

USAID MEDICINES, TECHNOLOGIES, AND PHARMACEUTICAL SERVICES (MTaPS) PROGRAM

Improved Access. Improved Services. Better Health Outcomes.

Quality Assurance Practices for Medical Oxygen Systems

Technical Resource for
Distribution- and Facility-Level
Medical Oxygen Systems

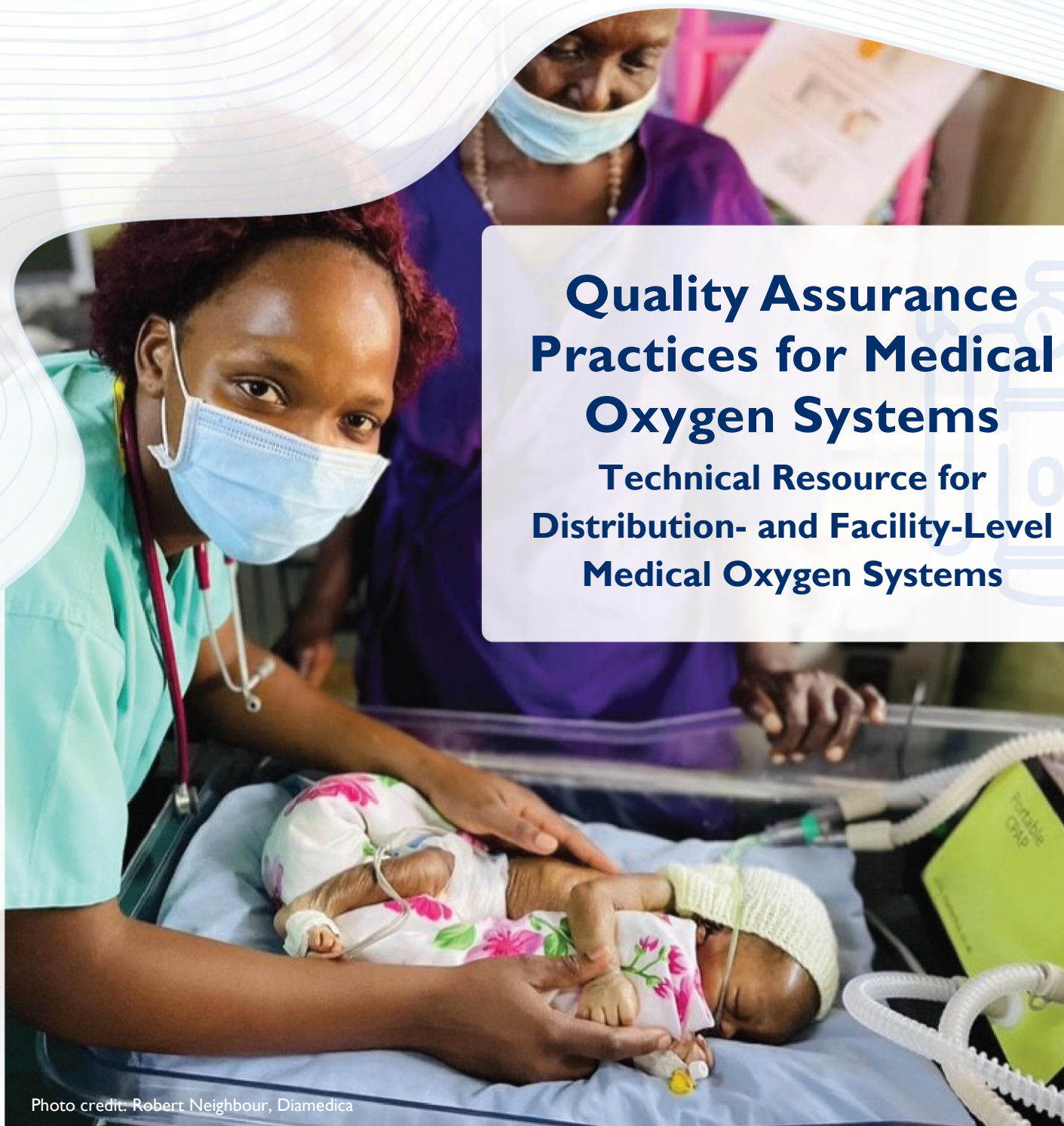


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The US Agency for International Development (USAID) Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program's *Quality Assurance Practices for Medical Oxygen Systems: Technical Resource for Distribution- and Facility-Level Medical Oxygen Systems* aims to support any entity—public or private sector, multilateral or not-for-profit—to establish and/or implement quality assurance practices related to sourcing and/or producing medical oxygen on-site and to its storage and distribution so patients receive oxygen that is safe, reliable, continuous, and of acceptable quality.

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ACRONYMS AND ABBREVIATIONS

AIA	authorized inspection agency
AP	authorized person
ASU	air separation unit
BP	British Pharmacopoeia
CAPA	corrective and preventive action
CO	carbon monoxide
CO ₂	carbon dioxide
CoA	certificate of analysis
CPD	continuous professional development
DOT	Department of Transportation (US)
EC	European Commission
EIGA	European Industrial Gases Association
GDP	good distribution practices
GHS	globally harmonized system
GMP	good manufacturing practices
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
LMIC	low- and middle-income countries
LOX	liquid oxygen
MTaPS	Medicines, Technologies, and Pharmaceutical Services
NRA	National Regulatory Agency/Authority
O ₂	oxygen (molecule)
Ph. Eur.	European Pharmacopoeia



Ph. Int.	International Pharmacopoeia
PIC/S	Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme
PPM	planned preventive maintenance
ppm	parts per million
PSA	pressure swing adsorption
QA	quality assurance
