

EIGA

MEDICAL OXYGEN IN HEALTHCARE FACILITIES



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

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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)



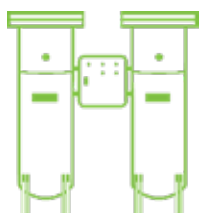
MLO is supplied to the HF as a cryogenic liquid by a tanker and stored on the HF site in a cryogenic storage tank and converting to a gas using an air heated vapouriser, as required to supply the MGPS.

2 Compressed Medical Oxygen (CMO)



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.

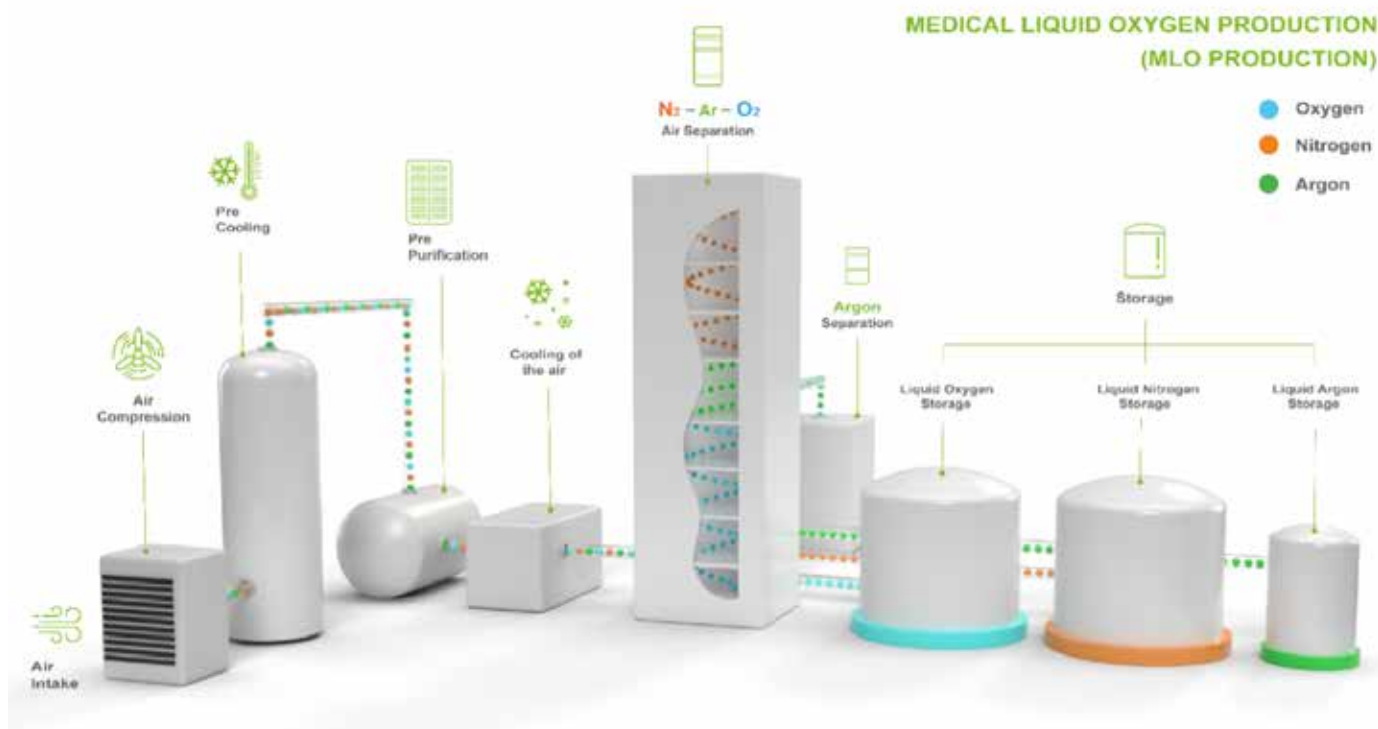
MLO Manufacturing Process

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 of 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 pre-cooled. 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.

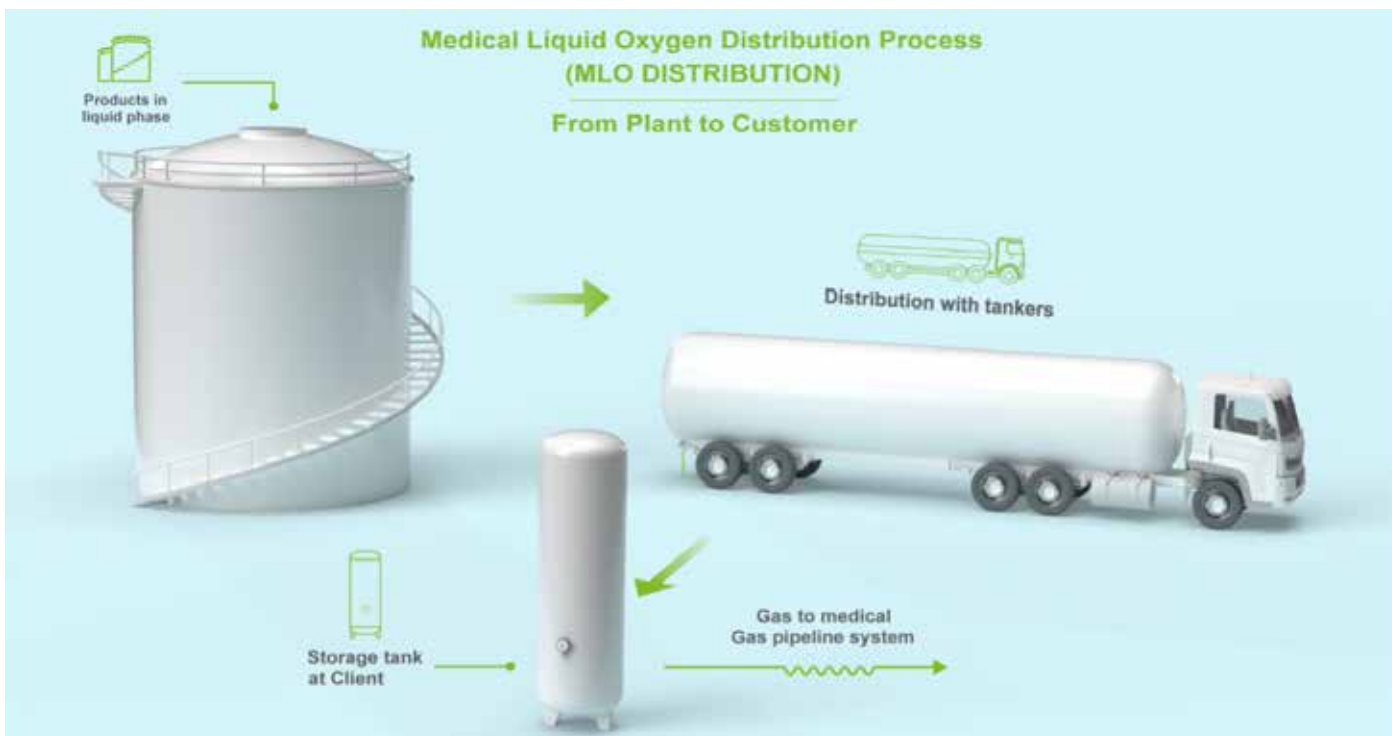
Argon is separated by taking an argon rich stream from the upper, low pressure column and then separating the argon in an additional distillation column. The crude argon produced is then purified further to produce a commercially pure product.

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.

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 Directive (PED), requiring them

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.

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 event 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 HF's, 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 HF's, 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.