

SAFE DESIGN AND OPERATION OF ON SITE GENERATION OF OXYGEN 93% FOR MEDICINAL USE

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ON SITE GENERATION OF OXYGEN 93% FOR MEDICINAL USE

Prepared by WG-15

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Amendments to 195/15

Section	Change
Title	Title change
1	General changes and new reference to the Medical Device Regulation
3.10	Definition change in line with the monograph Oxygen 93
4.1.5	Entire newly written paragraph
4.1.6	Entire newly written paragraph
4.3.1	Title change with reference to Configurations A and B
11	Updated references

Note: Technical changes from the previous edition are underlined

1 Introduction

Oxygen for medicinal use is a prime requirement for all healthcare facilities for both the treatment of patients with respiratory disease and for providing additional oxygen to patients being treated within the facility.

For those hospitals and clinics, where the demand is higher, oxygen is normally distributed throughout the facility using a medical gas pipeline system.

The design requirements for the supply source used to supply medical oxygen to the pipeline system are detailed in the standard, EN ISO 7396-1 *Medical gas pipeline systems; Pipeline systems for compressed medical gases and vacuum* [1]¹. Two different products are included in the standard:

- Medicinal oxygen supplied from liquid oxygen vessels and/or gaseous oxygen cylinders; and
- Oxygen 93 manufactured on-site within the healthcare facility, using an oxygen concentrator unit.

Medicinal oxygen supplied either in cylinders or as a cryogenic liquid, is required to be manufactured by an approved supplier with a manufacturer's licence (to demonstrate compliance with guidelines detailed in the European Commission's *Guide to Good Manufacturing Practice (GMP)*) [2]. Within the European Union, the supplier of medicinal oxygen is required to hold a marketing authorisation in accordance with Directive 2001/83/EC of the *European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use* [3], detailing the clinical indications and contraindications and specific warnings for the safe use of the product. The specification of this medicinal oxygen is detailed in the European Pharmacopoeia monograph for oxygen, which specifies a minimum purity of 99.5% oxygen. The quality, safety and efficacy of the medicinal oxygen are ensured by the medical gas supplier through a quality management system under the responsibility of a qualified person.

Oxygen 93 can be manufactured on-site within the healthcare facility, under the responsibility of the healthcare facility pharmacist, using an oxygen 93 supply system and meeting the appropriate and specific quality and safety criteria for medicinal products prepared in Pharmacies (see *Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme Guide PE010-4 Guideline to good practices for the preparation of medicinal products in healthcare establishment* [4]).

Oxygen 93 concentrator units are covered by the requirements for CE marking in accordance with the Medical Device Regulation, 2017/745 EU [5]). The specification of the oxygen manufactured using an oxygen 93 supply system is detailed in the European Pharmacopoeia monograph for oxygen 93, which specifies the oxygen content to be between 90% and 96% and gives appropriate limits and analysis methods of other possible contaminants during the production. As the oxygen 93 is produced by adsorbing the nitrogen from ambient air, the major contaminant in oxygen 93 is argon, which can be present up to 5%.

When the oxygen 93% monograph was introduced it was stated that the benefits of PSA oxygen (oxygen 93 per cent) are to allow production and supply of oxygen at sites where access for cylinder and liquid oxygen supply is difficult or impossible. PSA concentrators are in use in a number of fields particularly by the military (field hospitals).

Medicinal oxygen 99.5% is licensed under a marketing authorization, whereas oxygen 93 is a gas produced by a medical device. Therefore different regulations apply.

Where the regulatory authority accepts the use of the oxygen 93 manufacturing device in a healthcare facility, it is installed in a pipeline installation in which the control and management of the quality, safety and efficacy of the distributed oxygen 93 falls under the responsibility of the pharmacist of the healthcare facility.

¹ References are shown by bracketed numbers and are listed in order of appearance in the reference section.

The purpose of this publication is to provide a guideline where the use of an oxygen 93 concentrator system is permitted for the supply of oxygen into a healthcare facility pipeline system and to identify the best practices that should be used to ensure patient safety. There are recommendations concerning the design of the system, the continuity of supply, the quality management systems used to manage the production of the oxygen and the quality control requirements to ensure that the product quality remains within the specification range.

2 Scope and purpose

2.1 Scope

This publication applies to the planning, technical design, location, installation, operation, maintenance and quality management of oxygen 93 concentrator systems used when accepted for supplying medical gas distributions systems in healthcare facilities. It provides recommendations regarding the key roles and responsibilities required to manage such mode of supply.

References have been cited in this publication that give information relating to on-site oxygen generation, medical gases pipeline systems and related equipment, but the reference section is not intended to be all inclusive. National or local requirements and regulations are not listed in this guide. The operating manuals of the equipment supplier shall always be consulted.

This publication is intended to cover oxygen 93 produced from a pressure swing adsorption process (PSA). For alternative technologies such as vacuum swing adsorption (VSA) the principles of this publication may be applied.

This publication does not address the regulatory requirements related to supplying medicinal oxygen and oxygen 93 through the same medical gas pipeline system, as these are covered by specific local or national regulations.

This publication does not cover the use of an on-site generator for filling portable oxygen cylinders for use within the healthcare facility or for supply outside of the healthcare facility.

NOTE Supply of medicinal oxygen and oxygen 93 in the same medical gas pipeline system may be restricted by the regulatory authorities.

2.2 Purpose

This publication provides guidance for the safe design, installation, operations, maintenance and quality management of oxygen 93 concentrators systems used in healthcare facilities.

It is intended for use by EIGA Members, healthcare facility managers and responsible pharmacists, oxygen concentrators' manufacturers; and national regulatory authorities involved in the regulation and inspection of the manufacturing and administration of gases for medicinal use.

3 Definitions

3.1 Publications terminology

3.1.1 Shall

Indicates that the procedure is mandatory. It is used wherever the criterion for conformance to specific recommendations allows no deviation.

3.1.2 Should

Indicates that a procedure is recommended.

3.1.3 May and need not

Indicate that the procedure is optional.

3.1.4 Will

Is used only to indicate the future, not a degree of requirement.

3.1.5 Can

Indicates a possibility or ability.

3.2 Double-stage pipeline distribution system

Pipeline distribution system in which gas is initially distributed from the supply system at a pressure higher than the nominal distribution pressure and is then reduced to the nominal distribution pressure by line pressure regulator(s).

3.3 Failure Mode Effects Analysis (FMEA)

Risk analysis methodology which consists in analysing the potential consequences of the failure modes of an engineered system that allows the appropriate mitigation measures to be defined to decrease the probability and/or gravity of the identified consequences.

3.4 Gas for medicinal use or Medicinal Gas

Gas or mixture of gases having properties for treating or preventing disease in human beings which may be used in, or administered either with a view to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action, or to make a medical diagnosis.

3.5 Healthcare facility

Hospital, clinic or similar facility that provides patients with their healthcare needs

3.6 High pressure reserve storage

High pressure storage equipment connected together to provide reserve storage for the pipeline system.

3.7 Medicinal oxygen

Oxygen for medicinal use approved by competent national authorities through a Marketing Authorisation and produced by a purification process followed by cryogenic distillation of ambient air, where the oxygen concentration is $\geq 99,5\%$. It complies with the European Pharmacopoeia Monograph (0417) [6].

3.8 Oxygen 93 concentrator unit

Single stage unit working by adsorption purification of ambient air using zeolites according to European Pharmacopoeia Monograph 2455 [6].

3.9 Oxygen 93 supply system

Assembly which supplies the pipeline distribution system and which includes the three sources of supply

3.10 Oxygen 93

Oxygen 93 for medicinal use is a gas produced under the responsibility of healthcare facility pharmacist by an oxygen 93 concentrator unit located within the hospital facility in which the concentration of oxygen is in the range of between 90% to 96%. It complies with the oxygen 93 % European Monograph (2455) [6].

3.11 Primary source of supply

That part of the supply system which supplies the pipeline distribution system. (definition based on reference [1])

3.12 Reserve source of supply

That part of the supply system which supplies the complete, or parts(s) of the, pipeline distribution system in the event of failure or exhaustion of both the primary and secondary sources of supply. (definition based on reference [1])

3.13 Secondary source of supply

Portion of the supply system which supplies the pipeline distribution system in the event of exhaustion or failure of the primary source of supply. (definition based on reference [1])

3.14 Single fault condition

Condition in which a single means for protection against a safety hazard in equipment is defective or a single external abnormal condition is present.

NOTE: Planned maintenance of equipment is considered a normal condition.

3.15 Single-stage pipeline distribution system

Pipeline distribution system in which gas is distributed from the supply system at the nominal distribution pressure.

3.16 Source of supply

Part of the supply system with associated control equipment which supplies the pipeline distribution system.

4 General configuration for continuity of supply

EN ISO 7396-1 [1] specifies the general requirements for all supply sources used with medical gas pipeline systems. The basic principle is that supply system for gases used as patient life support should have three sources of supply (i.e. primary, secondary and reserve source of supply) to ensure that gas will be available in the event of a single fault condition. This means that the supply system should be able to provide an adequate supply of gas when two out of three sources of supply are out of service, such as when one source fails when another is out of service for maintenance. In this configuration it is intended that each source shall be able to supply the entire flow required including the peak consumption.

4.1 Considerations on the use of oxygen 93

Specific measures related to continuity of supply when using oxygen 93 include:

4.1.1. Dependency on electrical supply

As oxygen 93 concentrator units are dependent on the electrical supply, there needs to be either an emergency electrical supply, using a backup generator, or a second electrical supply to the facility that would not be impacted by the failure conditions of the primary supply.

For continuity of supply at least one of the three supply sources should be independent from the electrical supply, either a liquid storage container or high pressure gas cylinders or bundles of cylinders (either oxygen 93 or medicinal oxygen).

4.1.2 Supplying two distinct qualities of gas in the same pipeline

Where both medicinal oxygen (either cryogenic liquid or compressed in high pressure gas cylinders) and an oxygen 93 concentrator unit are used in combination to supply oxygen for medicinal use to a pipeline system, it shall be noted that the oxygen content of the gas at the pipeline outlet point can vary between 90% and 100% and is not always compliant with one of the individual European Pharmacopoeia monographs, as result some national or local regulatory authorities may restrict the supply of oxygen 93 with medicinal oxygen using the same pipeline system.