QC	quality control
QU	quality unit
RPV	residual pressure valve
SN	serial number
SOP	standard operating procedure
SRA	stringent regulatory authority
TU	terminal unit
UN	United Nations
UNDOS	United Nations Department of Operational Support
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
US FDA	United States Food and Drug Administration
USP	United States Pharmacopoeia
VIE	vacuum insulated evaporator
VSA	vacuum swing adsorption
V/V	volume concentration of a solution, expressed as a %
WHO	World Health Organization



CONTENTS

Acknowledgements	i
Acronyms and Abbreviations.....	ii
Executive Summary	vi
1. Introduction.....	1
1.1. Background.....	1
1.2. Rationale	2
1.3. Purpose and Scope.....	2
1.3.1. Purpose.....	2
1.3.2. Scope	3
1.4. How to Read this Document.....	4
1.5. Target Audience.....	4
1.6. Development Process.....	5
2. Overview: Medical Oxygen Systems and their Quality Systems	6
2.1. Medical Oxygen Systems	6
2.1.1. Sources.....	6
2.1.2. Transport and Storage	7
2.1.3. Distribution—Pipeline Network and Cylinder Use.....	8
2.1.4. Delivery to the Patient.....	9
2.2. Quality Systems for Medical Oxygen.....	9
2.2.1. Regulation of Medical Oxygen.....	10
2.2.2. Good Manufacturing Practices and Medical Oxygen	10
2.2.3. Quality Parameters of Medical Oxygen	11
2.2.4. Quality Assurance of Medical Oxygen at Health Facilities	13
2.2.5. Medical Gas Operational Plan—Quality Considerations.....	14
3. Applying QA and QC to Medical O ₂ Systems.....	16
3.1. Personnel.....	17
3.1.1. Entities External to Health Facilities	17
3.1.2. Personnel within Health Facilities	18
3.1.3. Capacity Building.....	20
3.2. Premises and Equipment.....	21
3.2.1. General Site Safety	21
3.2.2. LOX Reception Requirements.....	21
3.2.3. Oxygen Generator Plants in Hospitals.....	22
3.2.4. Premise and Equipment for Cylinder Filling	23
3.2.5. Pipeline Management	24
3.2.6. Pipeline and Cylinder Accessory Sets.....	24
3.2.7. Maintenance and Repair	25



