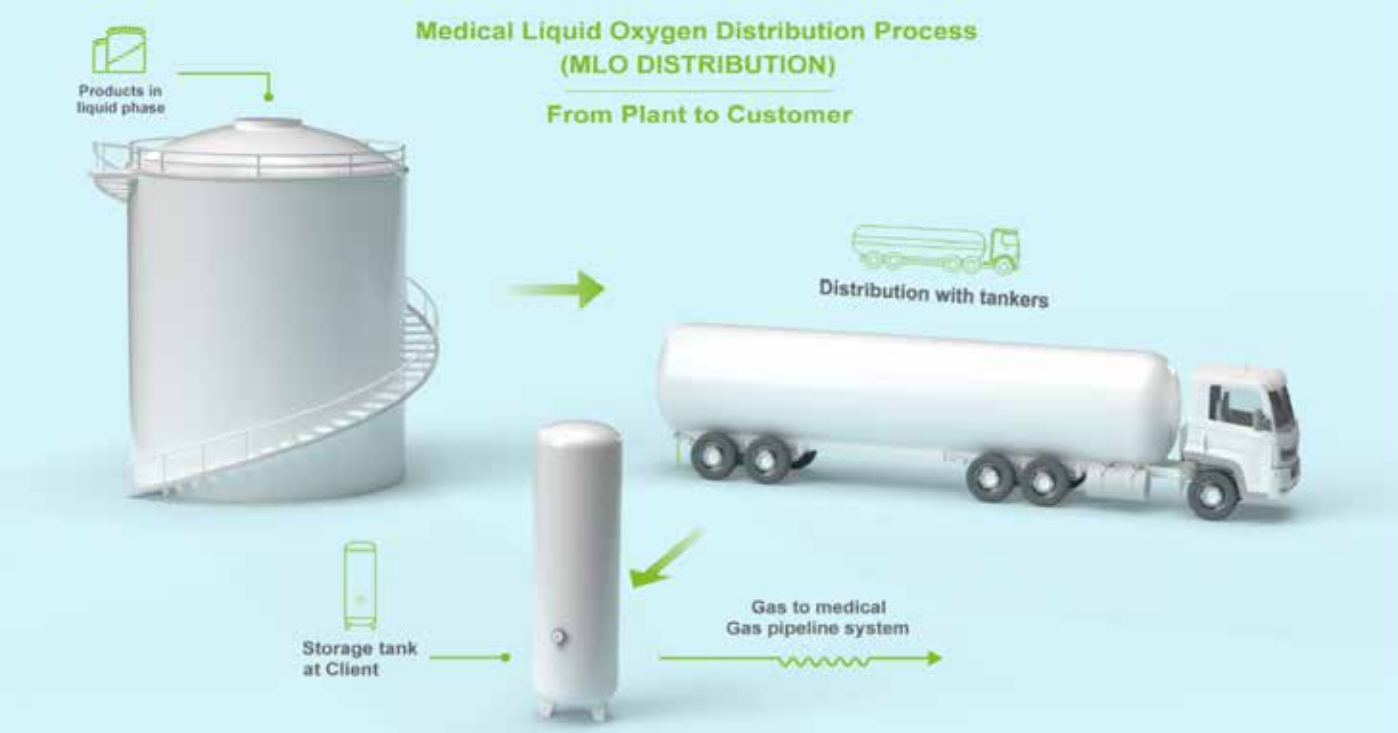
Separation of the ambient air into oxygen, nitrogen and argon is performed in a double distillation column, where the two columns operate at different pressures. The double column is used to take advantage of the difference of the boiling temperature of the gases at different pressures, allowing the recondensor of the high-pressure column to act as the reboiler in the lower low pressure column. The recondensor in the lower column converts the gas at the top of the column to a liquid to provide the reflux for the lower column. The reboiler at the bottom of the upper column converts the liquid at the bottom of the upper column to a gas for the final distillation in the upper low pressure column. As nitrogen liquifies at a lower temperature than the oxygen, the nitrogen is driven up the columns (allowing pure nitrogen gas to be produced), leaving pure oxygen in the upper column reboiler for transfer (as a liquid) to the storage tank.

Argon is separated by taking an argon rich stream from the upper, low pressure column and then separating the argon in an additional distillation column. The crude argon produced is then purified further to produce a commercially pure product.

LIQUID OXYGEN STORAGE

The liquid oxygen produced by the ASU collects in the upper column reboiler sump and is transferred as a liquid to the liquid oxygen storage tanks. These tanks are highly insulated with a capacity of up to several million litres of liquified gas. A paramagnetic Oxygen analyser is used to continuously monitor the assay of the liquid oxygen as it is fed from the plant to the storage tanks.

MLO Distribution Process



The liquid oxygen in the storage tank, transferred from the ASU, is to a single quality specification, which meets the specification in the European Pharmacopoeia monograph for Medical Oxygen. When the liquid oxygen in the main storage tank is either transferred to the MLO storage tank on site or filled directly into a tanker scheduled to make a delivery of MLO to a HF, it becomes designated as MLO, using the approved quality control procedures. Each batch of the MLO is analysed to certify that it meets the appropriate pharmacopoeia specification and finally released by the QP to document that it has been produced under GMP compliant procedures and meets the specification requirements.

The batch definition of the MLO is defined as the bulk pharmaceutical product (drug substance) filled and released into the dedicated MLO storage tank on site or the cryogenic road tanker scheduled to deliver to the HF. Once certified as MLO, it can be used to supply the product to the HF storage tanks. Where required the national Regulatory Authority, the supply is accompanied by a certificate of analysis for the batch.

The cryogenic road tanker is filled on the manufacturing site using a flexible cryogenic hose. In order to keep the tankers at cryogenic temperatures, it always retains some product from the previous delivery. Prior to starting the filling process, the tanker is analysed for oxygen purity to ensure that the residual product is still within the specification limits. As the cryogenic filling hose will be full of air, prior to loading the tanker the hose is purged to minimise any contamination being transferred into the tanker. After filling, a liquid sample from the tanker is analysed, using a paramagnetic analyser, allowing the load to be certified. The requirements for filling and testing the tankers must be compliant with the EU GMP Guidelines and the drivers appropriately trained to ensure the quality of the product meets the specification limits.

The distribution of the liquid oxygen as a cryogenic liquid is seen as a very efficient way of transporting the product. The gas to liquid volume ratio is in the order of 850:1, allowing much fewer deliveries compared to delivering Medical Oxygen in cylinders.

MGPS Supply Source

The MLO supply source used for the Medical Oxygen MGPS consists of a cryogenic storage tank on the HF's site using a double skinned tank, where the interspace between the inner and outer shell is vacuum insulated, to reduce the heat inleak into the storage tank. These storage tanks are required to be CE marked to the Pressure Equipment Decretive (PED), requiring them to be inspected every ten years. The storage tank is set up to operate at around 12 bar(g), meaning that no additional energy source is required to increase the pressure of the gas delivered from the supply source to provide the Medical Oxygen at the pressure required for the MGDS. In the evet of the storage pressure being too low the storage tank is fitted with a pressure raising coil, where liquid from the tank is passed through an air heated vaporiser, converting the liquid to gas and raising

the pressure to the correct level. The MLO delivery is added to the residual MLO in the HF storage tank and the mixed product is used as the Medical Oxygen supply source to the Medical Oxygen MGPS on the HF site.

The outlet of the storage tank is connected to an air heated vapouriser sized to convert the liquid oxygen for the MGDS to a gas at ambient temperature. For HFs, where the maximum design flowrates are high, two sets of vapourisers on an automatic changeover can be used to prevent the vapourisers being covered by ice (which reduces the heat inleak into the vapourisers). The changeover period allows the vapouriser to thaw during the period when it is off-line.

The vapourised gas is then fed to a control panel which controls the pressure of the gas in the MGDS. The control panel is designed so that it can provide sufficient gas to maintain the MGDS pressure whilst delivering the maximum design flow rate.

For larger HFs, MLO is used for both the primary and secondary supply source for the MGDS, as the demand is considered to be too high to enable cylinders to be replaced on a CMO supply source. Although the secondary supply source tank can be installed on the same plinth as the primary source storage tank, they are often sited at separate locations to provide more reliability for the MGDS. As the secondary supply source tank is not normally used, it has an economiser circuit that allows the gas produced by the heat inleak to the storage tank to be fed to the MGDS rather than being vented to atmosphere to relieve the pressure increase.

MLO Responsibilities

MARKETING AUTHORISATION HOLDER (MAH)

The **MAH** is responsible for:

- the quality of the product at the outlet of the control panel, where connected to the MGPS.
- supplying information about the safety and efficacy of the product using the approved indications for the MLO (SmPC and Patient Leaflet).
- all the production and distribution steps in the process, up to the point where the product is supplied from the HF storage tank and vapourised for supply to the MGPS for patient use.
- providing training material to ensure safe operation of the MLO system.
- performing the planned and repair maintenance of the MLO storage tank and associated equipment.

As the 'owner' of the storage tank, the supplier is responsible for ensuring that the storage tank and associated equipment complies with the technical requirements of **Pressure Equipment Directive** (PED, 2014/68/EU).

HEALTHCARE FACILITY (HF)

The **HF Pharmacist** is responsible for:

- ensuring that the MLO is supplied by an approved MAH
- the quality of the gas supplied from the MGPS terminal outlets, taking account the suitability and maintenance of the MGPS.
- obtaining the relevant information (SmPC and Patient Leaflet) from the MAH
- ensuring the MLO supply source is appropriately validated,
- ensuring there is no risk of cross contamination between other MGPS's on site and no potential for air ingress to the system.
- ensuring that there is sufficient product available in the MLO supply source(s) for patient use. However, the MAH will normally manage the supplies of MLO to the HF.
- ensuring that the MLO supplier provides the correct documentation with each delivery.