Where the products are permitted to be supplied in the same pipeline, the healthcare facility pharmacist is responsible for the safe administration to patients and the traceability of the product.

The healthcare facility management has to evaluate the following issues that could be caused by supplying medicinal oxygen and oxygen 93 using the same medical gas pipeline system:

- The oxygen from an oxygen 93 concentrator unit provides oxygen within the range of 90% to 96% in case of a supply of oxygen 93. The actual concentration of the oxygen in the supply source is dependent on the oxygen 93 concentrator unit design and will tend to be lower when the throughput of the supply system increases. Hence it is important that the supply system is designed to meet the maximum demands (including peaks) of the pipeline system, ensuring that the capacity is adequate for any potential increases in the pipeline demands throughout the operating life of the oxygen 93 supply system.
- The oxygen concentration of the gas supplied from the pipeline can vary between 90% and 100% in case there is a combined supply of oxygen 93 and medicinal oxygen. It is important that the healthcare facility verifies through a risk assessment that this variability in the oxygen content administered to the patients is compatible with the safe operation of the ventilators, anaesthesia machines and other medical devices used within the facility. In most cases, it is necessary that the healthcare professional responsible for administering the gas to the patient formally accepts the criteria and the output of the risk assessment and is aware of the potential change in concentration. The healthcare professional should be provided with warnings when the concentration range is likely to change.

4.1.3 Re-filling reserve source of supply

The following are safety issues associated with operating an oxygen 93 compressor for the re-filling of reserve cylinders:

- It is feasible to utilise the oxygen 93 supply system (used as the primary and or secondary supply) to fill high pressure gas storage system (either using individual cylinders permanently connected to a manifold system or a permanently installed high pressure storage system) to act as the reserve source of supply. This system shall comply with the national regulations and standards related to high pressure filling systems. In addition there could be additional local requirements for the operation of such equipment within healthcare facilities.

Where this configuration is used it shall be noted that the re-filling of the third source of supply is also dependant on the electrical supply.

- The operation of a high pressure oxygen 93 compressor within a healthcare facility creates additional safety issues for the management of the facility, including the risks of oxygen fires. This requires the introduction of the same level of management control and risk management as defined in gases industry standards and used by the licensed manufacturers of medicinal oxygen filled into cylinders.

4.1.4 Responsibilities of the healthcare facility pharmacist

On healthcare sites where oxygen 93 is manufactured, the healthcare facility pharmacist is responsible for the quality and safety of the oxygen 93 administered to patients. The healthcare facility pharmacist is also responsible for the quality management system, including the quality control and traceability of the product administered to patients, and investigating any reported adverse event.

4.1.5 Clinical considerations of 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.

- Consider the 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*)

- 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 References:

1. Parker CJ, Snowdon SL. Predicted and measured oxygen concentrations in the circle system using low fresh gas flows with oxygen supplied by an oxygen concentrator. *Br J Anaesth.* 1988; 61: 397-402
2. Dobson G, Chong M, Chow L, Flexman A, Kurrek M, Laflamme C, Lagacé A, Stacey S, Thiessen B. *Guidelines to the Practice of Anesthesia - Revised Edition 2018.* *Can J Anaesth.* 2018 Jan;65(1):76-104.
3. Prien T, Meineke I, Züchner K, Boantă A, Rathgeber J. Oxygen 93: a new option for European hospitals. *Br J Anaesth.* 2014; 113: 886-887
4. Behnke, A.R.; Yarbrough, O.D. Respiratory resistance, oil water solubility and mental effects of argon compared with helium and nitrogen. *Am. J. Physiol.* 1939, 126, 409–415.

4.1.6 Impact of Medical Device Regulation on PSA

a) For PSA manufacturers

Whereas the Medical Device Directive (MDD) had general requirements for medical devices only depending on their classification (I, IIa, IIb or III), and PSA are class IIb medical devices, the Medical Device Regulation (MDR) also introduces requirements specific to certain categories of devices

according to their classification and their intended use. Among these devices, there are the “active devices intended to administer and/or remove a medicinal product”.

Since Oxygen 93 meets the definition of medicinal product given in the 2001/83 directive and a PSA is an active medical device, PSA have to fulfil two specific additional requirements of the MDR compared to other active devices.

The first one is regarding the clinical evaluation consultation procedure as per Article 54 and requires that the notified body of the PSA manufacturer follows the procedure regarding clinical evaluation consultation as specified in Section 5.1 of Annex IX when performing the conformity assessment, which involves an expert’s panel. It is not possible today to know what will be the opinion of this experts panels but it may be expected that the quality of the oxygen 93 % and its potential contaminants will be taken into account.

The second additional requirement is found in the Annex I, the GENERAL SAFETY AND PERFORMANCE REQUIREMENTS, section 10.4.1. Design and manufacture of devices and concerns the thorough evaluation of the potential toxicity of materials used in the gas pathway, especially when that contain substances that are carcinogenic, mutagenic or reprotoxic (CMR) in a concentration that is above 0,1 % weight by weight (w/w). This can concern many non-metallic materials but metallic alloys as well.

b) For gas manufacturer

Whereas the MDD was containing requirements only for manufacturers, the MDR includes now the distributors in its scope. A company who would install a PSA in a hospital would be considered as a distributor under the MDR.

The general obligations for the distributors are listed in article 14 and include among others:

- the check that the PSA is CE marked and that the EU declaration of conformity been drawn up, accompanied by the appropriate manuals and that a Unique Device Identification (UDI) has been assigned;
- the information of the manufacturer and of the competent authority in case the PSA is suspected to present a serious risk;
- the co-operation with the manufacturer and with competent authorities in case of necessary corrective actions to bring the PSA into conformity, to withdraw or to recall it, as appropriate;
- the immediate forward to the manufacturer of any received complaints or reports from healthcare professionals, patients or users about suspected incidents related to the PSA;
- the keeping of a register of complaints, of non-conforming devices and of recalls and withdrawals, register available to the manufacturer for consultation;
- the provision upon request by a competent authority of all the information and documentation at disposal to demonstrate the conformity of the PSA;
- the cooperation with competent authorities, at their request, on any action taken to eliminate the risks posed by the PSA which they have made available on the market.

4.2 General configuration of an oxygen 93 supply system

One of the main principles of EN ISO 7396-1 [1] is that a medical gas pipeline supply system should comprise of at least three independent sources of supply.

For a medical gas pipeline, these three sources of supply are classified and defined as:

- primary source of supply, intended to supply the pipeline distribution system;

- secondary source of supply, intended to supply the pipeline distribution system in the event of exhaustion or failure of the primary source of supply
- reserve source of supply intended to supply the pipeline distribution system in the event of failure or exhaustion of both the primary and secondary sources of supply.

For oxygen 93:

- Primary and secondary sources are oxygen 93 concentrator units, supplying oxygen 93;
- Reserve source is oxygen 93 in permanently installed high pressure reservoir. This reservoir would be re-filled using a high pressure oxygen compressor using an oxygen 93 supply from an oxygen 93 supply system.

Where supplying both oxygen 93 and medicinal oxygen in the same medical gas pipeline system is allowed, the reserve source can be one of the following:

- liquid oxygen cryogenic vessel (mobile or stationary), supplying medicinal oxygen ($\geq 99.5\%$);
- medicinal oxygen in cylinders or bundles of cylinders;

The following are the likely configurations, to be used where permitted, for the supply sources for a system where an oxygen 93 supply system is required to be the primary and secondary source. Alternatives could be used for the reserve supply source:

Table 1 Configuration for the three sources of supply

Configuration with use of only oxygen 93:

	Primary	Secondary	Reserve
Configuration A	oxygen 93 concentrator unit (O ₂ 93%)	oxygen 93 concentrator unit (O ₂ 93%)	oxygen 93 reservoir / High Pressure compressor (O ₂ 93%)

Configurations with use of oxygen 93 in combination with medicinal oxygen:

Configuration B	oxygen 93 concentrator unit (O ₂ 93%)	oxygen 93 concentrator unit (O ₂ 93%)	oxygen cylinders or bundles (Medicinal O ₂)
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Other configurations, where the oxygen 93 concentrator unit is used as a reserve supply source are less likely to be used although they are theoretically possible. This type of configuration is not included within this publication.

Liquid oxygen is not recommended as the reserve source due to the natural evaporation and venting of the product when the vessel is not in use. If an economizer circuit is used, uncontrolled mixing of the product will occur in the medical gas pipeline

4.3 Description of the different type of supply sources

The examples of the typical concentrator units shown in 4.3 do not include all the instrumentation that could be required for compliance with the oxygen 93 monograph.

4.3.1 Oxygen 93 concentrator units (Configurations A and B)

A typical oxygen 93 concentrator unit for a medical gas pipeline system is shown in Figure 1:

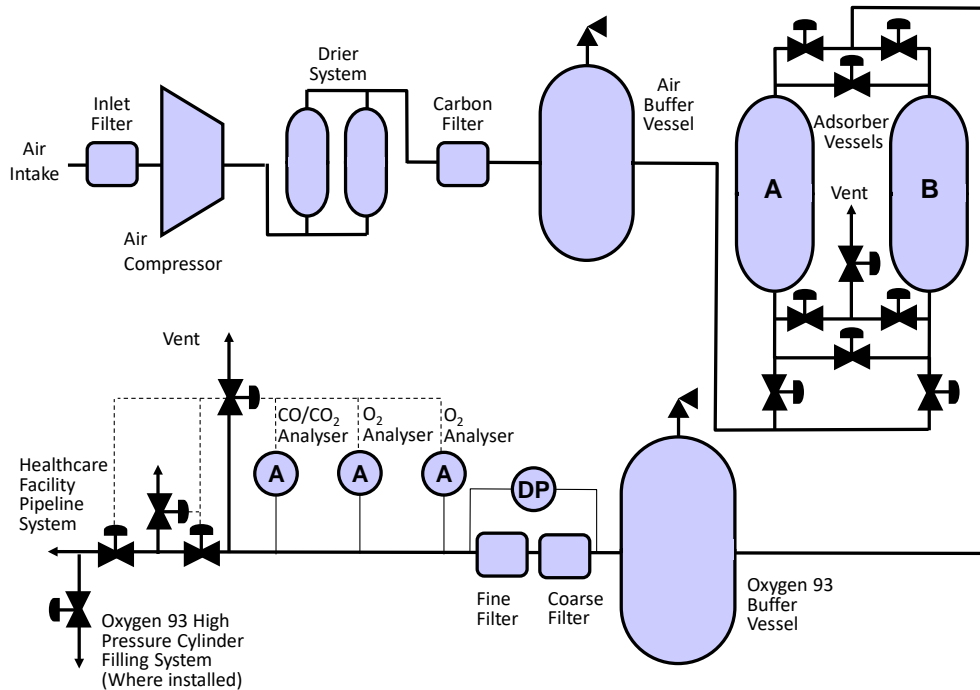


Figure 1 Simplified typical oxygen 93 supply system

NOTE: Location of individual components may vary according to the configuration of the specific concentrator units

The following are the components of a typical oxygen 93 supply system;

- air inlet filter;
- air compressor;

NOTE The air compressor used for oxygen 93 should be dedicated to the system and should not be shared with the medical air supply systems used on the healthcare facility site, to ensure the availability of the three sources of supply.