3.3. Source-Specific Requirements: Production or Procurement.....	26
3.3.1. LOX: Quality Assurance When Procuring Medical Oxygen.....	27
3.3.2. Oxygen Generator Plants: Quality Assurance When Producing in Hospitals.....	27
3.3.3. Cylinder Filling.....	28
3.4. Transportation and Storage.....	30
3.4.1. Bulk Liquid Oxygen.....	31
3.4.2. High-Pressure Gas Cylinders.....	32
3.4.3. Facility Reception Point QA Considerations.....	32
3.5. Documentation and Recordkeeping.....	33
3.6. Quality Control.....	34
3.6.1. Test Methods and Equipment.....	34
3.6.2. Sampling.....	35
3.6.3. Product Release.....	36
3.7. Complaints and Recall.....	36
3.8. Self-Audit/Inspection.....	37
Annex A: Role-Specific QA Supplements.....	38
A1: Job-aid for authorized person (typically head pharmacist).....	39
A2: Job-aid for head of production.....	41
A3: Job-aids for operators.....	42
A4: Job-aid for head of quality control.....	47
A5: Job-aid for quality controllers.....	48
A6: Job-aid for transporter (and distributor, if applicable).....	49
Annex B: Recordkeeping.....	51
On-site oxygen generator plant.....	51
Cylinder filling.....	52
LOX reception.....	53
Sample CoA.....	54
Annex C: Resources.....	55
References.....	59



EXECUTIVE SUMMARY

Medical oxygen is an essential medicine [1] and is needed at most levels of the health system. Access to it is necessary for newborns and children with respiratory distress, hypoxemia resulting from pneumonia, and other conditions. Vulnerable groups such as the elderly and pregnant women with obstetrical complications need oxygen on a regular basis, especially when experiencing critical health conditions. Oxygen is essential for surgery and trauma patients and has been a critical treatment during the COVID-19 pandemic.

Oxygen is available on the market for both industrial and medical applications. Medical oxygen differs from industrial oxygen in terms of the quality systems that are applied along its supply chain—manufacture, storage, and distribution—all of which must be documented to ensure that the product meets authorized specifications for identity, purity, and content and to avoid unacceptable risks for patients, such as those arising from cross-contamination. [2, 3] Industrial oxygen is not intended for medical use.

Since the COVID-19 pandemic, notable investments have been made in oxygen supply systems—either by installing new oxygen generating plants (PSA or VSA) or by purchasing liquid oxygen for use where available and appropriate. With a focus on supply, there must also be assurance that medical oxygen is of acceptable purity, without hazardous impurities, and deemed safe for patient use.

This USAID MTaPS technical resource document for ensuring the quality of medical oxygen, whether produced on-site or outsourced, aims to serve as a reference for country stakeholders, regardless of sector, to establish and/or implement and adhere to quality assurance practices along the medical oxygen supply chain. Tools for practical application are included.

This technical resource was drafted using relevant open-source materials to maintain accessibility for all end-users. A broad group of stakeholders representing public, private, multilateral, and not-for-profit entities that operate within the medical oxygen space were consulted in the process, and their feedback was incorporated into the document where relevant and applicable.

The document provides an overview of medical oxygen systems, complementing existing technical resource and guidance documents from WHO and WHO-UNICEF as well as other previously published resources. Also covered in the document are the theories of medical quality systems and quality parameters for medical oxygen, as well as how they can be applied to hospital production units and associated health facility oxygen systems. These theories are explored in detail, focusing on QA and QC for on-site production and outsourcing of oxygen, all along its supply chain, as the medicine moves through the medical oxygen system to and within health facilities.

The annexes include practical, role-specific job aids detailing specific activities and their requisite frequency and documentation requirements. Other resources provided in the annexes are required record-keeping templates and samples of certificates of analysis, as well as relevant resources for further exploration.

This final product is intended to serve as a global public good for low- and middle-income countries. It is hoped that the document will complement and enhance countries' existing quality assurance practices along the medical oxygen supply chain where needed or, for those countries with no established and/or structured practices, will serve as a resource to start developing and implementing such practices.