The **HF Technical Department** is responsible for:

- training the operational personnel to ensure the MLO supply source equipment is operated correctly as per the MAH supplier's procedures.

Features of MLO used as an MGPS Supply System

When choosing the supply system for the Medical Oxygen MGPS, MLO offers several features that can be considered by the HF when selecting the appropriate source for the primary, secondary and emergency source of supply:

OXYGEN AVAILABILITY

- MLO is only a suitable source of supply for a Medical Oxygen MGPS if there is a licenced supplier available, where the HF is within the agreed distribution area of the supplier.
- MLO is a suitable supply source for both the primary and secondary supply for the Medical Oxygen MGPS.
- MLO can be used as the emergency supply source, but due to heat inleak causing 'boil off' of product from a cryogenic tank that is not normally used, it requires careful management to maintain the stocks at a suitable level.
- The location of the storage tank is an important decision to ensure that the tank is always accessible to allow tankers to make deliveries.
- MLO provides the most efficient way of storing Medical Oxygen on the HF site, due to the difference in density of the cryogenic liquid and compressed gas (with a ratio of approximately 850:1 when comparing liquid to gas at atmospheric pressure).
- The size of the storage tank is determined by the HF's predicted Medical Oxygen average daily demand, taking account of the variability of the HF's usage, the delivery tanker capacity and the number of deliveries required to optimise its environmental impact.
- The capacity of the supply source control panel and vapouriser system is dependent on the maximum design flowrate of the MGPS.
- When selected as either the primary, secondary or emergency supply source for the Medical Oxygen MGPS, its ability to meet increases in HF MGPS's designed maximum flowrate capacity can be easily made by reviewing the capacity of the gas control panel and vapourisers.
- To meet increases in the HF's average demand, the size of the storage tank can be reviewed by checking that it is within the MLO supplier's acceptable delivery frequency.
- the supplier can manage the stocks in all storage tanks using a telemetry systems to determine when a delivery of the product to site is required to maintain storage tanks above the agreed minimum level for the HF site to maintain patient supply.
- large volumes of oxygen, which have been approved for use, can be stored on site, giving the HF the confidence that they have sufficient gas available to maintain the treatment of their patients.
- ability to install a secondary (and reserve source of supply) at a separate location, provides more reliability to the MGPS system.
- the manufacturer of the MLO normally stores significant quantities of bulk product on their site, meaning that there is sufficient product available to maintain the storage tank levels under emergency conditions.
- MLO storage tanks used, as a backup supply, are fitted with an economiser circuit to utilise any gas generated by the heat inleak for the MGPS to avoid product loss.

PRODUCT QUALITY

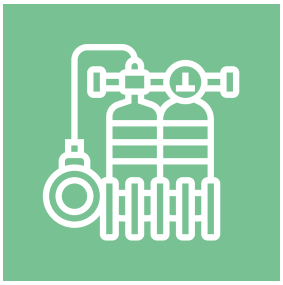
- Each load of MLO is certified by the QP to ensure the quality level of the MLO, where the assay meets the relevant Pharmacopoeia specification (at least 99.5%).
- The MAH takes the responsibility for the quality, safety and efficacy of the product.
- The quality of the Medical Oxygen supplied from the MLO storage tank does not vary with any variations from the HF's flowrates.
- Where Compressed Medical Oxygen (CMO) is used as a secondary or reserve supply source for the MGPS, the quality of the gas in the cylinders is compatible with the quality of the MLO, allowing it to be used as the alternative supply for the MGPS, at the appropriate product quality.
- As the storage tank is operated at a positive pressure, there is no risk of contamination of the product whilst it is being stored.
- although the MLO will have a finite storage life, this period is much longer than the time that the oxygen is stored on the HF site.

CLINICAL USE

- the high purity of the gas supplied allows the oxygen to be used for all clinical indications and all types of medical equipment (such as anaesthetic machines and ventilators).
- Due to its consistent quality levels, it allows the Medical Oxygen to be used to calibrate the medical device.

MAINTENANCE AND OPERATION

- The MLO supplier (and not the HF) takes the responsibility for the maintenance of the MLO supply systems. This also covers the compliance with the Pressure Equipment Directive.
- Maintenance has little impact on the availability of the system due to the system having no moving parts, leading to its reliability.
- The vacuum insulated storage tanks are designed to withstand pressures of up to 20 bar. As the liquid in the storage tank warms the vapour pressure will increase, providing sufficient pressure to maintain the MGPS at the design pressure.
- When the temperature of the MLO is very low (and the MLO has a low vapour pressure) the tank pressure can be increased using a secondary air vaporiser to increase the tank pressure without the addition of any external energy.
- As the MLO is stored at approximately -180°C, it only requires the heat from ambient air to vapourise the product and there is no additional energy requirement to vapourise the MLO and supply the gas to the MGPS at ambient temperature.
- although the MLO cannot be stored indefinitely (as the heat inleak to the storage tank will cause product to 'boil' and increase the storage tank pressure), if the product is not used, the relief valves fitted to the storage tank will keep the installation safe by venting the excess gas to atmosphere reduce the tank pressure.



COMPRESSED MEDICAL OXYGEN (CMO)

Section Summary:

Compressed Medical Oxygen (CMO) can be used as a supply source for the Medical Oxygen MGPS, where the demands tend to be lower, requiring the HF to provide the resource for exchanging cylinders on the changeover manifold systems used to provide the gas to the MGPS.

The CMO is produced by pumping approved MLO up to a high pressure, converting it to a high pressure gas, and passing it through an air heated vapouriser to fill the high-pressure cylinders. The gas is filled into cylinders, prepared in batches, and tested for quality and content before being certified by the QP, to demonstrate that the gas meets the appropriate Pharmacopoeia specification for Medical Oxygen.

For MGPS use, it is stored in large, high-pressure cylinders or cylinder bundles (multiple cylinders manifolded together) and filled to pressures up to 300 bar. CMO can also be supplied in smaller cylinders for direct use by the patient, where they are being transported or where there is no MGPS terminal outlets available.

Although the supplier is responsible for the quality of the gas supplied, the HF is responsible for connecting the cylinders to the MGPS' changeover manifold to ensure continuity of the supply to the MGDS to meet patient demand. They are also responsible for ensuring that the CMO cylinders are appropriately stored, stock rotated and used within their expiry date. The HF is responsible for ensuring that the appropriate operating procedures, supplied by the MAH, are operated correctly.

There are no requirements for the HF Pharmacist to perform any quality testing on the cylinders supplied. However, the HF Pharmacist is responsible for the quality of the gas supplied from the MGPS, (including the potential for air ingress or cross contamination between pipeline systems).

CMO Manufacturing Process

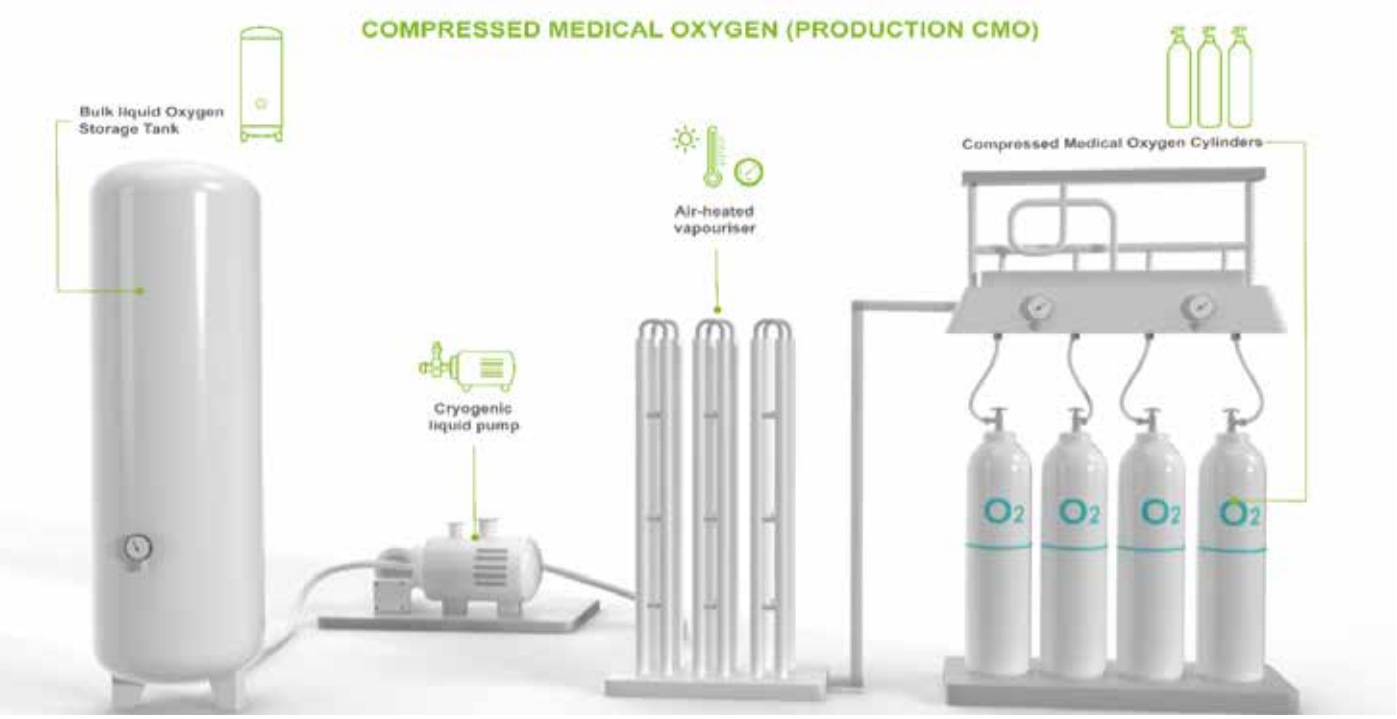
Compressed Medical Oxygen (CMO), used as a Medical Oxygen MGPS supply source is supplied to the HF in large, high-pressure cylinders, using a changeover manifold to supply the gas to the MGPS. The HF is required to connect the cylinders to the changeover manifold to maintain the supply of gas for patient use.