- dryer;
- filtration system;
- air buffer;
- oxygen 93 generator composed of two vessels containing the molecular sieves and a system to control the opening and closing of inlet and vent valves;

NOTE The oxygen 93 concentrator unit shall be designed so that at the maximum predicted demand, the oxygen concentration will not fall below the lower limit of 90% oxygen content;

- back pressure valve;

- an oxygen 93 buffer equipped with a pressure relief valve and a mean of purging; the buffer capacity shall be designed to take account of the variations in the pipeline demand at the output of the concentrator unit;
- two oxygen analysers, to continuously monitor and record the concentrator unit output. The analysers shall be connected to the supply system control and alarm systems so that the main shut off valve can be automatically shut in the event of the oxygen concentration falling outside of the relevant pharmacopoeia specification;
- carbon monoxide, carbon dioxide and moisture analysers connected to the supply system control and alarm systems so that the main shut off valve may be automatically shut in the event of the impurity levels exceeding the relevant pharmacopoeia specification.
- Sampling outlet to test for oil, nitric oxide, nitrogen dioxide and sulfur dioxide. It is the responsibility of the healthcare pharmacist to define if these impurities should be analysed continuously or periodically based on risk management plan, see 5.2 and 7.5.1.
- Booster compressor

NOTE A booster compressor could be required to ensure the supply gas is at the nominal pressure of the pipeline according to the values defined in EN ISO 7396-1 [1]. This is usually only required where a double-stage pipeline distribution system is used (where the nominal pressure needs to be between 8 bar(g) and 9 bar(g)).

- Main shut off valve; to allow the oxygen 93 supply source to be isolated from the medical gas pipeline of the hospital (when the oxygen 93 is out of specification or for maintenance or fire).
- A non-return valve preventing any back flow from the pipeline system to the oxygen 93 concentrator unit

4.3.2 Oxygen 93 high pressure reservoir filling system (Configuration A)

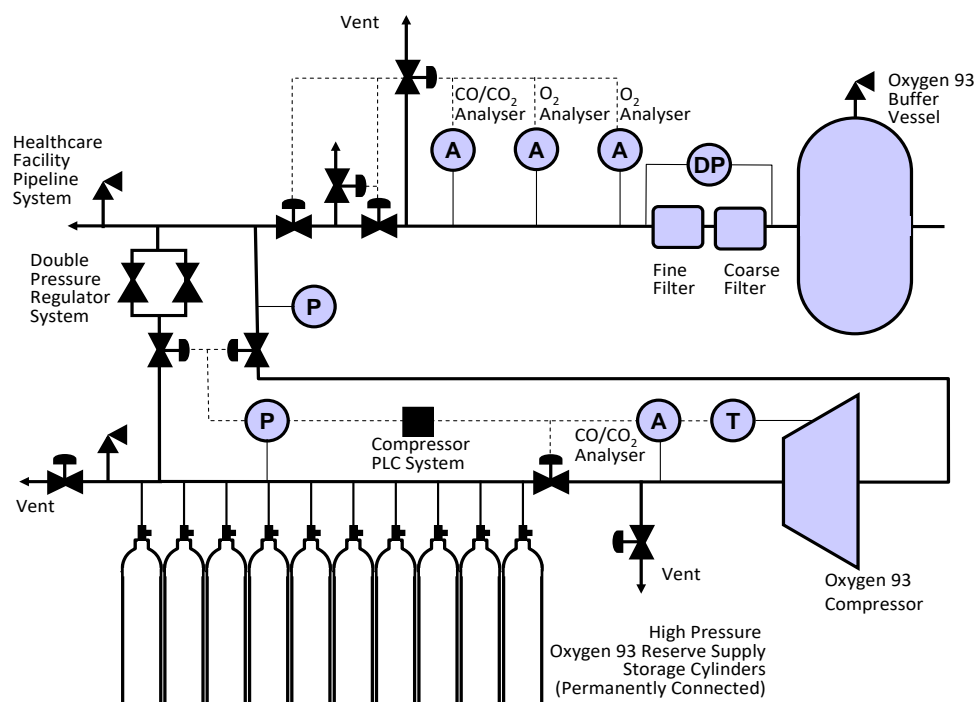


Figure 2 Simplified typical oxygen 93 high pressure reservoir filling system

The re-filling of oxygen 93 high pressure cylinders fixed and permanently installed, requires the use of a high pressure oxygen compressor. The risks related to operating these types of compressors are detailed in 5.2 and 6.13, and include fire, explosion and release of toxic products in the gas stream to the reserve cylinders.

The use of such oxygen high pressure compressor is considered as a critical process in term of safety in the industry, and its implementation in a healthcare facility requires a high level of safety measures to be put in place to limit the potential consequences of an oxygen fire in a public facility.

A typical oxygen 93 cylinders or bundles filling system comprises of the following:

- non-return valve to prevent any back flow to the oxygen 93 concentrator unit;
- high pressure compressor;

The high pressure compressor is used to re-fill the permanent reserve vessel(s) up to a pressure of 200 bar(g) (dependant on national regulations); it shall be isolated from the rest of the installation (enclosure) to avoid a possible fire propagation

- compressor monitoring and alarm system, that shall include at least the following components:
 - enclosure temperature;
 - output gas temperature;
 - power;
 - high pressure; and
- carbon monoxide and carbon dioxide analyser / alarm system, in order to ensure the safety of patients in case of temperature build-up or fire in the compressor;

NOTE In accordance with the PICs requirements, local authorities could require testing of the high pressure reservoir for full compliance with the oxygen 93 monograph and its batch management.

- the compressor monitoring system shall automatically shut down the compressor and close the compressor shut-off valve in order to avoid pollution of the reserve source in case of exceeding alarms threshold;
- shut-off valve, placed directly downstream of the compressor;
- high pressure reserve vessel(s).

NOTE The reserve vessels can consist of a large high pressure vessel or a number of high pressure cylinders manifolded together, acting as a single storage unit. The capacity of the storage vessels / cylinders shall be large enough to be able to supply the healthcare facility requirements in the event of a single fault failure, allowing for the time to re-establish either the primary or secondary supply source;

- analysis sampling point, downstream of the reserve vessel(s);
- automatic shut-off valve, downstream of the reserve vessel;
- means of purging the reserve vessel at start up or in case of contamination of the system;
- pressure regulation manifold to reduce the pressure of the supply gas to the nominal pressure of the pipeline; and
- personnel protection barriers.

As the reserve vessel(s) are filled using the oxygen 93 concentrator unit of the primary or secondary source, the system design shall take into account the filling requirements when sizing the supply system to ensure that the operation of the filling system does not affect the delivery of oxygen93 to the pipeline distribution system.

NOTE In some Member States, the national Competent Authorities consider that the compressors and the vessels used for the reserve supply system shall be CE-marked in accordance with the requirements of the Medical Device Regulation 2017/745 EU [5].

4.3.3 Medicinal oxygen cylinder / bundle manifolds (Configuration B)

Medicinal oxygen cylinder/bundle manifolds comprise of the following:

- at least two cylinder manifolds with pigtails for connecting banks of cylinders or bundles of cylinders;
- automatic changeover system to ensure continuous supply;
- pressure regulation system to reduce the cylinder pressure to the nominal pipeline pressure;
- alarm system to identify the status of each bank of cylinders connected; and
- analysis sampling point.

4.4 Capacity of the supply sources

4.4.1. Oxygen 93 supply source capacity

When designing the oxygen 93 supply system, specific attention shall be paid to the flow rate capabilities of the oxygen 93 concentrator units. The quality of the gas produced by the system is dependent on the flow requirements of the pipeline system, with the product quality of the gas falling if the demand exceeds the design capacity of the plant.

Throughput of the compressors is also dependent on altitude and allowances should be made for variations in barometric pressure.

As defined in EN ISO 7396-1 [1] each oxygen 93 supply source shall be able to supply individually the whole demand of the healthcare facility at any time, including peaks in demand, general increases in the normal running conditions and possible high pressure reserve filling. A survey of the healthcare facility requirements shall be undertaken, considering planned increases in the demand so that each oxygen 93 supply source is capable of always supplying product within the pharmacopoeia specification.

It shall be highlighted that when the healthcare facility demand exceeds the nominal capacity of the oxygen 93 supply source, there is a risk that the oxygen concentration at the outlet of the system will drop below the lowest set point of 90% purity.

Oxygen consumption in healthcare facilities is likely to fluctuate significantly according to different factors. The capacity of the oxygen supply system shall be defined based on the estimated flow profile and usage, taking into account:

- current average demand;
- daily activities;
- consumption peaks; and
- future requirements (for example extensions, new activities).