I. INTRODUCTION

I.1. BACKGROUND

Medical oxygen is an essential medicine [1] and is needed at most levels of the health system. Access to medical oxygen is necessary for newborns and children with respiratory distress, hypoxemia resulting from pneumonia, and other conditions. Vulnerable groups, such as the elderly and pregnant women with obstetrical complications, need oxygen on a regular basis, especially when experiencing critical health conditions. Oxygen is essential for surgery and trauma patients and has been a critical treatment during the COVID-19 pandemic.

Oxygen is available on the market for both industrial and medical applications. Medical oxygen differs from industrial oxygen in terms of the quality systems that are applied along its supply chain—manufacture, storage, and distribution—all of which must be documented to ensure that they meet authorized specifications for identity, purity, and content and to avoid unacceptable risks for patients, such as those arising from cross-contamination. [2, 3] Industrial oxygen is not intended for human use.

Sources of oxygen in low- and middle-income settings include oxygen concentrators, pressure swing adsorption (PSA) and vacuum swing adsorption (VSA) oxygen generator plants, and bulk-stored liquid oxygen (LOX) produced by large air separation units (ASUs).

At the outset of the COVID-19 pandemic, many health facilities were unable to deliver sufficient volumes of medical oxygen because demand exceeded supply. Globally, health facilities have been reassessing their oxygen needs and investing, either through domestic funds or donor support, to meet the increased demand. They have been doing so either by installing new oxygen generating plants or by using LOX—mostly industrial LOX¹ on an emergency basis when permissible—if available.

In addition to addressing oxygen-supply needs, efforts have been made to ensure that the oxygen administered to patients is safe and quality assured. However, the rapid scale up has raised concerns about the quality of medical oxygen and whether adequate systems, as well as global manufacturing and supply safety standards, are in place to ensure that it is of acceptable purity, without hazardous impurities, and deemed safe for patient use.

On May 26, 2023, at the 76th World Health Assembly, the *Increasing Access to Medical Oxygen Resolution*² was unanimously adopted by 194 member-state governments of the WHO. This resolution highlights the need for quality assured medical oxygen systems. [4]

Regulation of medicines, including oxygen and other medical gases, is a function of the National Regulatory Authority. Many countries do not have legal provisions and regulations in place for medical gases, but even those that do sometimes are unable to effectively regulate these gases, potentially leading to a lack of regulatory oversight for medical oxygen produced and administered to patients. According to a survey [5] carried out by the US Agency for International Development Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program in 2020, four out of nine countries had a

¹ At the time of writing, only a few ASUs in low- and middle-income countries (LMICs) produce medical grade LOX.

² This resolution was submitted by Uganda and co-sponsored by 33 member states of WHO



clear framework in place for regulatory approval of medical gases, including oxygen. However, only two of the four were effectively implementing and enforcing regulations.

The manufacture of medical oxygen from an ASU is guided by good manufacturing practices (GMP) standards for medical gases [6, 7, 8, 9, 10]. Technical specifications for PSA oxygen generating plants and oxygen therapy devices have been developed by WHO [11, 12, 13] to guide the selection and procurement of quality technologies, specifically for use in low-resource settings.

Quality assurance (QA) is an aspect of quality management focused on providing confidence that quality requirements will be continuously fulfilled. It gives suppliers a means of ensuring that their products consistently meet specified quality requirements and helps consumers trust that the products supplied will measure up to quality parameters. [14] The purpose of QA in this context is to make certain that the medical oxygen reaching a patient is safe and effective and that it meets specified quality standards. Appropriate practices for production, storage, and distribution of medical oxygen should be followed to ensure its quality and avoid unacceptable risks for patients through, for example, particulate and microbial contamination. [2, 3] QA activities should be comprehensive, spanning the entire manufacturing and supply process, from the time oxygen leaves the production unit up to the point of patient use.

1.2. RATIONALE

The management of a medical oxygen supply chain requires a multitude of activities, including but not limited to systems planning, manufacturing, procurement of goods and services, regulation of medicines and medical devices, and operational procedures. While each of these aspects has benefited from an increase in international guidance and/or technical resources, a gap has been noted in developing a holistic approach to quality assurance practices spanning the oxygen supply chain. Lack of such practices can have a negative impact on the quality of oxygen administered to the patient, thereby affecting health outcomes.