CMO cylinders are produced by the holder of an MIA, issued by a national Regulatory Authority and are responsible for filling, testing and releasing the cylinders for medicinal use, under GMP conditions. The MIA's QP is required to release each batch of cylinders to certify that it meets the specification of medical oxygen as described in the relevant Pharmacopoeia monograph and the specification detailed within the MA.

The cylinders are supplied to the HF by an MAH as a certified licensed medicinal product, requiring the supplier to hold the necessary MA licence issued by the national Regulatory Authority. The MAH is responsible for appropriately labelling the cylinders and that each cylinder has a unique batch number and expiry date label fitted.

The HF Pharmacist is only responsible for the correct storage and use of the cylinders, as defined by the MAH.

The following scheme shows a typical CMO manufacturing process:



The following steps and equipment are used in the manufacturing of MLO:

LIQUID OXYGEN STORAGE

Liquid oxygen, which has been approved for medicinal use, is used as the starting material for CMO. The liquid oxygen is stored on site in a vacuum insulated storage tank, dedicated to Medical Oxygen. The manufacturer of the CMO is required to use liquid oxygen to fill CMO cylinders that meets the requirements of the relevant Pharmacopoeia monograph for Medical Oxygen.

PUMPING LIQUID OXYGEN

The liquid oxygen is pumped to a high-pressure using a cryogenic liquid pump. Liquid oxygen is pumped (rather than the oxygen gas compressed) as the energy required to produce high pressures is significantly less.

VAPOURISING THE HIGH PRESSURE LIQUID

The high-pressure liquid oxygen is passed through an air-heated vaporiser to produce the high pressure gaseous oxygen. The stainless-steel vaporiser is designed with aluminium fins connected to the pipework to create a greater surface area. As the high-pressure liquid oxygen passes through the vaporiser pipework, it is warmed using heat transferred from the ambient air, which converts the cryogenic liquid oxygen to a high-pressure gas. The vaporisations process requires no additional energy to produce the gaseous product.

FILLING COMPRESSED MEDICAL OXYGEN CYLINDERS

The high-pressure oxygen from the air-heated vaporiser is then filled into the medical oxygen cylinders, using dedicated cylinder filling manifolds.

The cylinders are inspected prior to filling to ensure that they are in an externally clean condition, within their statutory test date and suitable for filling. Each cylinder valve is also inspected to ensure its outlet is clean and the valve undamaged. Having connected the cylinder packages to the filling manifold, they are initially vented to atmosphere to remove any contents from the previous use and then either evacuated or purged to remove any residual gas to prepare them for filling.

When the pre-fill preparations are complete, the cylinders are filled to the specified pressure. Although filling cylinders in a batch to the correct pressure is the usual way of controlling the content, it is possible to fill cylinders individually by weight.

Gas Package Specification

HIGH PRESSURE CYLINDER SPECIFICATIONS

The contents of a high-pressure cylinder is dependent on its water capacity and the pressure to which it is filled when the gas is at 15°C. (referred to as the working pressure). The cylinder design pressure is set at 1.5 times the working pressure, allowing for the increase in pressure if the gas temperature rises up to 65°C. Storage conditions for high pressure cylinders must be controlled to ensure cylinders are not subjected to high temperature.

Cylinders used for supplying Medical Oxygen can be manufactured either from high tensile steel or aluminium alloy and can either be of a standard construction or have additional strength added by being wrapped with carbon fibre (referred to as composite cylinders). The choice of materials for the cylinders is dependent on the way that the cylinder is used. For portable cylinders, used to supply patients with an ambulatory source of supply, composite aluminium cylinders tend to be used as these offer the lightest option. For cylinders used to supply medical oxygen for a MGPS, high tensile steel cylinders are the preferred option as the cylinder weight is of less importance.

The cylinders are manufactured by specialist companies and are designed to specific international (ISO) standards and approved for use (in Europe) under the TPED Regulations.

HIGH PRESSURE CYLINDER VALVE SPECIFICATIONS

An important component of a medical gas cylinder package is the valve fitted to control the use of the gas when supplying Medical Oxygen to the patient.
The valve can be a simple shut-off valve, which requires an additional pressure regulator / flow meter to be fitted to reduce the supply pressure down to a level which can be used for patient administration.

Alternatively, the valve can be a shut-off valve that has an integrated pressure regulator (referred to as a VIPR - Valve with Integrated Pressure Regulators). These can be fitted with a flowmeter to administer the gas directly to the patient and a pressure outlet to connect the cylinder package to a medical device, such as a ventilator. These are typically used for cylinders intended for portable use by homecare patients, for patients being transferred between HF departments or where there are no MGPS outlets available within the HF. Although the VIPR is considered a medical device (because it delivers a measured flow of gas to the patient) and needs to be CE marked to the Medical Device Regulations, it is also considered as the closure for the medicinal product container. Consequently, it must comply with both the medical device and the pharmaceutical regulations.
For cylinders that are used as a supply source for an MGPS, a simple shut-off valve is used as the pressure of the gas used to supply the MGPS is controlled by a pressure regulator in the changeover manifold control panel, which is designed to handle the maximum HF flowrate accurately.

Another development in the design of cylinder valves is the incorporation of a residual pressure device within the valve design, which retains a small amount of pressure in the cylinder after use. The residual pressure (approximately 3 bar) retained in the cylinder ensures that a cylinder is not contaminated when empty, even if the user leaves the valve open. This type of residual pressure valve (RPV) is being adopted into medical gas service to further ensure the quality of the gas being supplied. Another feature of the residual pressure device fitted to the RPV is that it acts as a backflow protection device, which closes if the downstream pressure exceeds the cylinder pressure.

CMO Distribution Process

The distribution of CMO is a much simpler process than the used for the delivery of MLO, the cylinders only requiring to be approved and certified prior to being supplied to customers.

The distributor of the CMO must hold a Wholesale Distributor Authorisation (WDA), specifying the distribution and storage sites licenced by the national Regulatory Authority. They are required to comply with the EU Good Distribution Practice (GDP) guide. The distributor is responsible for checking that the customers are approved for receiving the medical gas cylinders, to ensure that the cylinders are only used for medicinal purposes. In most cases the manufacturer of CMO is also the distributor of the cylinders, holding the appropriate WDA.

MGPS Supply Source

The CMO supply source used for the Medical Oxygen MGPS utilise the larger cylinders (typically 40-50 litre water capacity), fitted with a standard valve. The valves can be fitted with a residual pressure device to prevent any back-feeding into the cylinder from another MGPS.

Throughout Europe, the cylinders that are normally connected to the MGPS supply source are filled to 200 bar(g), but higher-pressure cylinders are now being made available to improve the efficiency of the system. The use of higher pressure cylinders means that the cylinders connected to the MGPS need to be changed less frequently, improving system efficiency.

CMO is only used as a primary supply source for the MGPS where the demand is relatively low, as the workload of changing cylinders on the changeover cylinder manifold, with higher demands, can become unmanageable.

The changeover manifold consists of two banks of cylinders, with one bank on-line and the other as standby. The number of cylinders connected to the auto-changeover manifold system determines the frequency of cylinder changeover and the ability for the manifold to continuously supply the MGPS. Although the manifold changes over automatically, the changeover period needs to be controlled (by design) to enable there to be sufficient time and manpower to enable the empty cylinders to be disconnected and full ones fitted.

However, CMO may be used as the secondary or emergency source of supply, as their use is likely to be for a relatively short period for when the primary source of supply is not available for use (for maintenance or due to system failure). However, the secondary and emergency systems need to be able to supply the design flowrate when in use.

A benefit of CMO when used as a supply source for the MGPS, unlike MLO (which needs to be refilled because of evaporation loss from the storage tank due the cryogenic liquid boiling), there are no losses from the cylinders, allowing them to be retained indefinitely until the product is used (or it passes its expiry date).

CMO can also be supplied in cylinder bundles, where a number of cylinders are manifolded together in a frame and fitted with a single outlet valve. These only require a single connection to the changeover system, reducing the time to exchange cylinders. However, this type of package is normally used as a reserve supply source as bundles require suitable equipment to manoeuvre the manifolded unit into place.

CMO Responsibilities

MARKETING AUTHORISATION HOLDER (MAH)

The **MAH** is responsible for:

- the quality of the product at the outlet of the cylinder.
- supplying information about the safety and efficacy of the product using the approved indications for the CMO (SmPC and Patient Leaflet).
- all the production and distribution steps in the process, up to the point where the product is supplied to the HF cylinder storage area.
- provision of information for training HF staff to ensure that the HF is aware of the safety requirements for the storage and handling of CMO cylinders and how to connect them correctly to the supply system of the Medical Oxygen MGPS.
- the maintenance and repair of the cylinders and the associated testing to comply with the TPED.

As the 'owner' of the cylinder packages, the MAH is responsible for ensuring that they comply with the technical requirements of **Transportable Pressure Equipment Directive** (TPED, 2014/68/EU).