Switching to an oxygen 93 concentrator unit, used as a secondary source requires that the duration of the start-up is taken into account in the sizing of the oxygen buffer. The oxygen buffer of the oxygen 93 supply source in standby shall be permanently able to supply the nominal flow rate at the required pressure (single-stage or double-stage pipeline systems) during all the start up stage of the oxygen 93 supply source; the worst case condition being considered. The oxygen buffer shall be designed and sized also to take account of short-term consumption peaks.

It is not acceptable to use the reserve source of supply when switching from the primary source to the secondary source or vice versa.

4.4.2 Reserve source capacity – Medicinal oxygen

The capacity of the reserve source of supply shall be based on risk management principles, taking into account:

- average daily consumption rates for the healthcare facility, including significant increases due to seasonal effect; and
- maximum period between gas deliveries

As the reserve source will be used infrequently, it is not appropriate that medicinal liquid oxygen is used as the reserve supply source. It is therefore recommended to use cylinders or bundles with medicinal oxygen.

4.4.4 Reserve source capacity – Oxygen 93 high pressure reservoir re-filled on-site

As the reserve source of supply will only be used when the primary and secondary source of supply is not available, the capacity needs to be large enough to allow either of the oxygen 93 supply source (primary or secondary) to be reinstated. Considering the fact that it will not be possible to replace the reserve cylinders once they will be empty, it is recommended that the capacity shall be sized to ensure continuity of supply whilst additional new supply is being arranged or until primary or secondary sources are reinstated.

Additional factors that need to be considered when carrying out the risk assessment to determine the capacity of the reserve supply source include:

- average critical daily consumption, assuming that the healthcare facility manage the consumption during the shutdown period;
- distance from an alternative source of supply;
- availability of the oxygen 93 supply system maintenance provider;
- reliability of the site electricity supply; and
- maximum time required to re-fill the reserve cylinders after restart of at least one of the oxygen 93 supply source and the capacity of this oxygen 93 supply source compared to the nominal demand.

4.5 Reliability of supply

The expected reliability of the configurations shown in Table 1 (chapter 4.2) are discussed in the following section.

4.5.1 Configuration A

	Primary	Secondary	Reserve
Configuration	oxygen 93 concentrator unit [O ₂ 93%]	oxygen 93 concentrator unit [O ₂ 93%]	oxygen 93 reservoir / high pressure compressor [O ₂ 93%]

The reliability of the oxygen 93 concentrator unit compared to supply sources using either compressed or liquid medicinal oxygen is lower. This is due to both the complexity of the concentrator unit and to the fact that it is dependent on a reliable electrical supply.

The most common technical problems that are likely to occur with oxygen 93 concentrator units relate to the reliability of the air compressors, the adsorbers' system valves, the process monitoring equipment and analysers.

Some common modes of failure between primary and secondary sources exist, including:

- electrical power failure; and
- part of the monitoring system shared by the two concentrator units
- pollution of the local air supply.

It is recommended that the oxygen 93 supply system be connected to the hospital electrical emergency supply. A check shall be made to ensure that the healthcare facility emergency electrical supply has sufficient capacity to operate the oxygen 93 supply system at its design capacity.

By using a reserve source of supply that utilises permanently connected oxygen 93 high pressure reservoir the system is not affected by the common failure modes identified above.

The capacity of the reserve source of supply needs to be sized to enable product to be supplied for a period that is long enough to enable one of the oxygen 93 supply source to be restarted after an electrical power failure or a technical problem (see 4.4.1).

The risks related to the use of oxygen 93 high pressure compressors are detailed in 5.2 and 6.13.

4.5.2 Configuration B

	Primary	Secondary	Reserve
Configuration	oxygen 93 concentrator unit [O ₂ 93%]	oxygen 93 concentrator unit [O ₂ 93%]	oxygen cylinders or bundles of cylinders [Medicinal O ₂]

The expected reliability and availability of the primary and secondary sources are the same as identified in Configuration A.

This configuration shall be permitted, where required, by the national authorities for the combination of use of both oxygen 93 and medicinal oxygen and with the restrictions of use defined in this authorisation. In this configuration both products are supplied in the medical gas pipeline systems after emergency use of the sources when switching on the reserve.

As the reserve source of supply is completely independent of the oxygen 93 supply sources allowing the cylinders / bundles to be easily replaced when emptied, this configuration has less risk associated with the design in term of product supply continuity management.

The number of cylinders connected to the manifold system of the reserve source of supply shall be sufficient to allow for continuity of supply. The manifold system shall include a changeover system to enable the manifold with the empty cylinders to be changed over automatically to the manifold with full cylinders.

4.6 Variability of the oxygen concentration in the pipeline distribution system

The variability of the oxygen concentration supplied by an oxygen 93 concentrator unit is inherent to the principle of generation (swing adsorption of nitrogen contained in the air by a molecular sieve).

At the output of the oxygen 93 concentrator unit, this variation is controlled and maintained in the range 90%-96% according to the definition of Oxygen 93 per cent in the European Pharmacopoeia.

Switching from one oxygen concentrator supply source to another oxygen concentrator supply source can create a variation of the oxygen content supplied to the patients, maximum from between 90% and 96% (or vice versa). Switching from an oxygen concentrator supply source to a medicinal oxygen supply source (configuration B) will also lead to a variation in the oxygen concentration within the medical gas pipeline system.

When opting for this mode of supply, whatever the configuration, the healthcare facility shall perform a risk analysis and validate with the different medical staff using oxygen that the oxygen concentration and its variability range will be compatible with the safe treatment of patients and the safe usage of the different medical devices existing in the health facility (such as ventilators, anaesthesia machines), in conformity with their specifications and intended use. In case of variation of the oxygen content the clinical alarm system shall be used to inform the relevant hospital personnel.

4.7 Summary and key elements for decision

Table 2 provides a summary of the key elements to be considered when designing an oxygen supply system using oxygen 93 concentrator units.

The configurations described are compared to a reference configuration using medicinal oxygen as liquid or cylinders as primary, secondary and reserve sources and not manufactured on site.

Table 2 Summary of key elements for decision

Configuration	Clinical	Occupational Safety	Reliability of Supply	Regulatory
Reference Configuration	No fluctuation of the oxygen concentration (> 99,5%)	No specific issue other than those related to oxygen storage	All sources independent from each other and from site electricity supply. High level of availability.	Medicinal oxygen under Marketing Authorizations
Configuration A	Oxygen concentration fluctuation range (90% to 96%) in normal conditions	Risks of ignition and fire/explosion linked to high pressure oxygen compression	Limited capacity of the reserve could jeopardize the supply continuity. All 3 sources dependent on site electricity supply and ambient air quality	Oxygen produced under pharmacist responsibility Specific attention to Pressure Equipment directive (reserve) and fire regulations
<u>Configuration B</u>	Oxygen concentration fluctuation range (90% to 100%) under emergency conditions	No additional issue than those inherent to oxygen 93 concentrators	Reserve independent from primary, secondary and site electricity supply	Oxygen prepared for medicinal use under pharmacist responsibility Combination of oxygen 93 and medicinal oxygen shall be permitted where required by the local authorities or national regulations Special clinical supervision for the variation between 90% to 100%

5 Hazards - Risk analysis and critical control points

5.1 General considerations

As oxygen 93 concentrator units are CE marked devices, their manufacturer shall perform a risk analysis complying with the requirements of EN ISO 14971 *Medical devices; Application of risk management to medical devices* [7], taking into account the device and its installation, control, supervision, and use.

If some risks are eliminated or reduced at acceptable levels by an inherently safe design and construction, some others imply on active participation of the users, such as correct reactions to the alarms, maintenance of the safety devices or considerations of aspects specific to the location of the system.

Therefore, before final decisions on-site selection for an oxygen 93 supply system are made, a comprehensive safety review shall be conducted to consider:

- All hazards identified by the manufacturer of the oxygen 93 supply and the associated recommendations to reduce the probability of their occurrence and their consequences. The review should be structured and systematic to examine all relevant parts of the equipment design including both normal and malfunctioning operations.

- Possible interaction with nearby and associated equipment and suitability for use of the product stream, particularly in case other than specified purity is generated, are also important factors to consider. A review procedure not only exposes potential hazards in the process but also identifies problems in its operation.
- Aspects related to the control of the product delivered to the installation in accordance with the responsibilities of the pharmacist of the facility. The review shall take care that the product is safely and correctly administered to patients and services connected to the pipeline
- Aspects specific to the healthcare facility including organizational aspects
- Restrictions of the use of the product according the specific authorisation of the local healthcare authorities or national regulation for the use of oxygen 93 in the healthcare facility
- Critical aspects related to healthcare internal therapeutic protocols that have been developed and validated on efficacy with medicinal oxygen versus oxygen 93%
- If the medical devices used to administer the product to the patients (usually intended for use with medicinal oxygen and accordingly CE marked) are explicitly approved for the use with oxygen 93 and, if the case, the off label use responsibility (when they are not intended for use with oxygen 93).

The healthcare facility, with the possible support of the manufacturer of the oxygen 93 supply system, shall implement and maintain a documented quality management system to ensure that potential product purity/contaminations risks that could be a hazard to patient health and safety can be identified and controlled.

The following are the principles of the hazard review:

- conduct a hazard analysis and identify potential hazards;
- identify the critical control points (CCP) where a potential hazard shall be mitigated by prevention or control;
- establish preventive measures and critical limits at each critical control point to ensure that the CCP is under control;
- establish procedures to monitor the critical control points;
- establish corrective actions required when a critical limit has not been met;
- establish verification procedures to confirm that the risk management process is working effectively;
- establish effective record of the document to confirm that the risk management process is working as intended; and
- complete regular reviews to ensure there have been no changes that would impact on the operations or controls of the system.

Responsibilities shall be defined by the healthcare facility regarding the control, maintenance and regular checks of the effectiveness of each CCP. Part of these responsibilities can be delegated to a third party providing there is a documented agreement between the two parties.

5.2 Hazards and critical control points

From a generic hazard review, the following critical control points (CCP) have been identified as specific to the oxygen 93 supply system. This list is not exhaustive and shall be completed by a risk

analysis conducted on the healthcare facility supply system. It shall include the critical control points defined in EN ISO 7396-1 [1] and related to the quality and continuity of supply.