1.3. PURPOSE AND SCOPE

1.3.1. Purpose

This document serves as a technical resource for health facilities to ensure that oxygen provided for patient care is safe and effective.

The aim is to provide clear, practical guidance for implementing QA and quality control (QC) measures along the oxygen supply chain, taking into consideration the principles of good manufacturing and good distribution practices and associated controls within the overarching quality system framework. Any entity looking to procure medical oxygen or manage oxygen systems may refer to content herein to establish or determine quality requirements and quality assurance practices to implement.

Complementary to pre-existing technical resource and/or guidance documents, this technical resource could enhance the capacity for national regulatory authorities to inspect health facilities producing medical oxygen to ensure that appropriate quality assurance procedures are documented, appropriate practices are being followed and recorded, and the medical oxygen supply conforms with national quality specifications.



1.3.2. Scope

In light of the recent rapid scale-up of access to oxygen supply, MTaPS has developed this technical resource document to support entities in the public or private, multilateral or not-for-profit, sectors to establish and/or implement and adhere to quality assurance practices along the medical oxygen supply chain—from acquisition of LOX or production via PSA/VSA oxygen generator plants to transportation and storage to distribution to and within health facilities—to continuously ensure the quality of medical oxygen for clinical care.

This document serves as a technical resource for health facilities related to personnel, premises, production, transportation, and storage. It also serves as documentation of associated processes and their validation and control, where applicable, to ensure the quality of medical oxygen—its identity, strength, and purity—as well as its safe delivery.

In addition to quality systems theory and an oxygen systems overview, this resource will provide tools for practical application in the form of job-aids related to QA and QC practices, all of which are intended to serve as a global public good for LMICs.

The content herein complements *The International Pharmacopoeia* [15], the US Food and Drug Administration's (US FDA's) pharmacopoeia (USP), the European Commission's (EC's) pharmacopoeia (Pharma. Eur.), [16] and their respective GMP publications. [6, 7, 8] It also complements other publications pertaining to medical oxygen, such as the WHO-UNICEF *Technical specifications and guidance for oxygen therapy devices*, WHO's *Priority medical devices list for the COVID-19 response and associated technical specifications*, WHO's *Technical Specifications for Pressure Swing Adsorption (PSA) Oxygen Plants*, and WHO's *Foundations of medical oxygen systems*. [11, 12, 13, 17]

The facility-level medical oxygen supply chain will be explored from the perspective of quality assurance, covering the roles and responsibilities of personnel and recommended activities to enhance and maintain the quality and safety of medical oxygen.

This technical resource document will not cover:

- Oxygen system implementation strategies. It will not cover how to select source types, execute procurements, carry out installations, or commission, operate, or maintain medical oxygen systems. Guidance on those topics is covered in UNICEF's *Oxygen System Planning Tool* [18], UNDOS' *United Nations Procurement Manual* [19], and WHO's *Foundations of medical oxygen systems* [17].
- Health financing, a requirement for the continued functioning of any health system (including medical oxygen systems), must be considered. WHO's *Health Financing* website hosts resources such as guidance documents, training, and policy statements. [20]
- Recommendations on the industrial manufacture of medical oxygen, which is covered in WHO's *Good Manufacturing Practices for Medicinal Gases—Interim version*. [6]
- QA practices for manufacturing LOX for use in oxygen therapy medical devices. Where existing technical resource and guidance exists, references will be made.
- QA or technical guidance for installing, testing, or commissioning of medical oxygen systems, inclusive of ancillary requirements such as power supply.
- QA measures for the procurement of associated medical oxygen therapy devices (such as nasal prongs, gauges, flowmeters, etc.).
- Oxygen concentrators, for which substantial technical and operational guidance already exists. Current specifications can be found in WHO's *Priority medical devices list for the COVID-19 response and associated technical specifications* [13]; more comprehensive, technical guidance can be found in WHO-UNICEF's *Technical specifications and guidance for oxygen therapy devices* [12].
- Guidance on the clinical application of medical oxygen or patient monitoring during use of medical oxygen. End-users of medical oxygen should consult relevant and appropriate clinical guidelines for the safe and appropriate application and delivery of medical oxygen to patients, such as WHO's *Oxygen therapy for children* [21] and WHO's *Living guidance for clinical management of COVID-19* [22].