HEALTHCARE FACILITY (HF)

The **HF Pharmacist** is responsible for:

- ensuring that the CMO cylinders are supplied by an approved MAH
- the quality of the gas supplied from the MGPS terminal outlets, taking account the suitability and maintenance of the MGPS.
- obtaining the relevant information (SmPC and Patient Leaflet) from the MAH
- ensuring there is no risk of cross contamination between other MGPS's on site and no potential for air ingress to the system.
- CMO cylinders are appropriately stored, stock rotated and used within their expiry date.

There are no requirements for the HF Pharmacist to perform any testing or maintenance on the cylinders supplied.

The **HF Technical Department** is responsible for:

- training the personnel to ensure CMO cylinder packages are handled correctly.
- changing of cylinders on the supply source changeover manifolds to ensure a continuous supply to the MGPS for patient use.
- maintenance of the changeover manifold systems and any associated equipment.

Features of Compressed Medical Oxygen used as a MGPS Supply System

When choosing the supply system for the Medical Oxygen MGPS, CMO offers several features that can be considered by the HF when selecting the appropriate source for the primary, secondary and emergency source of supply:

OXYGEN AVAILABILITY

- CMO is only a suitable source of supply for a Medical Oxygen MGPS if there is a licenced supplier available, where the HF is within the agreed distribution area of the supplier.
- CMO is a suitable supply source for the primary, secondary and emergency systems for the Medical Oxygen MGPS. However, as it requires the HF to change over cylinders on the manifold, it is only considered as a suitable supply source for primary and secondary systems where the HF has the resources available to change over cylinders frequently
- CMO can be used as the emergency supply source as, providing cylinders are connected correctly, there is no risk of product loss from the system when it is in a standby condition.
- The CMO supply source requires to be located in a suitable building to keep the cylinders and associated equipment in a suitable condition. The building needs to be sized to enable the cylinders to be connected to the changeover manifold and sufficient space to store a reserve supply of cylinders.
- The size of the changeover manifold is determined by the predicted average daily demand, the variability of the HF's use of Medical Oxygen and the capacity of the cylinders used on the manifold. Its output is also dependent on the design of the changeover manifold control panel.

- The HF is responsible for ensuring that the CMO supply source changeover manifold and control panel is designed to meet the maximum product demand and design flowrate of the MGPS.
- When CMO is selected as the supply source for the Medical Oxygen MGPS, its ability to meet increases in the HF's demand and flowrates can be met by adding additional cylinder connections to the manifold and reviewing the capacity of the manifold control panel.
- The cylinder storage area must be large enough to hold the required stock of cylinders, allowing for suitable segregation of the different products and the full and empty cylinders. The HF is responsible for the storage of the cylinders and their stock rotation.
- There should always be suitable access for the delivery vehicle to deliver cylinders to the cylinder store.
- The HF is responsible for ordering replacement cylinders to ensure they have sufficient product for continuous supply
- The MAH is responsible for ensuring they have sufficient cylinders available to meet the demand of the HF. The MAH is normally responsible for delivering the cylinders on time to the HF site.
- The HF can instal additional secondary and emergency sources of supply at separate locations to provide more reliability to the system.

PRODUCT QUALITY

- Each CMO cylinder is certified by the QP to ensure the quality level of the CMO, and the assay meets the relevant Pharmacopoeia specification (at least 99.5%), requiring no further approval by the HF Pharmacist.
- The MAH takes the responsibility for the quality, safety and efficacy of the CMO product.
- The quality of the Medical Oxygen supplied from the CMO cylinder remains constant, irrespective of the HF's flowrates.
- Where CMO is used as a secondary or emergency supply source for the MGPS, the quality of the gas in the cylinders is compatible with the quality of the MLO used as the primary supply source, allowing it to be used as the supplementary supply for the MGPS, at the appropriate product quality.
- As the CMO cylinders are maintained at a positive pressure, there is no risk of contamination of the product whilst it is being stored, allowing it to be used up to its expiry date.

CLINICAL USE

- The high specification for the assay of the CMO allows the Medical Oxygen to be used for all clinical indications and all types of medical equipment (such as anaesthetic machines and ventilators).
- The CMO can be used to calibrate the medical devices used to administer the gas due to its product specification being greater than 99.5%.

MAINTENANCE AND OPERATION

- The CMO MAH (and not the HF) takes the responsibility for the maintenance of the CMO cylinders supply systems. This also covers the compliance with the Transportable Pressure Equipment Directive.
- The HF has the responsibility for maintaining the equipment associated with the CMO supply source.
- As the CMO cylinders are filled up to 300 bar, there is no requirement to add any energy to the supply the gas to the MGPS.
- It is the HF's responsibility to ensure that the Medical Oxygen MGDS ability to manage the flowrate and the quantity of gas available online to ensure availability of the product and the flowrates required for the facility up to the capacity of the MGPS is under the responsibility of the HF,
- In the event of a failure of the MGPS, CMO cylinders can be used to administer product directly to the patient.
- CMO cylinders can also be used for back-feeding into the MGPS when maintaining the pipeline system.
- CMOs are best suited as a supply source for ambulatory /portable use, especially when the cylinder is fitted with a VIPR.

ON-SITE OXYGEN PRESSURE SWING ADSORPTION (PSA) PLANT

Section Summary:

Pressure Swing Adsorption (PSA) plants can be used as an alternative source of supply for the Medical Oxygen MGPS, using a plant that is installed and run on the HF's site. As the PSA plant may be the only Medical Oxygen source of supply available to the HF, its use must be strictly controlled due to the fact that the Oxygen produced is supplied directly to the MGPS without being batched and tested before use.

Depending on the design of the plant, it produces the Medical Oxygen to the appropriate grade, using zeolites and molecular sieves in adsorption bed(s) to remove the nitrogen and argon from ambient air, producing oxygen at concentrations varying between 90% and close to 100%.

The concentration of oxygen is dependent on the plant design and its output (relative to the specified design output) in order to comply with the relevant pharmacopoeial specifications, The plant capacity should be designed to meet the maximum demand for the HF to maintain the oxygen concentration within the specification limits. As the plant is using ambient air as its starting material, the HF is responsible for risk assessing the PSA plant design and installation to assess the potential for contaminants in the ambient air that could impact on the quality of the oxygen produced.

Where PSA plants are used as the supply source for the MGPS, the risk assessment should take into account the need for three independent sources of supply oxygen, all of which are designed to meet the daily demand for the MGPS at the maximum design flow requirements for the HF. It also needs to consider whether the electrical supply for the plant is compliant with the requirements to manage single fault conditions.

As the PSA Oxygen is produced on the HF site and only intended for HF use, the HF Pharmacist is responsible for the quality of the gas being delivered to the patient via the MGPS. An MA is not required to cover the PSA Oxygen used on site, but as it is considered as a medicinal product, it must comply with the requirements set out in the general monograph for Pharmaceutical Preparations[1].

In Europe, there is no clear regulatory status for Oxygen from a PSA plant.

The HF Pharmacist is also responsible for ensuring that the plant operation and the product testing follows the requirements for Good Manufacturing Practice, as required by the national Regulatory Authority, as well as being responsible for the indications and contra-indications for which the products can be used for patient treatment.

Where alternative sources of supply are used as the secondary or emergency source of supply for the MGPS, the HF Pharmacist should consider the consequences of changing the product specification with respect to patient treatment. The traceability of the product supplied and the responsibilities for pharmacovigilance reporting also needs to be considered.

PSA Manufacturing Process

An alternative source of supply for Medical Oxygen MGPS is for the HF to install an Oxygen PSA plant to produce the gas on site.

The Oxygen PSA plant uses ambient air as its starting material and passes it through adsorption bed(s) containing zeolites and molecular sieve material in order to separate the oxygen from the ambient air, producing an oxygen supply that can vary between 90.0% and up to 100%, dependant on the plant design and the MGPS demand.

Conventional Oxygen PSA plants utilise a single stage adsorption bed system which can produce oxygen that complies with the European Pharmacopoeia monograph for Oxygen 93%, where the monograph allows the oxygen content to vary between 90% and 96%. The single stage PSA plant does not remove the argon from the ambient air (which represents approximately 4% of the PSA oxygen supply), with the balance of the gas being nitrogen.

Further developments in PSA plant design have introduced plants with a secondary adsorption bed (containing activated carbon) which can remove the argon remaining in the oxygen from the first stage adsorbers, producing oxygen to a higher quality. The Oxygen 98% European Pharmacopoeia monograph allows the oxygen concentration to vary between 96% and 100%.

A key factor when using a PSA plant on an HF site is that the HF becomes the manufacturer of the PSA Oxygen and that the HF Pharmacist is responsible for the quality of the gas produced and delivered to the patient by the MGPS. As the oxygen is produced on-site, it is considered a pharmaceutical preparation, requiring the manufacture to follow the procedures set out in the general monograph for Pharmaceutical Preparations[1].

As the product is produced and immediately distributed for patient use via the MGPS, the procedures used for testing and releasing the product for patient use require careful consideration.

A feature of PSA plant is that the oxygen concentration is dependent on its output, where it exceeds the plant's designed output, and can lead to oxygen concentrations falling to below the specified monograph limits. It is very important that the plant capacity is designed to meet the maximum flowrate requirements for the HF so that the oxygen concentration will remain within the specification limits, taking account of any planned increases in Medical Oxygen demand over the life of the plant.

Although oxygen at 90% is adequate for most patients suffering from respiratory disease, where the oxygen is administered via a medical device that monitors the quality of the gas delivered to the patient (such as patient ventilators and anaesthetic machines), large variations in the product quality can have an adverse effect on both the device operation and the patient's treatment. There are also indications where high argon content may not be suitable for the treatment of some patients. When considering whether an HF should instal a PSA plant, the HF's risk assessment should consider these types of issues before deciding whether a PSA plant is suitable for the HF's use.