Table 3 Hazards and critical control points

	Critical Control Point (CCP)	Target level	Comment
HAZARD: Air Quality - Incoming air supply to air compressor abnormally contaminated by, for example vehicle exhaust, smokes consecutive to a fire inside the healthcare facility, pollution of ambient air due to accidental release of contaminants			
CCP 1	Plant area vigilance procedure.	No air pollution above the specified limits	See 6.2.1 Where there is a likelihood of high levels of atmospheric nitric oxide, nitrogen dioxide and sulfur dioxide contamination in the air intake additional critical control points can be considered for continuous monitoring of these impurities as specified in the oxygen 93 monograph.
CCP 2	,CO, CO ₂ continuous analysis in oxygen 93 produced by the oxygen 93 supply system	As specified in European Pharmacopoeia Monograph for oxygen 93 (EP 2455) [6]	The possible contamination with carbon monoxide, carbon dioxide and toxic fumes can also be the consequence of a combustion in the air compressor.
HAZARD: Oxygen concentration drop / malfunction of the concentrator unit – the oxygen concentration drop in the oxygen 93 produced by the concentrator is the consequence of various failure modes of any oxygen 93 concentrator units			
CCP 3	Double continuous analysis of the oxygen concentration in the oxygen 93 produced by each concentrator unit	> 90%, as specified in European Pharmacopoeia Monograph for oxygen 93 (EP 2455) [6]	One analyser for process control, one analyser for quality control
CCP 4	High Flowrate detection at the outlet of each concentrator unit	< maximum design flowrate	The oxygen concentration drop can be the consequence of a high flowrate above the concentrator unit capacity
HAZARD: Zeolite particles release in the oxygen 93 distribution pipeline – such contamination is the consequence of a fine filter breakthrough downstream the concentrator adsorbers.			

	Critical Control Point (CCP)	Target level	Comment
CCP 5	Double particle filter downstream the concentrator bed sieve	Always one filter in operating conditions	
CCP 6	Monitoring the differential pressure across the particle filters downstream the concentrator adsorbers	According filter manufacturer instructions	The objective is to detect any malfunction of the filter
HAZARD: Fire in the oxygen 93 supply system room – a fire is the possible consequence of an oxygen 93 release in the room (loss of containment), or a malfunction of a compressor and/or oxygen 93 booster			
CCP 7	Room atmosphere oxygen detection system	19,5% < oxygen content < 23,5%	The system shall also detect low oxygen content (nitrogen release from the concentrator adsorbers venting lines)
CCP 8	Oxygen 93 boosters and HP compressors containment with enclosure temperature control	According normal operating temperature range	The containment shall limit fire propagation
HAZARD: Contamination of the oxygen 93 with carbon monoxide, carbon dioxide and other toxic combustion by-products – a contamination of the oxygen 93 with carbon monoxide, carbon dioxide and toxic by-products is the possible consequence of a combustion in an oxygen 93 booster or HP compressor (non-metallic materials inflammation)			
CCP 9	Oxygen 93 temperature monitoring at each compression stage of boosters and HP compressors	According normal operating temperature range, to detect overheating	The objective is to trip the compressor in case of malfunction
CCP 10	Carbon monoxide/carbon dioxide continuous analysis in oxygen 93 downstream oxygen 93 boosters and HP compressors	As specified in European Pharmacopoeia Monograph for Oxygen 93 (EP 2455) [6]	A non-metallic material inflammation will release carbon monoxide, carbon dioxide and toxic fumes

6 Installation & equipment

6.1 General supply system considerations

An oxygen 93 concentrator unit for medical use is defined as a class IIb medical device. Therefore all of its components including the assembly shall be designed, manufactured, tested and marked in accordance with the requirements of the Medical Devices Regulation 2017/745 EU) [5] and shall comply with all other relevant national or European codes and standards. The maintenance of the supply system shall follow the requirements detailed in the instructions for use issued by the concentrator manufacturer. Any components used in the maintenance or repair of the units shall be comparable with the component originally supplied by the manufacturer.

The manufacturer shall also provide documentation for all components, equipment, instrumentation and materials used in the entire oxygen 93 supply system, including but not limited to the following:

- Pressure testing certificates for all pressure equipment as defined by *Directive 2014/68/EU of the European Parliament and of the Council of 15 May 2014 on the harmonisation of the laws of the Member States relating to the making available on the market of pressure equipment Text with EEA relevance* [9]
- Certificate of cleaning for oxygen service in accordance with EIGA Doc 33 *Cleaning of Equipment for Oxygen Service Guideline* [9] for the relevant equipment, piping and instrumentation.
- Certificate of calibration for instrumentation including transmitters, analysers.
- Process and instrument diagram.
- Equipment lay out
- General piping arrangement
- Electrical/control wiring diagrams
- Sequence of operation, including system controls and interlocks
- Installation manual.
- Operating and maintenance manuals
- Equipment specifications (including compressors, blowers, filters, dryers, refrigerators, vessels, adsorber vessels)
- Piping and fitting specifications.
- Pressure regulators and safety valve specifications
- Instrumentation specifications, including pressure and temperature gauges, temperature/flow/pressure transmitters, including oxygen analysers, carbon monoxide/carbon dioxide analysers, differential pressure analyser.
- Performance test of the concentrator units including certificate and testing report.
- Hazard review- See details in section 5
- SDS- Safety data sheets for the material used.
- Transportable Pressure Equipment Directive [10] for cylinders and cylinder valves

6.2 Oxygen 93 supply system location

Oxygen 93 supply system's site selection shall begin with a safety assessment of the proposed location.

6.2.1 Air intake quality

Oxygen 93 concentrator units shall be installed in a location where the risk of air intake contamination from engine exhaust, ventilation and vacuum system discharges, scavenging system and other source of contamination can be minimized. In all cases, the installation shall conform to applicable standards as well as all national and local regulations.

Since air is the raw material for these supply systems, the quality (type and degree of contamination with foreign materials such as hydrocarbons, carbon monoxide, carbon dioxide, acid gases, nitrogen

oxides, sulfur dioxide and particulate matter) is probably the major concern in selecting a suitable site. Trace quantities of contaminants in the compressed air, particularly oil, heavy hydrocarbons, and acid gases and engine exhaust have a direct relationship to the safe operation and performance of oxygen 93 concentrator units. In general, the air compressor suction shall never be near the above sources of contamination, moreover these contaminants are not permanently monitored in a continuous production directly administered to patients. The healthcare facility pharmacist has to take responsibility in whether these contaminants could be supplied to the patients without continuous monitoring.

It is recommended to consult with the oxygen 93 supply system manufacturer to determine the acceptable levels of air contamination considered in the equipment design.

Site surveys should be made over a significant area around a proposed location. Attention should be given to the potential future development of the site in addition to the current use. Depending on the surroundings, it could be necessary to investigate sources of air contamination. If the evaluation of atmospheric conditions at the site is deemed unfavourable from a study of air contamination sources such as storage of other chemicals and wind data, then other sites should be considered if adaptive engineering modifications to the supply system are not practical. If the investigation does not yield definitive results, more quantitative information should be obtained by monitoring the components in the air at the supply system site over an extended period.

Potential fire or explosion hazards from nearby chemical storage or neighbouring industrial facilities should be investigated and mitigation measures taken as required to minimise risk to the operation of the generator.

6.2.2 Oxygen enrichment and deficient atmospheres

The oxygen 93 supply system location shall be defined to ensure that atmospheric oxygen content will be monitored and maintained between 19,5% and 23,5% in all areas frequented by personnel while performing operational and maintenance activities. Additionally, rotating equipment shall not be exposed to oxygen-enriched atmospheres since it may have oil-lubricated parts.

Consideration shall be given in building ventilation design to accommodate possible accumulation of product or waste gases. Ventilation shall be provided to prevent localized oxygen-deficient or oxygen-rich atmospheres. As a recommendation, the building should have a minimum of six air changes per hour.

The ventilation / air conditioning system shall be designed to maintain the temperature and humidity of the room in an operating range according manufacturer's requirements.

6.2.3 Fire protection

The rooms where are located the oxygen 93 concentrators and oxygen 93 compressors shall be fitted with fire suppression systems, including smoke detection and sprinkler systems. Typically, the primary fire protection for generators is from fire hydrants. Depending on the system size, there shall be an adequate number of fire hydrants, chemical-type fire extinguishers, hoses, or a combination of these should be strategically located close to the oxygen 93 concentrator units, compressors and boosters so that a fire can be approached from any direction.

Oxygen compressor fires typically produce high velocity oxygen jets containing molten-metal and metal oxides. Protective barriers should be used to isolate oxygen compression equipment to protect personnel and other equipment in case of a fire (see EIGA Doc 10 *Reciprocating Compressors for Oxygen Service* and EIGA Doc 27 *Centrifugal Compressors for Oxygen Service* [11,12]).

Some oxygen 93 concentrator units can have specific equipment that necessitates consideration such as a refrigeration system using a hydrocarbon refrigerant. In these cases, the appropriate provisions of national and local codes shall be followed for fire protection.

Automatic isolation valves and emergency remote shutdown shall be used to prevent oxygen sources from feeding a fire.

CAUTION: Storage of flammable and combustible materials should be avoided in buildings housing oxygen 93 supply systems and shall be in accordance with local regulations.

6.2.4 Occupational safety

Sufficient space shall be maintained around the equipment to allow for personnel access for the maintenance.

Personnel protection such as guard rails, platform gates, and ladder enclosures should be provided to prevent falls from elevated locations.

Specific means shall be provided to protect the personnel in case of an emergency. Example of this include emergency lighting, emergency remote shutdown, safe multiple exit routes, fire retardant clothing, alarm systems, and equipment isolation valves.

6.3 Materials of construction

Materials of construction shall be carefully selected according to existing codes and standards, ensuring their compatibility with oxygen for medicinal use, and depending on the service pressure and gas velocity at the different steps of the process

Non-metallic materials including gaskets, valve packing and compressor piston rings shall be compatible with oxygen service for medicinal use, taking into account the risks of toxic products release in case of combustion or overheating. See EIGA Doc 73. *Design Considerations to Mitigate the Potential Risks of Toxicity when Using Non-Metallic Materials in High Pressure Oxygen Breathing Gas Systems* [13]

Lubricants likely to be in contact with oxygen shall be compatible with oxygen.