I.4. HOW TO READ THIS DOCUMENT

This document provides clear, practical, technical guidance for quality assurance practices for medical oxygen to and within the health facility, up to the point of clinical application. It is intended to serve as a reference document and complement other relevant publications.

- Chapter 2 provides an overview of medical oxygen systems, complementing existing technical resource and guidance documents from WHO and WHO-UNICEF, as well as other previously published resources. This chapter also covers the theory of quality systems, quality parameters for medical oxygen, and how quality systems can be applied to hospital production units and associated health facility oxygen systems.
- Chapter 3 delves into the particulars of quality assurance practices as they relate to the transport of medical oxygen to, and the production and distribution of medical oxygen within, health facilities.
- The annexure comprises:
 - Role-specific quality assurance supplements for health-facility oxygen systems in a job-aid format, complete with activity, description, and requirements for frequency and documentation.
 - Documentation and recordkeeping requirements, templates, and samples.
 - Resources for further exploration. Hyperlinks to many of the technical resources or guidance documents referenced herein, as well as descriptions of their purpose and/or scope, are provided.

Links to QA tools and resources in this document's annex will be found in text boxes throughout, where applicable.

Disclaimers:

- National laws, where they exist, shall take precedence over any suggested practices contained in this technical resource. Users shall familiarize themselves with local regulation and adapt the content herein accordingly.
- While every attempt has been made to develop a comprehensive document, it should not be assumed that all local standards, procedures, or tests have been captured.
- Any abnormal or unusual event shall warrant an investigation by competent engineers and the facility's authorized person (AP) until a resolution has been reached.

I.5. TARGET AUDIENCE

The target audience for this document is entities and institutions involved with facility-level medical oxygen systems, including on-site production or outsourcing and the associated supply chain. The audience will include:

- Ministries of Health
- National Regulatory Authorities/Agencies (NRAs), including regulatory inspectors
- Suppliers and distributors of medical oxygen
- Transporters of medical oxygen
- Health facilities procuring/producing and handling medical oxygen
 - Management and administration
 - Pharmacists
 - Clinical staff
 - Technical staff (including engineers) and those operating and maintaining oxygen generator plants and cylinder filling stations



I.6. DEVELOPMENT PROCESS

MTaPS, after multiple meetings with WHO, developed an outline for a technical resource document for QA of medical oxygen that would complement existing WHO resources and initiatives. MTaPS engaged a consultant with extensive experience in the medical oxygen space to draft this technical resource document. Materials used to support the development of this technical resource have been referenced, where applicable. Most materials used are open-source and therefore available to the public without fees, should any user of this document wish to seek further information. The most pertinent resources have been compiled in Annex C, complete with links and descriptions.

The draft document was first reviewed by the MTaPS team, which then shared it with a broader group of stakeholders representing public, private, multilateral, and not-for-profit entities that work within the medical oxygen space and solicited their written feedback over a set period. A subsequent virtual workshop was held on March 21, 2023. Outstanding comments, questions, and ideas from the draft dissemination were discussed broadly with the stakeholders in attendance. Any comments that fell outside the scope of this document were also acknowledged.

All feedback in this process was consolidated and incorporated into the document where relevant and applicable.



2. OVERVIEW: MEDICAL OXYGEN SYSTEMS AND THEIR QUALITY SYSTEMS

This chapter provides a brief overview of medical oxygen systems. It also provides an overview of quality systems for medical oxygen and how their principles can be used to establish best practices for the medical oxygen supply chain for health facilities.

2.1. MEDICAL OXYGEN SYSTEMS

This section will provide a brief overview of the components of medical oxygen systems—from manufacture through delivery—with a focus on how these systems are incorporated into health care facilities. The intention is to provide adequate context to serve as a point of reference for the application of quality assurance practices along the medical oxygen supply chain.



