

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

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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 manufacturers 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, Snowden 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.