6.4 Cleaning for oxygen service

All materials potentially in contact with oxygen shall be cleaned for oxygen service according EIGA Doc 33 *Cleaning of Equipment for Oxygen Service Guideline* [9].

6.5 Electrical requirements

Electrical equipment shall comply with the applicable national codes

The reliability of the electricity supply shall be specifically reviewed. There shall be a back-up electrical supply such as an emergency generator.

The level of isolation of the electrical supplies to primary and secondary oxygen 93 supply sources shall be established by risk management in order to implement the appropriate level of independence required to ensure the supply continuity.

In areas where oxygen enrichment is likely to occur, electrical equipment with open or unprotected make and break contacts should be avoided. Generally, the location of electrical equipment inside such areas should be avoided to eliminate potential hazards.

6.6 Emergency shutdown system

An emergency shutdown system is required. The system shall be designed to permit shutting down the concentrator from one or more locations, by tripping the appropriate switchgear to disconnect power. Local regulations may specify additional requirements for emergency shutdown.

6.7 Automatic operations

Precautions shall be taken to ensure that equipment cannot be automatically re-started without the knowledge of personnel in the area around the equipment. These precautions include but not limited to:

- a lock-out procedure before the commencement of any work including maintenance; and
- warning signs (visual and audible alarms) indicating the potential of automatic restart of the supply system.

Specific recommendations are included in EIGA Doc 132 *Unmanned Air Gas Plants: Design and Operation* [14].

6.8 Noise

The noise produced by the oxygen 93 supply system including air and oxygen 93 compressors, adsorber vessels, vents and pressure relief valves, shall be considered for the potential hazard or nuisance to employees, patients as well as to neighbouring areas. Noise abatement and use of personnel ear protection shall be in accordance with national and local regulations.

6.9 Venting

An oxygen 93 supply system will produce a significant volume of waste gas (oxygen-depleted air or oxygen-enriched air) likely to create oxygen deficient atmospheres or oxygen-enriched atmospheres in the surroundings of the gas vents. The use of signs warning of asphyxiation and oxygen enrichment should be considered, see EIGA Doc 04, *Fire Hazards of Oxygen and Oxygen Enriched Atmospheres* [15] and EIGA Doc 44, *Hazards of Inert Gases and Oxygen Depletion* [16]. In addition, dust material from the adsorber beds is an irritant and can also be present in the waste gas vent.

All vents shall be directed to a safe location outside of the buildings, away from personnel and equipment. Consideration shall be given to reduce the noise to an acceptable level according to local legislation. The inlet to an air conditioner is an example of a location where discharge shall be prohibited.

Pressure relief valves shall be located so that their discharge cannot impinge on personnel or other equipment. They should not discharge into working or operating areas frequented by personnel.

Pressure relief devices (PRDs) located outside should have discharge outlets protected from weather and water freezing. Vents shall be unrestricted.

Vents shall be routed and protected from damage by other nearby activities such as vehicular traffic.

6.10 Dusting

In order to ensure that the particle level in the gas supply from an oxygen 93 concentrator unit is maintained below the level specified in EN ISO 7396-1 [1], a filtration system shall be used.

The filtration system shall be located downstream of the adsorber vessels in order to prevent any release of molecular sieve dust. It shall be designed such that breakthrough of any part of the system will not result in particulates entering the pipeline. This can be achieved by installing a double filter.

The pressure differential across the filtration system shall be monitored to ensure that it is operating effectively and that the adsorbers are not deteriorated.

6.11 Fluid discharge/solid disposal

Considerations shall be given to the disposal of the different waste materials generated during the life of the oxygen 93 supply system. This includes:

- condensates from the dryer, as it may contain small quantities of oil;
- spent zeolite (molecular sieve) after replacement;

- filter elements;
- lubrication oil used in the compressors; and
- coolants.

The maintenance procedures shall consider potential hazards for the personnel handling any waste material, according to the relevant Safety data sheets.

6.12 Air compression and filtration

A drying and filtration system shall be installed downstream the air compressors to ensure the delivery of dry and oil-free air at the inlet of the adsorber vessels. The drying system design shall prevent any contact of the coolant with the gas in normal and single-fault condition.

Operating gas temperature and pressure shall be monitored at each stage of compression, with alarms and automatic shutdown in case the thresholds are reached.

Wherever possible, food grade lubricants and oils should be used. Appropriate means shall be included in the concentrator units design to ensure that the oxygen 93 oil content is in the limit specified in the European Pharmacopoeia Monograph for oxygen 93 (EP 2455) [6].

6.13 Oxygen 93 compression

Additional hazards linked to the compression of oxygen 93 are the ignition of materials due to a temperature increase caused by:

- mechanical friction due to malfunction of the compressor;
- particle impingement leading to localized high temperature; and
- adiabatic compression

The main consequences of such ignition can be a loss of containment and projection of molten metal at high pressure, and a release of a toxic combustion by-product.

Therefore, such hazards shall be mitigated by the following measures:

- monitoring of the compressor operating conditions, including gas pressure and gas temperature, with automatic shutdown and alarms when the threshold is exceeded;
- confinement of the compressor inside a dedicated enclosure;
- the correct selection of materials used within the compressor, including non-metallic materials, cleaning agents, lubricating oils; and
- carbon monoxide and carbon dioxide analysis downstream the compressor to detect any release of combustion by-products

For more information on oxygen compression, refer to the following publications:

- EIGA Doc 27 *Centrifugal Compressors for Oxygen Service* [11],
- EIGA Doc 10 *Reciprocating Compressor for Oxygen Service* [12],
- EIGA Doc 33 *Cleaning of Equipment for Oxygen Service Guideline* [9];
- EIGA Doc 13 *Oxygen Pipeline Systems* [17]

6.14 Product storage

6.14.1 General

The hazards associated with the storage of oxygen depend on the conditions under which they are stored. Each storage system shall be suitable for the temperatures, pressures, and fluids involved.

6.14.2 Cryogenic liquid storage

For guidance on cryogenic liquid storage refer to EIGA Doc 115 *Storage of Cryogenic Air Gases at Users' Premises* [19].

6.14.3 Low pressure vessels

Buffer Vessels used for air and oxygen 93 shall be designed, manufactured, marked and tested in accordance with the requirements of the Directive 2014/68/EU [8] and in accordance with the requirements of the relevant national codes and standards.

The pressure vessels shall be installed, tested, and protected by relief device(s) in accordance with the applicable local regulations, codes and standards. Vessels should be internally inspected for cleanliness before being placed in service.

6.14.4 High pressure vessels

High pressure vessels shall be constructed in accordance with regional and national requirements and shall have in place and in service inspection regime.

Consideration shall be given to the potential risk of material fatigue due to the frequent pressurisation of the steel high pressure vessels.

6.15 Plant piping

6.15.1 General

Piping systems shall be suitable for the temperatures, pressures, and fluids involved. These should consider the applicability of applicable local regulations, codes and standards.

Medical gas pipelines shall comply with EN ISO 7396-1 [1] Guidance is given on oxygen pipeline systems in EIGA Doc 13, *Oxygen Pipeline systems* [17]

PRDs should be provided on any system that can be over pressurized. PRDs should be tested periodically to ensure functionality and that the design set pressure is correct.

6.15.2 Pressure reducing stations

A pressure reducing station is required whenever the produced and/or stored product pressure is higher than the pipeline distribution pressure.

A PRD should be installed on the low pressure side of the reducing station if regulator failure can allow pressure to exceed the user's maximum allowable working pressure (MAWP).

6.15.3 System isolation

Isolation capability should be included at readily accessible points or branches of the lines for test purposes, maintenance, and in the event of a system failure or fire.

6.15.4 Aboveground piping

Lines installed aboveground shall be supported in accordance with applicable piping standards. Expansion joints or loops should be used as necessary to compensate for expansion and contraction due to temperature changes. Piping systems should be separated from external sources of heat, mechanical damage, and excessive vibration. Piping layouts should avoid tripping and/or bumping hazards.

6.15.5 Underground piping

Lines installed underground should not be of threaded or flanged construction. Lines shall be adequately supported to prevent damage. In all cases, sufficient flexibility should be provided by piping loops or expansion joints to compensate for the expansion and contraction due to temperature changes. External coating material should be used on the line to minimize ground-induced external corrosion. Where underground lines pass under roadways, they should be encased in pipe sleeves that are vented to atmosphere. Where underground conditions warrant, cathodic protection should be used.

6.15.6 Insulation

Measures shall be in place to either protect personnel or make them aware of either hot or cold surfaces. Insulation should be used to help prevent the freezing of moisture in process and instrument lines including those in compressed air service that can be exposed to cold ambient conditions. Insulation should be used to prevent condensation from cold process, instrument lines, or both that can cause slippery conditions.

7 Quality management system

7.1 Quality management system – Medicinal oxygen supply

Where medicinal oxygen is supplied as a finished product to the healthcare facility either as a bulk gas (as a cryogenic liquid) or in cylinders, the gas manufacturer and/or the supplier will be responsible for the quality, safety and efficacy of the gas supplied, dependant on the national, regional or local regulations. The supplier will be required to hold a Marketing Authorisation that will be issued by the national health agency authority.

The gas manufacturer shall operate a Quality Management System that will demonstrate that the medicinal oxygen has been manufactured following the principles set out in the EU Guide for Good Manufacturing Practice (GMP), (http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm) [2], on a site that is registered with the Regulatory Authority.

The healthcare facility responsibilities are limited to the management of the medical gas pipeline system to ensure that it does not impact on the quality and safety of the medicinal oxygen. Documented procedures shall be established to ensure that the persons are trained and qualified to operate, maintain and use the medical gas pipeline system.

7.2 Quality management system – On site generation oxygen 93

7.2.1 General

Where oxygen 93 is authorised to be manufactured on site as a medicinal product, the quality management system shall define how the oxygen 93 is controlled and released for safe administration to patients, taking into account that the supply system produces product continuously.