Caution:

While oxygen itself is not flammable, it greatly supports and accelerates combustion.

Fire risk increases significantly in oxygen enriched environments.

- Detecting an oxygen-enriched environment is difficult—the gas is colorless and odorless.
- Quality assurance practices across the medical oxygen supply chain can help minimize fire risks associated with oxygen enrichment.

2.1.1. Sources

No matter the source, the raw material for medical oxygen is ambient air.

Liquid oxygen is manufactured at an ASU located off-site from health facilities (Figure 1). Reaching purities in excess of 99%, when used for medical applications it is referred to as Oxygen 99³ on pharmacopoeia monographs. [16] Where LOX sources are available and appropriate, their use is typically justified when a facility demand is more than 75m³ of gas per day. [24] When LOX is used at health facilities, it is either via a vacuum insulated evaporator (VIE) system that converts the liquid to gas or via high-pressure gas cylinders holding LOX that has already been converted into its gaseous state.

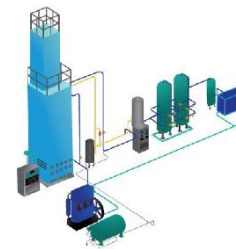


Figure 1: ASU for LOX production [23]

The operating principles behind PSA and VSA oxygen generator plants (Figure 2) are very similar to one another,⁴ and both types can produce oxygen that is up to 96% pure. When the oxygen they produce is used for medical applications, they can contain no less than 90% and no more than 96% and is referred to as Oxygen 93 on pharmacopoeia monographs. [16] These units are typically located within a hospital. Since the oxygen is already in its gaseous form, it can be conveyed directly to the bedside if the facility has a piped distribution network. It also can be compressed to fill high-pressure gas cylinders.



Figure 2: On-site oxygen generator plant, PSA type [23]

³ It is also sometimes referred to as Oxygen 99.5.

⁴ The key difference between PSA and VSA is how pressure in the sieve beds, where the oxygen is concentrated, is achieved. A more in-depth comparison can be found in WHO's *Foundations of medical oxygen systems*. [17]



Bedside concentrators are another source of gaseous oxygen that can provide lower-flow oxygen directly to the patient, but they are beyond the scope of this document. Details related to quality assurance of these products can be found in WHO's *Priority medical devices list for the COVID-19 response and associated technical specifications* [13] and WHO-UNICEF's *Technical specifications and guidance for oxygen therapy devices*. [12]

2.1.2. Transport and Storage

Medical oxygen can be transported in its liquid and gaseous states, with each form requiring varying degrees of supportive infrastructure. A brief description is provided herein, but more details can be found in WHO's *Foundations of medical oxygen systems*. [17]

LOX can be moved great distances using “ISOtainers” on ships, trains, or trailer trucks (Figure 3), or it can be transported in purpose-built tanker trucks (Figure 4) if road conditions allow for safe passage. If the manufacturer of the LOX is not moving its own product, any enlisted third party—such as a wholesaler or distributor— will be responsible for preserving the chain of custody, which refers to the documented practice of maintaining the integrity of the product.

To use LOX at a health facility, on-site storage is needed. This can be achieved using large vacuum insulated storage tanks, smaller “MicroBulk” tanks, or specialized LOX cylinders for medical application. Before use, LOX must be converted from liquid to gas. A VIE system or MicroBulk can facilitate the conversion for larger supply, liquid cylinders can too if they are equipped with a vaporizer coil. Once the oxygen is vaporized, a piped distribution network in the hospital is needed to move the gas to the patient.

A far less common configuration is cylinder filling directly from LOX, which requires specialized equipment (cryopump, high-pressure vaporizer) as well as separate housing.

Oxygen in its gaseous form can be stored and transported in ubiquitous high-pressure gas cylinders. Gaseous oxygen is far less dense than its liquid counterpart, which results in significantly less efficient storage. However, cylinders have a high degree of portability and can reach almost any destination because they are quite small compared to typical LOX storage vessels. Once at their destination, gaseous oxygen cylinders can be connected to a pipeline network via a manifold or be used at the bedside with minimal supportive infrastructure. Facilities using cylinders must have structured reception and inspection procedures and a system for storage that keeps full cylinders separate from empty cylinders and oxygen separate from other gases.