There are situations where the only source of supply of Medical Oxygen is from a PSA plant, and in these circumstances the HF Pharmacist should ensure that the HF's clinical staff are aware of the implications of using PSA Oxygen for treating patients.

PSA Plant Design and Installation

A major difference when using a PSA plant as the supply source for a MGPS is that the plant has a finite capacity and only has a limited capability to manage increases in demand. This is especially relevant where the increase in demand is due to long term increases in patient treatment (rather than short term requirements). As the PSA plant is often chosen as a suitable source of supply where other supply sources are not available, it is necessary to ensure that the capacity of the plant is set so that it can manage any increases in patient demand over the expected lifetime of the plant.

In order to manage single fault conditions with the supply sources, the Medical Oxygen MGPS should have three independent Medical Oxygen supply sources. Each supply source should be capable of meeting the maximum demand and flowrate conditions (and not having to use the secondary or emergency supply source to supplement the output of the primary supply source to meet the peak demands). It is possible to fill high pressure cylinders using the excess gas when the MGPS is not using the plant output by compressing the gas into cylinders and allowing them to supplement the supply when the demand increases, but this depends on the number of available cylinders and the duration f the high flowrate conditions. It should also be noted that the filling of Medical Oxygen cylinders can present a number of risks to the HF, where the handling of high pressure oxygen can lead to serious incidents.

When developing the PSA plant design, it is also necessary to ensure that the scope of the risk assessment includes a review of the potential quality of the ambient air in the area where the air compressor air intake will be installed. This is to identify any additional potential contaminants that are likely to be present in the ambient air, and the need to monitor the finished product for their presence. Typically, the risk assessment needs to review location of the air intake, the industries within the locality of the HF and the likelihood of them venting contaminants into the ambient air and the location of vehicles that could lead to higher than normal levels of carbon monoxide. The identification of any additional potential contaminants that could be present, which would adversely impact on the quality of the PSA Oxygen produced, will impact on the necessary quality control procedures to manage their control.

Dependant on the variability in the demand for oxygen for the MGPS, there are several options that can be adopted to ensure adequate supplies for patient treatment. The basic throughput of the plant is determined by the sizing of the air compressor that controls the maximum amount of air that can be processed by the plant. A standard feature of PSA plants is the use of a compressed air buffer to allow the air compressor to run at a constant throughput when the demand is varying, allowing the buffer to be used to supplement the compressor during high flow conditions. However, the adsorption beds need to be sized to allow for the maximum throughput, including any variability

of the MGPS demand to ensure the PSA Oxygen assay does not go outside the pharmacopoeia specification. A high pressure buffer, using high pressure cylinders filled using the excess product produced by the plant when the throughput is low, can be to supplement the supply to the MGPS, but the capacity of the buffer is a limiting factor. The use of high pressure cylinders on the HF site also adds to the HF's responsibilities to maintain the cylinder and comply with the regulatory requirements, such as the TPED and PED regulations in Europe.

As with all supply sources for the Medical Oxygen MGPS, to be compliant with the principles specified in ISO 7396-1, there is a need to have three sources of supply to deal with single fault conditions, to ensure that the MGPS system can always meet the maximum potential patient demand. Where other sources of Medical Oxygen are not available, there is a requirement for three PSA plants to be installed, with each plant being capable of supplying the full demand for the MGPS.

It is also necessary to ensure that the electricity supply used to operate the PSA plant is also compliant with the requirements for single fault conditions. This means that there should be available alternative supplies to ensure that an adequate electrical supply is always available to run the plant, even under single fault conditions.

Multiple Supply Sources

Ideally, when using an Oxygen PSA plant on site, the most appropriate arrangement is that there should be three supply systems, each consisting of an independent PSA supply sources, delivering gas to the same specification requirements and capable of producing sufficient product to maintain supplies to the MGPS, irrespective of the planned time that they may be in use. for the specified duration. This arrangement could utilise either three separate plants or a combination of plants and high pressure cylinder storage, where the cylinders are filled using excess gas produced and compressed into cylinders. This avoids any issues with respect to creating large variations in the assay of the Medical Oxygen being supplied (up to the limits in the Pharmacopoeia specification). Using three PSA Oxygen plants addresses any issues concerning the quality of the gas being used to cover any specific pharmacovigilance responsibilities. It should be noted that the secondary or emergency supply source should not be used to supplement the primary source under high flowrate conditions, bit used to maintain supplies to the MGPS under single fault conditions. However, it is important for each supply source to be designed so that it is capable of supplying the total demand for the MGPS system, which potentially could be at the maximum design flowrate.

If an Oxygen PSA plant is used for the primary source of supply and a different type of supply sources is used for secondary and/or the emergency source, the appropriate mode of operation should be followed to avoid issues concerning the quality of the gas supplied to the MGPS and the responsibilities concerning the efficacy of the product and the appropriate pharmacovigilance responsibilities where there is a need to report an adverse event.

In all cases, the HF Pharmacist is responsible for the quality of the gas being supplied to (and from) the MGPS and any notifications that are required to alert the HF's clinical staff of the potential change in the assay of the Medical Oxygen. It is acceptable that there may be a short term variation in the assay of the Medical Oxygen where a different supply source is brought onto line, as the new gas is used to purge the pipeline system.

Where a decision is taken to have different supply sources for the Medical Oxygen MGPS, it should be noted that:

- Some national Regulatory Authorities do not permit the mixing of two different Medical Oxygen supply sources for the MGPS
- The HF Pharmacist would be responsible for the ultimate quality of the gas being available for administering to patients as it would be considered as an additional Pharmaceutical Preparation that had been suitably risk assessed prior to its use.
- The HF Pharmacist is responsible for reporting any adverse event related to the pharmacovigilance requirements.

The following schematic shows a typical PSA Plant with its main process steps:

AIR COMPRESSION

Oil lubricated compressors are normally used to compress the atmospheric air. the is initially filtered to remove any particulate and then compressed to a suitable pressure to achieve separation in the adsorber beds.

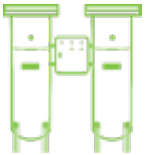
Normally, the air is compressed to a pressure that is high enough so that the gas supplied from the plant does not need to be compressed further before being fed to the MGPS.

PRE-PURIFICATION

Prior to passing the compressed air through the adsorber beds, it is dried using a molecular sieve and the oil from the compressor removed, using a carbon filter.

The cleaned compressed air is then stored in a buffer vessel before being fed to the adsorber bed(s).

ADSORPTION



The cleaned compressed air is continually fed through adsorber bed (A) until the beds cannot adsorb any more nitrogen (and the oxygen concentration starts to fall). At this point, the adsorber bed is 'changed over' and the compressed air is passed through the second adsorber bed (B).

The first adsorber bed (A) is then regenerated by passing heated air back through the bed to release the adsorbed nitrogen (and other removed contaminants) from the zeolite material.

STORAGE/SUPPLY TO MGPS

The oxygen produced from the adsorber bed(s) is fed to a buffer vessel.

This enables the PSA plant to run at a consistent throughput, as well as allowing for variations in the demand for the MGPS.

As the gas is fed to the buffer vessel, its quality is continually monitored for oxygen content, using a paramagnetic oxygen analyser.

Generally, as the demand for oxygen increases, the PSA plant can adjust its throughput by passing more gas through the adsorber beds. However, this will eventually lead to the oxygen content of the gas supply reducing, eventually to below the lower specification limit. The oxygen content of the supplied gas should be continually monitored to ensure that the gas stays within the specification limits and is used to manage the adsorber changeover period.

The quality control of the process uses a separate oxygen analyser to ensure that the process remains within the specification limits, as well as continually analysing the supply gas for Carbon Monoxide, Carbon Dioxide and moisture to ensure that it meets the relevant pharmacopoeia specification.

The double stage PSA plant uses the same adsorber beds for the initial separation of the ambient air but has an additional step where an activated carbon adsorber is used to remove the argon (and the residual nitrogen from the first stage adsorber). The second stage of the process allows the oxygen purity to be increased to between 96% and 100%.

Oxygen PSA Responsibilities

OXYGEN PSA PLANT MANUFACTURER / INSTALLER

The **Oxygen PSA plant manufacturer / installer** is responsible for:

- the design of the plant so that it can meet the relevant pharmacopoeia specifications at the HF's design throughput under maximum flowrate conditions.
- assisting with the risk assessment to ensure that the Oxygen PSA plant is correctly designed and the quality control testing regime established to address any specific requirements.
- the necessary documentation of the plant to demonstrate its approval as a medical device, dependent on the national Regulatory Authority requirements.
- the necessary documentation covering the operating and maintenance procedures to ensure the safety operation of the pant and the quality of the product produced
- providing suitable training / training material for the safe operation of the plant by HF personnel.

Where the Oxygen PSA plant is used to provide excess gas for compressing into manifolded high pressure cylinders to help supplement the output of the plant, the PSA plant manufacturer will be responsible for supplying suitable cylinders that comply with the technical requirements of Transportable Pressure Equipment Directive (TPED, 2014/68/EU) and Pressure Equipment Directive (PED, 2014/68/EU).