The healthcare facility pharmacy shall establish their own quality management system to ensure that the oxygen 93 is safe to be administered to the patients for medicinal use and that the supply system is available at all times to provide adequate supply of gas, even under single fault condition, and to ensure that the quality of the gas meets at all times the Pharmacopoeia monograph specifications.

The quality management system that is established shall incorporate the principles of Good Manufacturing Practice (GMP), as described in the EU Guide for Good Manufacturing Practice and PIC/S Guide PE010-4 *Guide to good practices for the preparation of medicinal products in healthcare facilities* [4], including any other specific local requirements

7.2.2 Responsible Person

The responsibility for the quality of the oxygen 93 manufactured for medicinal use shall be assigned to a nominated person within the healthcare facility, normally the head pharmacist.

The responsible person shall:

- have a knowledge of the clinical use of oxygen 93, taking into account the clinical considerations of the use of oxygen 93 (chapter 4.1.5);
- ensure audits of the quality systems are carried out at intervals to confirm that the gas being supplied to the patients will not adversely affect any patient safety for whatever treatment;
- ensure that the oxygen 93 is continuously controlled and released according to the required specifications and prescribed conditions;
- manage the CAPA process (Corrective Actions and Preventative Actions) following any defects reported by the healthcare facility; and
- report any adverse events to the national Regulatory Authority as part of a pharmacovigilance system

7.3 Requirements

7.3.1 General

Where oxygen 93 is manufactured on site, the supply system shall comply with the requirements detailed in EN ISO 7396 -1 [1] and any other conditions required in the authorisation of the onsite manufacturing by the local authorities.

The typical supply source configurations are detailed in section 4 of this publication.

7.3.2 Premises

The area where the oxygen 93 supply system is located should be maintained so that the risks of product being supplied to patients outside the specification are kept to a minimum.

Specifically, the air intake for the supply system shall be located in such a place as to minimize the risk of drawing in air to the supply system that has a level of contamination that is likely to either cause the supply system to supply product that is out of specification or cause the supply system to fail. A supervision system shall be put in place to ensure that:

- any adverse event in the vicinity of the supply system (including fire and pollution) that could affect the quality of the air will be detected and its impact being addressed immediately;
- any changes to the local environment are assessed to ensure they will not impact the air quality used in the supply system; and
- the access to the supply system shall be controlled and restricted to authorized persons.

Requirements regarding premises are detailed in section 6.

The source of supply shall be maintained at a temperature of between 10° C and 40° C in accordance with EN ISO 7396-1 [1]

7.3.3 Equipment

Within the EU, the supply system manufacturing oxygen 93 for medicinal use shall be CE marked according to the Medical Device Regulation 2017/745 EU [5].

Where oxygen 93 is manufactured on site, the supply system shall undergo a formal validation program to demonstrate that it is fit for purpose. See section 8 for detailed requirements.

7.4 Product quality

The quality management systems shall ensure that the quality of oxygen 93 supplied from the supply system always comply with the following European Pharmacopoeia monograph requirements (EP2455) [6]:

Table 4 Product Quality

Product	Requirements
oxygen assay	90.0% - 96.0 % V/V
carbon monoxide	≤ 5 ppm V/V
carbon dioxide concentration	≤ 300 ppm V/V
Oil	≤ 0,1 mg/m ³
Water	≤ 67 ppm V/V
Nitric oxide / nitrogen dioxide	≤ 2 ppm V/V
Sulfur dioxide	≤ 1 ppm V/V

NOTE A US Pharmacopoeia monograph exists for oxygen 93.

7.5 Responsibilities

As noted in 7.2, the healthcare facility shall nominate a person, normally the head pharmacist, responsible for the quality of the oxygen 93 manufactured on site at the points of use.

The nominated responsible person may delegate duties for the day-to-day operations to a number of nominated persons on the site including:

- A person nominated as head of production for the manufacture of the oxygen 93

- A person nominated as head of the quality control of the oxygen 93
- These roles shall be carried out by persons who are independent of each other. The heads of production and quality control shall formally assign their duties to nominated deputies to ensure that a nominated qualified deputy is available at any time.
- All nominated persons shall be trained and assessed for their competency to carry out the tasks documented within the relevant procedures.
- All nominated persons shall have a detailed job functional description describing their duties and responsibilities related to operating the supply system.
- An organisation chart showing the organisational reporting structure shall be documented.

7.5.1 Head of production responsibilities

The head of production shall:

- ensure that the oxygen 93 is manufactured according to the instructions for use provided by the equipment suppliers and any other documentation in order to obtain the required quality;
- approve any instructions for the manufacture and ensure their implementation through training and audit;
- ensure that the manufacturing records are routinely produced and evaluated;
- ensure the equipment maintenance is carried out according to the maintenance plan;
- control any contractors employed to maintain / repair any of the manufacturing equipment, using a permit to work system. See EIGA Doc 40 *Work Permit Systems* [19];
- ensure that the manufacturing supply system undergoes an appropriate validation program; and
- ensure the air quality to the supply system is monitored based on a risk management plan

7.5.2 Head of quality control - Responsibilities

The head of quality control shall:

- ensure that the quality control process is working effectively and continuously to identify any deviation of the oxygen 93 quality out of the specifications;
- review the quality control records produced to ensure that the product being supplied for use on site complies with the specification;
- ensure that all necessary quality control testing is carried out;
- approve the test procedures and frequencies, based on a risk management plan;
- ensure that the equipment used for quality control and manufacture is calibrated and maintained at the specified frequency;
- ensure the manufacturing equipment is subject to a validation programme;
- ensure that the personnel carrying out any manufacturing or quality control functions are trained for the activity and the training documented; and

- ensure that any identified non-conformances are investigated and appropriate corrective actions are carried out.

7.6 Quality control

7.6.1 Continuous monitoring – Process control

The process control system is all the measurements used to continuously control the settings of the supply system and activate the alarm systems.

The frequency of testing of each potential contaminant shall be determined from the risk analysis performed on each site. The responsible person shall ensure that the alarms set points and frequency of testing comply with the requirements.

The process control system shall include as a minimum:

- the critical control points identified through a risk management. See section 5 for generic hazard review;
- the European Pharmacopoeia requirements; and
- any other local regulations where applicable.

Table 5 Non-exhaustive list of parameters

Process control points	European Pharmacopoeia	Critical control point (risk analysis)	Intervals
Oxygen assay	X	X (double analysers)	Continuous
Carbon dioxide	X	X	Continuous
Carbon monoxide	X	X	Continuous
Moisture	X		Continuous NOTE Moisture content increase would lead to an accelerated damage of the oxygen 93 concentrator adsorbers.
Sulfur dioxide	X		According local regulations, or as a result of the risk analysis (air intake contamination), continuous monitoring can be required. At commissioning, and after any modification or significant intervention (mandatory)

Process control points	European Pharmacopoeia	Critical control point (risk analysis)	Intervals
Nitric oxide / nitrogen dioxide	X		According local regulations, and as a result of the risk analysis (air intake contamination), continuous monitoring can be required. At commissioning, and after any modification or significant intervention (mandatory)
Oil	X		According local regulations, and as a result of the risk analysis, continuous monitoring can be required. At commissioning, and after any modification or significant intervention (mandatory)
Oxygen flowrate 93		X	Continuous
Particle filters dP		X	Continuous
Oxygen concentration (room air)		X	Continuous
Gas temperature (compressors)		X	Continuous – Air compressors, oxygen 93 boosters and compressors

7.6.2 Supply source control

7.6.2.1 Traceability of sources in operation

As the oxygen 93 is continuously manufactured and consumed, there is no identified batch of product that can be recalled. The only requirement for traceability is to ensure that adequate records are maintained so that if an adverse event with a patient is identified, a link can be made to any other patients who were administered the same product can only be identified in a dynamic way, identifying conventional range of time during which the product can be expected to be homogeneous.

When any parameter out of specifications has been identified, the responsible person shall notify the clinical staff so that they are aware of the problem and can investigate whether it has had any impact on patients.

When the responsible person receives the notification from the clinical staff of an adverse event with a patient being administered oxygen 93, they shall identify which supply source(s) were operational from the relevant process control records.

When required by the medical staff, a notification shall be available to inform them of a potential change in the oxygen content of the gas supplied by the medical gas pipeline system. This requirement shall be identified by the risk management system.

7.6.2.2 Oxygen 93 reserve supply source

Where the oxygen 93 concentrator unit is used for the filling of cylinders / cylinder bundles for use as a permanently fitted reserve supply source, the process of filling should also be covered by the principles of GMP and other requirements required in the local authority's authorisation. It can also be necessary to comply with other pressure system legislation to demonstrate that the cylinders are suitable for filling and that they are not subjected to conditions outside their design range. Production records should be maintained to ensure there is a traceability of the product filled into the reserve supply source.

The healthcare facility should periodically fully empty the high pressure reservoir, filled with 93% oxygen, in order to avoid an enrichment of impurities which could build up over time due to the frequent top-filling of the reservoir.

7.7 Documentation

7.7.1 Operating procedures

Comprehensive operating procedures based on the manufacturer's instructions for use and the result of the risk analysis shall be available to ensure that the supply system is operated correctly. It is recommended that the operating instructions should incorporate check lists to ensure that critical tasks are performed at the defined frequency.

Procedures shall be approved by the head of production, who should ensure that they form part of the training material for all operational and maintenance personnel, including nominated deputies as defined in 7.5.

Procedures shall be updated whenever any changes are made to the supply system and should be reviewed at least every two years to ensure that they are still current.

7.7.2 Production Records

As the oxygen 93 is continuously manufactured, batches can only be defined as product produced between specific time lines. The definition of the batch should be based on risk management, to ensure that should there be any reason for the supply system to operate outside its set limits that the non-conformance can be identified and corrective actions implemented.

Records should be maintained of the analysis results and process control parameters as defined in 7.6.1, as well as supply source operational status as defined in 7.6.2. These results should be collected on-line via a validated data logging system or recorded manually at a defined interval based on risk management. The production records should be maintained for at least five years. If manual records are taken, these should be recorded on approved record sheets and filled out in pen; any errors should be clearly crossed out, initialled and, where appropriate, the reason for the error indicated.

Calibration records for the on-line analysers should also be kept and maintained with the production records.