HEALTHCARE FACILITY (HF)

The **HF Responsible Pharmacist** is responsible for:

- Ensuring the supply of Medical Oxygen from the HF on-site Oxygen PSA plant (and its operation) is compliant with the general requirements associated with producing a medicinal product (as described in the Ph.Eur. monograph on Pharmaceutical Preparations[1]
- Carrying out the initial risk assessment for the Oxygen PSA plant, to ensure that the testing requirements take account of the environment where the PSA plant air intake is located.
- Identifying the appropriate analytical requirements to monitor the potential contaminants (not normally found in atmospheric air), identified from the initial risk assessment that could potentially be present from local industrial sources.
- Establishing the QMS system covering the GMP compliant operation of the Oxygen PSA plant and defining the quality control requirements to ensure compliance with the relevant pharmacopoeia monograph(s), taking account of the results from the initial risk assessment.
- Minimising the risk of supplying out of specification (OOS) product.
- Defining the testing regime and quality control requirements to document and control the quality and traceability of the gas delivered to the patient.
- Reporting any adverse events related to the Oxygen PSA plant output in the HF's Pharmacovigilance and Materiovigilance systems (where the Oxygen PSA plant is classed as a medical device).
- the suitability of the gas supplied from the MGPS, if different types of supply sources are used, to ensure the quality and efficacy of the gas and that there is no impact on patient safety when used with all devices used for its administration.

The **Healthcare Facility Management** is responsible for the following:

- Carrying out a formal risk assessment to ensure if each Oxygen PSA plant is designed to meet the HF's maximum predicted flowrate, even under pandemic situations and single fault conditions.
- Ensuring the Oxygen PSA plant operations and maintenance procedures are clearly defined and documented, in line with the plant manufacturer's Instruction for Use.
- Maintaining and calibrating the analytical and plant instrumentation.
- Training the HR staff to correctly to operate and maintain the plant using information provided by the Oxygen PSA plant manufacturer.

Features of On-Site Oxygen PSA Plant used as a Supply Source for the MGPS

When choosing the supply system for the Medical Oxygen MGPS, Oxygen PSA plants installed on the HF's site offer several features that can be considered by the HF when selecting the appropriate source for the primary, secondary and emergency sources of supply:

OXYGEN AVAILABILITY

- The Oxygen PSA plant installed on the HF's site may be the only option for a suitable supply source for a Medical Oxygen MGPS if there are no licenced MLO or CMO suppliers available within the area.
- As the oxygen PSA plant is produce Medical Oxygen on site, it is not subject to product availability or distribution issues from a third party supplier, especially in remote locations.
- Failure to size the Oxygen PSA plant correctly will lead to a reduction in the assay of the Medical Oxygen when the demand exceeds the design flowrate.
- Medical Oxygen buffers can be used in conjunction with the Oxygen PSA supply system to assist with the requirement to supply sufficient product to meet patient demand, without affecting the purity of the gas within the specification limits. However, the size and the management of the buffer system needs to ensure that there us always sufficient product available to supplement the supply system whenever it is required.
- There are no risk associated with shortage of supply of starting material, as ambient air is used as the supply the Oxygen PSA plant.
- Where PSA supply sources are used, each PSA plant must be provided with a reliable source of electricity that can maintain supplies even under single fault conditions. A backup electricity generator may be required to maintain supplies. Where supply sources are installed at remote locations, a reliable independent electricity supply source is required for each plant location.

PRODUCT QUALITY

- As the output from the on-site Oxygen PSA plant is not 'put on the market', it does not require an MA to cover the safety, efficacy and quality of the product used for patient treatment. The HF Pharmacist is responsible for preparing this information and providing it the relevant HF staff.
- The HF Pharmacist is responsible for ensuring that the plant operation is compliant with the general requirements associated with producing a medicinal product (as described in the Ph.Eur. monograph on Pharmaceutical Preparations[1]
- As the Medical Oxygen produced by the PSA plant is not batched and released prior to it being fed to the MGDS, the product must be continuously analysed for assay and for any contaminant specified by the relevant Pharmacopoeia monograph or potential contaminant identified during the initial risk assessment.
- The oxygen concentration from the Oxygen PSA plant is dependent on its output, where increases in the output can lead to a lower oxygen concentration (hence the allowance in the monograph for variation in the specification levels).
- The Oxygen PSA plant should be validated to demonstrate that at its maximum design flowrate, the quality of the Medical Oxygen continuously produced meets the lower limits of the product specification. The maximum design flowrate should take account of any increases due to any planned growth, even under pandemic conditions.
- If the analysis of the product goes out of specification, the supply of the gas should be stopped immediately, and an alternative source started to maintain supplies. Where there is a finite time to start the secondary supply source, means should be provided to store sufficient product to maintain supplies until the secondary/emergency supply source is producing sufficient product of the correct quality.

CLINICAL USE

- With the variable specification for the assay of the gas produced by the Oxygen PSA plant, the gas should only be used for medical equipment (such as anaesthetic machines and ventilators) that are specifically designed for use with PSA Medical Oxygen. The gas should not be used with devices where it is used to calibrate the medical device.
- As the Medical Oxygen produced by the Oxygen PSA plant on-site is not covered by an MA, the HF Pharmacist should inform the clinical staff the clinical indications where the PSA Oxygen can be administered to patients and the specific indications where it is contra-indicated.

MAINTENANCE AND OPERATION

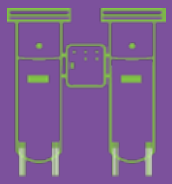
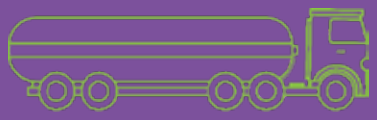
- As an Oxygen PSA plant has many moving parts, the maintenance of the plant has to be correctly managed to minimise impact on the availability of each system. Adequate spare parts need to be available locally to minimise any downtime due to component failure.
- The HF takes the responsibility for the maintenance of the Oxygen PSA supply sources supply systems. This also covers the compliance with the Transportable Pressure Equipment Directive. The HF
- The HF has the responsibility for maintaining the equipment associated with the CMO supply source and calibrating the quality control and process instruments.
- It is the HF's responsibility to ensure that the Medical Oxygen MGDS ability to manage the flowrate and the quantity of gas available online to ensure availability of the product and the flowrates required for the facility up to the capacity of the MGPS is under the responsibility of the HF,
- The noise levels associated with the PSA plant may be significant and may need to be addressed, dependent on the plant location. By installing the plant in a building may reduce the impact of noise and provide a suitable location for the plant.

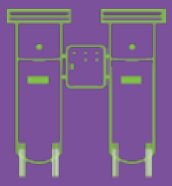
COMPRESSING OXYGEN

- The capability to use any excess gas from the plant to be filled into high-pressure cylinders can provide additional storage of gas for use when the flowrates are high. This gas can be produced by running the plant at a constant throughput so as to maintain a stable product quality level from the Oxygen PSA plant.
- Irrespective of the regulatory requirements, extreme care is needed to ensure that the specification and condition of the cylinder package does not jeopardise either patient safety or the safety of the person filling the cylinder. This covers both the specification of the valve and cylinder shell and the internal and external condition of the package.
- Where excess Medical Oxygen from the Oxygen PSA plant is compressed into high-pressure cylinders, the HF is responsible for providing training to the HF personnel about the risks associated with handling and compressing oxygen and in the procedures for filling Medical Oxygen cylinders. The procedures need to address the risks associated with compressing oxygen and the need for pre-fill examination and suitable cylinder preparation before commencing any filling. Annex 6 of the EU GMP Guide gives specific advice about the GMP requirements for filling Medical Oxygen cylinders.
- The HF will be responsible for maintaining the high-pressure cylinders, as required by PED and TPED requirements.
- Individual cylinders filled on-site can only be used on the site where they are filled. If high-pressure cylinders are used to supply other HFs on different sites, the HF is responsible for obtaining an MA to cover the supply and producing the relevant documentation for the Medical Oxygen, including the SmPC and Patient Leaflet.
- Where the high-pressure cylinders are used to store the excess gas to supplement the Oxygen PSA plant output, they need to be connected permanently to the Oxygen PSA supply source. The HF Technical Department will be responsible for maintaining the cylinders and associated equipment to meet the PED requirements.

APPENDIX 1 COMPARISON TABLE

The following comparison Table highlights the different features and responsibilities for the three different supply source normally used for supplying Medical Oxygen to the MGPS.

Feature / Supply Source	PSA	MLO	CMO
			
Starting Material	Ambient air	Ambient air	Approved liquid oxygen
Purity	At least 90,0%	At least 99,5%	At least 99,5%
Impact of Demand on Purity	Oxygen concentration is dependent on output, where higher output leads to lower concentrations.	The quality of the product supplied from the storage tank is the same irrespective of the flowrates that are required by the HF.	The quality of the product supplied is the same irrespective of the flowrates that are required by the HF.
Back Up Electricity Requirement	Required to power compressors, adsorbers, and control systems.	Not required.	Not required
Supply Source Storage	Short term storage (buffer vessel) and potentially high-pressure cylinders.	Long term storage on site. Highly insulated low loss cryogenic storage tanks.	Long Term Storage. High-pressure cylinders with spare cylinders stored on site.
Regulation	Considered a pharmaceutical preparation and should comply with the general monograph for Pharmaceutical Preparations[1]. Regulatory Authorities should take measures to ensure that specific guidelines address the continuous on-site manufacturing of particular medicinal products, such as gases for medicinal use, when it is carried out in the hospital premises under the responsibility of the hospital pharmacist.	MA held by supplier /issued and regulated by national Regulatory Authority.	MA held by supplier /issued and regulated by national Regulatory Authority.