7.7.3 Training records

The training records of all operational and maintenance personnel including nominated deputies shall be logged to demonstrate when the training was performed and that they understood the training. Ideally, they should undergo competency assessments to ensure that they are capable of operating the supply system correctly and are aware of the actions that should be taken when the supply system goes outside its normal operating conditions.

There should be a programme of refresher training for all personnel to ensure that they are continuing to operate and maintain the supply system correctly.

7.8 Audit and self-inspection

As part of the quality management system, there shall be a self-inspection plan that ensures that the supply system is audited on a routine basis. The frequency and scope of each inspection should be defined in an audit plan.

The results of the audits should be formally documented, detailing any non-conformances identified and the appropriate corrective and preventive actions agreed, including any specific timeframes which need to be met.

7.9 Product quality review

Product quality review is a regular periodic quality review of oxygen 93 production data and metrics which are conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications to highlight any trends and to identify production and process improvements.

The product quality review report should contain at least the following:

- review of critical in-process controls;
- review of all manufacturing cases where oxygen 93 produced failed to meet established specification(s) and their investigation;
- review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;
- review of all changes carried out to the processes or analytical methods;
- review of the results of the stability monitoring programme and any adverse trends;
- review of adequacy of any other previous process or equipment corrective actions;
- qualification status of relevant critical equipment and utilities; and
- a review of agreements and contracts in place to ensure that they are up to date, e.g. maintenance contract.

8 Process validation

8.1 General

Process validation is the means of ensuring and providing documentary evidence that the process is capable of consistently producing a finished product of the required quality in all operational conditions and that all safety measures are implemented and are efficient.

Prior to product being supplied to patients, the system shall be validated. It shall be verified that all process control parameters such as defined in 7.4, are within specified limits. During validation the system shall be challenged in order to verify that the oxygen 93 supply from the oxygen 93 concentrator units is stopped in case that critical process parameters are outside the specified limits. In this case the back-up source (secondary or reserve) shall automatically supply the oxygen demand.

The process validation shall be carried out under the supervision of the Responsible Person of the healthcare facility.

Clause 12 of EN ISO 7396-1 [1] (Testing, commissioning and certification) shall apply for the testing, commissioning and certification of the supply system.

All measuring devices used for the process validation shall be calibrated prior to their use. Their resolution and accuracy shall be appropriate for the values to be measured.

8.2 Installation qualification (IQ)

The IQ is a documented verification that the equipment or systems, as installed, comply with the approved design, the manufacturer's recommendations and/or user requirements.

The IQ shall include as a minimum:

- CE certificate of conformity of the oxygen 93 supply system;
- process and instrument diagram (P&ID) of the installation as installed;
- operational manuals of all the components of the supply system and the complete installation; and
- maintenance manuals of the components of the supply system and the complete installation

8.3 Operational qualification (OQ)

The OQ is a documented verification that the equipment or systems, as installed, perform as intended throughout the anticipated operating ranges.

The OQ shall include as a minimum:

- test of the different supply sources
- test of the monitoring and alarm systems, including all process control parameters

8.3.1 Test of the supply sources

Each source of supply shall be verified against its manufacturer's specifications and tested for all specified operating and emergency conditions including:

- switching conditions from one source of supply to another;
- switching from the main power supply to the hospital emergency power supply; and
- recovering from a total electrical power loss.

8.3.2 Tests of monitoring and alarm systems

The performance of all monitoring and alarm systems shall be tested in all specified operating and emergency conditions

Only one function shall be tested at a time.

The value at which each alarm or control is activated or reset (e.g. pressure, oxygen concentration, automatic shut-off and vent valves) shall be recorded.

All audio, visual and remote alarmed signals shall be checked and confirmed as functioning.

The correct behaviour of monitoring and alarm systems shall be verified in particular in the following conditions:

- switching from the main power supply to the hospital emergency power supply; and
- recovering from a total electrical power loss.

8.4 Performance qualification (PQ)

The PQ is documented verification that the equipment, software and ancillary systems, as connected together, can perform effectively and reproducibly.

The PQ shall include as a minimum:

- performance of each supply source: capability of the source to supply the correct oxygen concentration at different flowrates up to the maximum design flowrate. The sampling point for oxygen concentration shall be upstream the oxygen 93 buffer; and
- test of all impurities included in the European Pharmacopoeia. The sampling point shall be immediately downstream the oxygen 93 buffer.

9 Operations and maintenance

9.1 General

Standard operations procedures shall be defined based on manufacturers operating and maintenance manuals, and risk management. All personnel involved in operations and maintenance of the supply system shall be trained and their competencies verified. See 7.7 for requirements related to procedures and training.

These procedures shall cover the following operations:

- start up;
- automatic and manual shutdown;
- preventive maintenance;
- troubleshooting and repair; and
- safety checks.

9.2 Start up

A procedure shall define the necessary verifications and actions to be carried out before starting up a supply source after a planned or unplanned shutdown. Before any re-start, it shall be verified that all process parameters, including online analysis, are within the specified limits.

If maintenance has been performed, the procedure shall include formal confirmation that:

- the work has been completed, checked, and approved;
- all safety permits have been cleared and the equipment is ready to start. See EIGA Doc 40 *Work Permit Systems* [19]; and
- the maintenance operations (including cleaning and purging), do not adversely affect the quality of oxygen 93. In case of maintenance operations involving breaches of the system's integrity, it should be verified and recorded that the equipment is free from any contamination that could adversely affect the quality of the oxygen 93.

After starting the supply system, it shall be checked that all operating conditions are normal before letting the supply system run unattended. These conditions shall be re-checked after the system has been running for several hours.

9.3 Shutdown

A procedure shall define the necessary verifications and actions to be carried out before shutting down a supply source.

When shutting down an oxygen 93 generator either planned or unplanned (e.g. by power or utility failure, or by equipment malfunction), there is usually a built-in, fail-safe system of shutdown events.

According to the supply system's design, a number of actions will happen automatically to leave the supply system in a safe standby condition.

If there is no automatic system or if the automatic system fails, a procedure for manual shutdown listing all the necessary actions (such as product disposal and equipment venting) shall be implemented.

9.4 Maintenance

9.4.1 Maintenance safety

Any maintenance operations shall be managed using a permit to work system, which requires a risk assessment to be carried out prior to commencing any maintenance activities on the supply system.

Generic hazards for maintenance personnel include but not limited to:

- Electricity. Safe electrical work practices shall always be followed, including de-energizing, locking out and tagging of all equipment before performing maintenance. These procedures are designed not only to prevent electric shock but also to prevent automatic starting when an operator is servicing equipment.
- Pressure. The system shall be depressurized prior to disconnecting any element under pressure.
- Oxygen-deficient atmosphere. The maintenance personnel shall wear an individual oxygen detection device while working on the supply system.
- Oxygen-enrichment, increasing the risk of fire.
- Dusting. The maintenance personnel shall wear the appropriate protection equipment when opening the molecular sieve containing zeolite, changing the filters on the concentrator unit, etc.
- Oxygen ignition. Any parts used for replacement shall follow the same specifications as the original ones, including material compatibility and cleaning for oxygen service.

9.4.2 Preventive maintenance program

The preventive maintenance program shall be part of the quality management system.

This program shall include as a minimum periodic verification of the following:

9.4.3 Safety checks

The critical control process parameters shall be checked at intervals, based on the risk assessment.

The result of the safety checks shall be documented. This shall include but not limited to:

- Low oxygen concentration alarm (90%) and associated automatic shutdown function. The check could be made by applying gas mixture of 10% nitrogen in oxygen.

- Carbon monoxide and carbon dioxide high level alarms and automatic shutdown functions. The check could be made using the appropriate calibration gases for the detectors.
- Oxygen monitoring system in the room to measure high or low oxygen concentrations. Follow oxygen detection device manufacturer's instructions. Visual and audible warning signs shall be verified. Additionally, oxygen analyser cells shall be replaced on a regular basis, depending on the usage and manufacturers recommendations.
- Gas temperature measurement and automatic shutdown functions. Follow the compressors maintenance manuals.
- Filter differential pressure measurement and automatic shutdown functions.
- Continuity of supply
- The functionalities of switching from one source to another shall be verified periodically, including the corresponding alarms.

9.4.4 Analysers calibration and maintenance

All analysers controlling and safeguarding the oxygen 93 produced shall be calibrated periodically using a certified calibration gas and in accordance with the manufacturer's instructions.

The calibration gases shall be used as specified in the European Pharmacopoeia monograph (EP2455) [6].

The maintenance shall be performed according to the analysers' manufacturer maintenance instructions.

9.4.5 Compressor maintenance

Compressor maintenance shall be in accordance with the manufacturer's operating and maintenance manuals.

9.4.5.1 Filter replacement

Compressed air filters, air inlet filters and product filters shall be cleaned or replaced on a regular basis depending on the environment and the manufacturers recommendations.

9.4.5.2 Pressure equipment

Part of the oxygen 93 supply system equipment shall comply with the definition of Pressure Equipment according to the regulation, such as the Directive 2014/68/EU [8]. This includes but is not limited to adsorber vessels, buffers, reserve source cylinders and bundles re-filled on site.

Manufacturers shall state the design life of the vessels.

There shall be in place an inspection program to monitor the pressure equipment according to their specific conditions of use, in compliance with national legislations and statutory inspection. This can require internal inspections, wall thickness measurement, non-destructive testing inspections of welds and/or hydrostatic pressure tests. Depending on the local legislation, pressure vessels may require to be inspected by a third party inspection body at specified intervals.

Pressure testing and repairs of vessels and pipes shall be carried out according to the applicable code and local regulations. Vessel repairs could require a re-certification by a notified body. Even when that re-certification is not required, vessels and piping shall be leak tested before start up.

10 Waste

Waste materials such as used lubrication oils, adsorbent, and/or drier desiccant and other used repair materials shall be disposed of in accordance with regulations. Refer to the appropriate safety data sheets for details.

11 References

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- [7] EN ISO 14971 *Medical devices. Application of risk management to medical devices* www.cen.eu
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- [18] EIGA Doc 115 *Storage of cryogenic air gases at users' premises* www.eiga.eu
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