Feature / Supply Source	PSA	MLO	CMO
			
Responsibility for Quality	HF Responsible Pharmacist responsible for the quality of gas produced and supplied to MGPS.	MAH responsible for product quality in HF storage tank. HF Pharmacist responsible for product quality at MGPS outlet.	MAH responsible for quality of gas in cylinders. HF Pharmacist responsible for product quality at MGPS outlet.
Maintenance	HF responsible PSA plant maintenance, Maintenance requirements significant due to PSA plant having many moving parts.	MLO supplier responsible for maintenance of supply system Maintenance requirements minimal due to lack of moving parts.	CMO supplier responsible for cylinder maintenance, HF responsible for supply source maintenance.
Delivery Logistics	No deliveries required as oxygen is manufactured on-site.	Requires regular deliveries by road tanker, frequency determined by demand and storage tank capacity, monitored by supplier using telemetry system.	Requires regular deliveries of cylinders, frequency determined by product demand and the number of cylinders connected to changeover manifolds.
QMS	HF is responsible for establishing and managing a GMP compliant QMS, covering the operation of the plant and controlling the quality of the supply gas.	MLO MAH is responsible for establishing and managing a GMP compliant QMS, covering the operation of the plant and controlling the quality of the supply gas.	CMO MAH is responsible for establishing and managing a GMP compliant QMS, covering the operation of the plant and controlling the quality of the supply gas.
Reliability	Oxygen supply dependent on plant operating. Limited backup stocks held to allow for plant failure and changeover to replacement plant. Possibility of using excess gas not delivered to the MGPS to fill cylinders using GMP compliant procedures. Extreme care is needed to assure patient safety and the safety of the person filling the cylinder.	MAH holds significant volume of MLO for HF supply in the event of an emergency. Minimum levels of product maintained in storage tank to allow for delivery failure. Use of telemetry to maintain stock levels. Possibility of having primary, secondary and emergency sources of supply in separate locations.	MAH holds significant number of CMO cylinders for HF supply. HF cylinder stock levels provide for additional security. Possibility of having primary, secondary and emergency sources of supply in separate locations.

APPENDIX 2 - WHAT IS OXYGEN (O2)

Introduction

The word oxygen comes from the Greek "-ὀξύς" (oxys), "acid" and "-γενής" (-genes), "producer", literally "generator". Oxygen is the most abundant element on Earth, and after hydrogen and helium, it is the third most abundant element in the universe. Oxygen constitutes (by weight) 46% of the earth's crust (oxides, silicates, etc.), 89% of the earth's water and 62% of the human body (in the form of molecules). In its diatomic form (O2), it constitutes about 21% of the Earth's atmosphere and is a tasteless, odourless and colourless gas, essential for life[1].

Chemical-physical properties

- Oxygen is the chemical element with the symbol O (in its monatomic form) and atomic number 8.
- Oxygen is a gas under normal atmospheric conditions (15 °C, and 1 atm).
- At atmospheric pressure and temperatures of -183°C, it liquefies, turning into a light blue liquid, slightly heavier than water.
- Oxygen is a highly reactive gas, which combines directly with most of the elements forming oxides according to the temperature conditions.
- Oxygen is essential for combustion and reacts violently with organic substances.
- In its diatomic form, it has two unpaired electrons which give it paramagnetic properties.
  This intrinsic property of oxygen has been used for the analytical instruments for measuring its content (oxygen assay) using a paramagnetic analyser (Ph. Eur. Current. Ed).
- Trace oxygen present in other gases can be measured using an electrochemical cell (Ph. Eur. Current Ed.) or through gas-chromatographic techniques.

PHYSICAL PROPERTIES	
Formula[2]	O_2
Atomic number[2]	8
Molecular Weight[2]	31.9988 g mole $^{-1}$
Molecular dimensions[2]	4.2-2.8 A
Ionization potential[2]	12.059 and V
Gas density[2]	1 .4289 Kg.m^3
Triple point[3]	T (° C): -218.799 Pressure (bar): 0.00152 Latent heat (kcal.kg $^{-1}$): 3,322
Boiling point[3]	T (° C): -182.97 Latent heat (Kcal.kg $^{-1}$): 50.869 Liquid density (kg.m $^{-3}$): 1141.0 Gas density (kg.m $^{-3}$): 4.475
Critical point[3]	T (° C): -118.574 Pressure (bar): 50.43 Density (kg.m $^{-3}$): 436.1)
Isotopes[4]	^{16}O: 99.759% (A.W. 15.9949g) ^{17}O: 0.037% (A.W. 16.9999g) ^{18}O: 0.204% (A.W. 17.9991g)

The following molecule phase diagram shows the transition phases for oxygen between solid, liquid and gas as a function of temperature (OK) and pressure (bar).

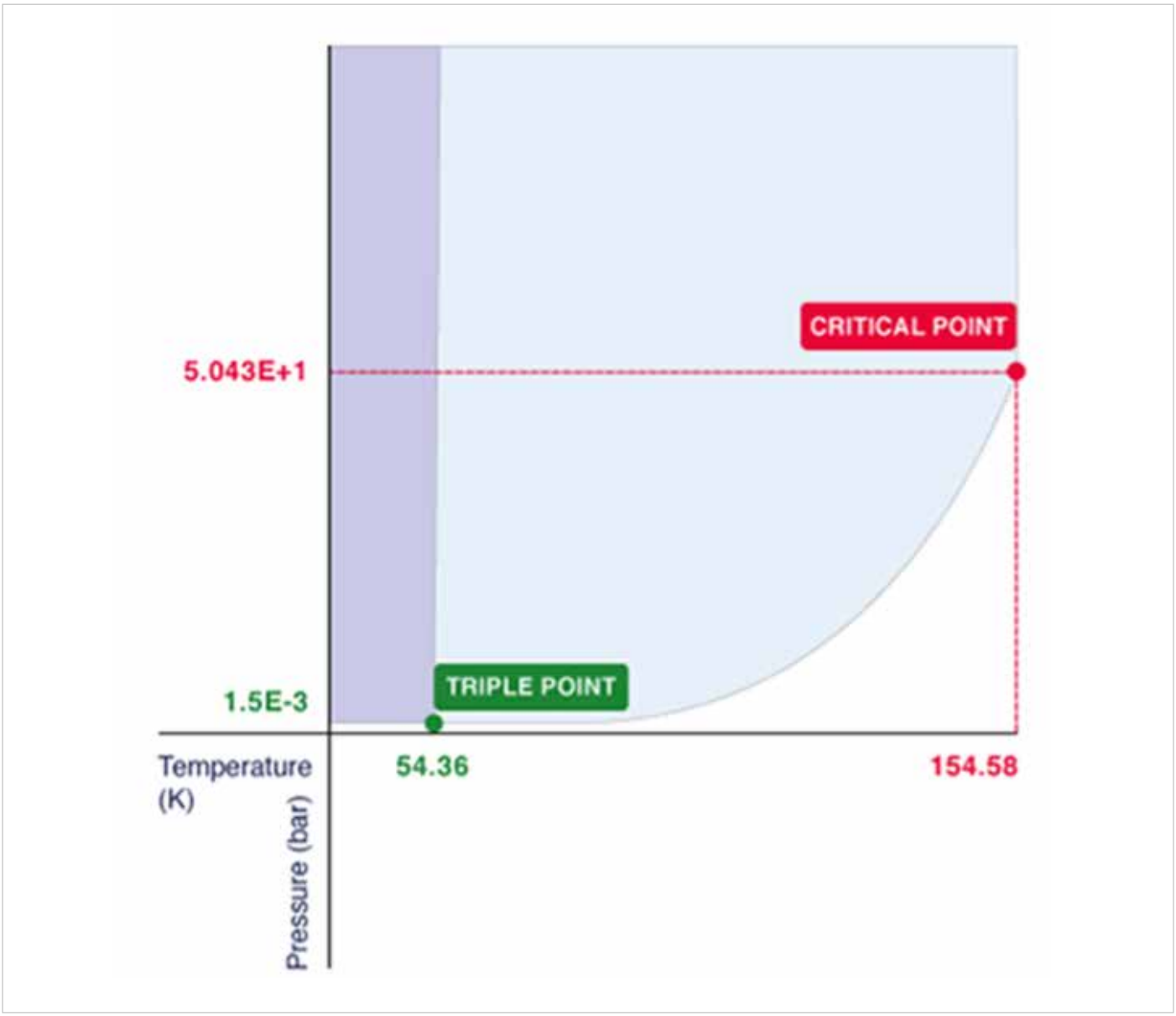


Fig 1 Molecular Phase Diagram for Oxygen

Outline of the history of oxygen

The existence of oxygen was documented for the first time in 1604 by Michael Sendivogius who in his work entitled "De Lapide Philosophorum Tractatus duodecim e naturae fonte et manuali experientia depromti" described a substance contained in the air referring to it as "cibus vitae"[5].

However, the discovery of oxygen came in 1771, when Carl Wilhelm Scheele, a pharmaceutical chemist, generated what he called "air of fire" obtained by burning mercury oxide, silver carbonate, magnesium nitrate and other nitrite salts[6]. Carl Wilhelm Scheele communicated his discoveries by letter to Antoine Lavoisier in 1774, without however documenting the discovery until 1775 when he published his work[6]. Meanwhile, on August 1, 1774, the British pastor Joseph Priestley, focusing sunlight into a glass tube containing mercury oxide, released a gas he called "deflogistic air"[7] of which he declared: *"The feeling of it to my lungs was not sensibly different from that of common air, but I fancied that my breast felt peculiarly light and easy for some time afterwards."*[8]. Because he first published his findings, Priestley is given the authorship of the oxygen discovery. However, it is with Antoine Lavoisier that oxygen is recognized as a chemical element; Lavoisier, thanks to the exchange of information he

had with Scheele and Priestley, was able to repeat their experiments with more sophisticated laboratory equipment. He called the odourless gas "oxygen" based on his belief that it was essential for all acids. He proposed the role of oxygen in the oxidation of metals and in respiration, demonstrating that it was absorbed by the body during the inhalation phase to allow cellular respiration through the combustion of organic substrates[6].

At the end of the 19th century, scientists realized that air could be liquefied and its components separated thanks to a compression and cooling process. In 1877 the Swiss Raoul Pierre Pictet, first, and the French Louis Paul Cailletet, later, announced that they had discovered a method for liquefying oxygen, even if the quantities were just a few drops[9]. Only in March 1883, two Polish scientists, Zygmunt Wróblewski and Karol Olszewski managed to liquefy oxygen for the first time in a stable state[10]. The first commercially viable process for producing liquid oxygen was developed independently in 1895 by the German engineer Carl von Linde and the British engineer William Hampson and consisted of lowering the air temperature to liquefaction and subsequently separating the gas according to their boiling points.

In 1902, the French physicist Georges Claude invented what still today is the procedure for obtaining liquid air and therefore preparing oxygen on an industrial scale. The air-cooling process consists of isenthalpic expansion, with only pressure reduction, followed by isentropic expansion, with production of work.

Oxygen in medicine

Oxygen was first used for therapeutic purposes in 1783, by a French doctor who treated a young woman suffering from tuberculosis by administering her oxygen for inhalation daily [11].

In 1799, in Bristol, the Pneumatic Institution, founded by Thomas Beddoes, James Watt and Humphry Davy, was the first to use the gas for what is now referred to as oxygen therapy. It was used to heal patients with asthma, paralysis and other diseases that ordinarily failed to heal [11]. Oxygen therapy developed during twentieth century, thanks to the rapid discoveries of its benefits and the technological advances that have allowed its clinical application. In the early twentieth century. A breakthrough in its clinical use was when John Haldane described the rationale behind oxygen therapy and a method of measuring oxygen content in the blood, when treating acute and chronic patients. During World War I, oxygen was also used to save the lives of many soldiers who were poisoned by phosphine gas, as well as treating them for trench nephritis or acute bronchitis [12].

The increase in survival due to the use of therapeutic oxygen was initially documented in 1928. However, it was not until the end of the 1960s, that a clinical study on patients with COPD (Chronic Obstructive Pulmonary Disease), showed the efficacy and benefits of the use of oxygen with patients suffering from chronic lung diseases[6]. This study initiated other randomised multicentre clinical trials using various oxygen-based therapies, including long-term administration. Among these, the most important was the NOTT trial (1974), which aimed to determine the duration of daily oxygen administration to maximise clinical benefits of oxygen. In the following years and up to the present day, numerous clinical trials have been conducted with the aim of highlighting the benefits of oxygen-based therapy on brain function[13], on pulmonary hypertension[14], in moderate hypoxia[15], during physical exercises[16], in transient hypercapnia[17] and in nocturnal desaturation[18].

In addition to the therapeutic use of oxygen, it is also used for life support of patients when they are not able to breathe normally. It is administered to critically ill patients, using a ventilator, to deliver the gas to patients unable to breathe normally, to maintain their blood gas level of oxygen. It is also used extensively in the operating theatre, where the oxygen is administered to patients undergoing major surgery, using an anaesthetic machine to deliver the anaesthetic agent with the oxygen. Oxygen is also used by the emergency services, where a person has undergone a major trauma, leading them unable to breathe normally.

Today, oxygen therapy is widely used in hospitals (both under normobaric and hyperbaric conditions), representing well over 95% of the volume of medicinal gases used by healthcare facilities. It is also now provided to patients at home who are suffering from respiratory disease, allowing them to have a more normal life at home during the onset of the disease.

Oxygen can also be administered to patients mixed with other medicinal gases for their treatment in hospital. When mixed with 50% nitrous oxide, it is used as an analgesic, providing short term pain relief. It is used extensively in maternity wards during childbirth, where its benefit is that it can be self-administer by the patient when they are in need of pain relief, but once the administration of the gas ceases, the patient can return to normal. Oxygen is also mixed with helium, where the helium is used to replace the nitrogen in normal air, allowing the gas to be breathed much easier due to the lower density of helium, this is used when patients have restricted airways, allowing them to get sufficient oxygen into their lungs with significantly less respiratory effort. Carbon dioxide can also be used as a mixture with oxygen (where the oxygen concentration is normally 5%) as a respiratory stimulant. It is also used to allow the expulsion of toxic molecules, (such as carbon monoxide) more quickly, when the patient s suffering from carbon monoxide poisoning.

Following the publication of the European Directive 2001/83 / EC and subsequent amendments, Medical Oxygen has been classified as a drug, therefore its production requires compliance with GMP and its marketing, requires obtaining the Marketing Authorization (MA).

APPENDIX 3 - CLINICAL ASPECTS WITH MEDICAL OXYGEN PRODUCED BY PSA

The clinical comparisons for the use of different grades of Medical Oxygen are given in the table below. It provides a comparison for Medical Oxygen produced by an ASU (where the oxygen assay is greater than 99.5%) and Medical Oxygen produced by an Oxygen PSA plant (where the oxygen assay can vary between 90% and 96%)

	MAIN INDICATIONS
OXYGEN ≥ 99,5 % (V/V)	**Normobaric oxygen therapy (oxygen therapy at normal pressure):** ■ Treatment or prevention of hypoxia and hypoxaemic conditions. ■ Treatment of cluster headache. **Hyperbaric oxygen therapy (oxygen therapy at high pressure)** ■ Treatment of serious carbon monoxide poisoning irrespective of the COHb content in the blood (in particular essential in patients who after exposition to carbon monoxide have lost consciousness, have neurological symptoms, cardiovascular failure or serious acidosis or pregnant patients). ■ Treatment of decompression sickness, or of air/gas embolism of a different origin. ■ As supporting treatment in cases of osteoradionecrosis. ■ As supporting treatment in cases of clostridial myonecrosis (gas gangrene).
OXYGEN 93 (90-96% (V/V))	As oxygen 93 is not a medicinal product under a MA there is no typical indication list available. However generally it may be used for the same indications as oxygen, but special care has to be taken and risks should be considered, especially where it is being administered by medical devices designed specifically for oxygen (99.5).

Main risks and considerations with oxygen administration

Oxygen therapy is a symptomatic therapy of hypoxaemia. The treatment should be as short as possible, under consideration of the pathophysiological processes of the disease.

During each longer-lasting oxygen administration in spontaneously breathing or mechanically ventilated patients an appropriate monitoring (pulse oxymetry and/or blood gas analysis) must be performed, to be able to assess the respiratory overall situation.

Normobaric oxygen therapy

There are no absolute contraindications for normobaric oxygen therapy.

Hyperbaric oxygen therapy

One absolute contraindication for hyperbaric oxygen therapy is an untreated pneumothorax, including a restrictively treated pneumothorax (without a chest tube).

Oxygen toxicity

Oxygen can be administered safely in the following concentrations, for the periods indicated:

- Up to 100% less than 6 hours
- 60-70% 24 hours
- 40-50% during the second 24-hour period

Oxygen is potentially toxic after two days in concentrations in excess of 40%.

Special Considerations when administering Oxygen 93

- For normobaric treatments the gas flow must be adjusted to achieve the target oxygen saturation, commonly monitored by pulse-oximetry (SpO2).
- Consider the potential accumulation of argon in anaesthesia systems.
- Consider the efficacy of the oxygen content 93% vs 100% in few special situations.
- When the intended therapeutic effect is critically dependent on 100% oxygen concentration, e.g. carbon monoxide poisoning *(Clinical Reference 3)*
- Consider the use in hyper baric oxygen therapy, in hyperbaric chamber as hyperbaric argon potentially could have sedative/anaesthetic action.

There are rare case reports of narcosis associated to argon gas under hyperbaric conditions (deep dive) *(Clinical Reference 4)*

Clinical considerations for the use of oxygen 93

- Consideration has to be given to the use of oxygen 93 for administration to patients for medicinal use, for the treatment and/or prevention of hypoxemia. It is intended as an alternative product to medicinal oxygen with a concentration of oxygen 100%.
- Oxygen 93 – concentrator oxygen - is commonly used for Long Term Oxygen Therapy for the oxygen enrichment of inspired air in patient with e.g. Chronic Obstructive Pulmonary Disease (COPD). The gas flow must be adjusted to achieve the target oxygen saturation, commonly monitored by pulse-oximetry (SpO2).
- Specialised literature and experts show different opinions on the use of oxygen 93 produced by a concentrator in life-threatening situations.

The following should be taken into account for the risk assessment that has to be conducted according to section 5.

Potential accumulation of argon in anaesthesia systems.

Argon is an inert gas and has no toxic effects. However, the use of low-flow anaesthetic techniques may result in accumulation of argon and the consequent dilution of oxygen and nitrous oxide in the circuit. Thus, there is a small but potential risk for dilution of gas in the circle system and subsequent inadequate anaesthetic gas concentration as well as hypoxic mixture. Multi-gas monitoring is thus essential, as in general recommended, when low/minimal flow is used with oxygen 93 as oxygen source for the fresh gas. *(Clinical References 1,2)*

Efficacy of the oxygen content 93% vs 100% in few special situations.

When the intended therapeutic effect is critically dependent on 100% oxygen concentration, e.g. carbon monoxide poisoning (Clinical Reference 3)

- Consider the use in hyper baric oxygen therapy, in hyperbaric chamber as hyperbaric argon potentially could have sedative/anaesthetic action.

There are rare case reports of narcosis associated to argon gas under hyperbaric conditions (deep dive) *(Clinical Reference 4)*

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Pharmaceutical preparations are considered a medicinal product.

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