Figure 3: ISOtainer [25]



Figure 4: LOX tanker truck [26]



2.1.3. Distribution—Pipeline Network and Cylinder Use

Pipeline networks for the distribution of medical oxygen within a health facility can enhance management of the medical gas supply and greatly improve provider workflows. These distribution networks can cover an entire facility, from source (either LOX or oxygen generator plants such as PSA and VSA) to all wards and services where oxygen would be used, or they can be installed in higher priority wards or services and receive oxygen either directly from the source or from a cylinder distribution manifold. Examples of such configurations can be found in WHO's *Foundations of medical oxygen systems*. [17]

Where the National Regulatory Authority permits, gaseous LOX and oxygen from an on-site generator plant can be used in combination on a pipeline system. [27, 28] Such an arrangement could have quality implications, though, as the oxygen content at the pipeline outlet point can vary between 90% and 100% and may therefore not always be compliant with Oxygen 93 or Oxygen 99 monographs of applicable pharmacopoeias.

Only professionals experienced in medical gas pipeline networks shall be engaged in system design to ensure that quality is held paramount and system security is managed according to facility need. Installation and maintenance shall be carried out by personnel trained and experienced in medical pipeline networks.

Note: There has yet to be a global public good published with firm recommendations on the appropriate and practical design, materials, and installation methods for medical gas pipeline systems in LMICs. It is recommended that implementers use the following resources when planning and installing medical gas pipeline systems:

- HTM-02-01: Medical Gas Pipeline Systems, Parts A and B [24, 29]
- European Industrial Gases Association (EIGA) Document 13/20: Oxygen pipeline and piping systems [30]
- NFPA 99: Health Care Facilities Code [31]
- International Organization for Standardization (ISO) 7396-1: Medical gas pipeline systems [27]

While pipeline installations have notable financial implications, notwithstanding costs for recommended redundancies to ensure continuity of supply, planners and decision-makers shall weigh the ongoing costs of sourcing oxygen cylinders, including associated logistics.

Until more robust research is done, using non-metals for the pipeline network should be avoided. [30]

Another aspect of distribution includes the flowmeters used in terminal wall units of a pipeline distribution network as well as pressure regulator and flowmeter sets used on cylinders. These are medical devices that regulate the pressure and flow, respectively, of medical oxygen, facilitating the safe and comfortable delivery to the patient. Also used are humidifiers, which enhance comfort in delivery by adding moisture to the otherwise dry medicine to avoid irritating the patient's airway. More details can be found in WHO-UNICEF's *Technical specifications and guidance for oxygen therapy devices*. [12] As these are reusable devices, QA must be upheld, and they therefore will be discussed herein.



2.1.4. Delivery to the Patient

This is the final stage in the medical oxygen supply chain, comprising the interface used for patient delivery, from more simple interfaces such as nasal prongs through a range based on clinical need to more complex interfaces such as those used in ventilatory support (both invasive and non-invasive).

Delivery interface products are typically single-use, and thus facilities do not need to consider their longer-term maintenance. They do need to rely on robust procurement practices, such as ensuring that all medical devices procured are registered in country and that stock is appropriately managed within the facility, typically by the pharmacy. However, oxygen delivery to the patient and associated interface devices are considered out-of-scope, and this technical resource will not cover these products. For further technical reference, refer to WHO-UNICEF's *Technical specifications and guidance for oxygen therapy devices* [12] and WHO's *Priority medical devices list for the COVID-19 response and associated technical specifications* (Interim guidance) [13]. For clinical reference, refer to WHO's *Oxygen therapy for children* [21] and WHO's *Living guidance for clinical management of COVID-19* [22].

2.2. QUALITY SYSTEMS FOR MEDICAL OXYGEN

Quality systems set the overarching structure in the manufacture and distribution of medical products. These help to ensure that every medicine consumed by a patient and every medical device used on a patient meets quality requirements, remains effective in its purpose and is safe for both the patient and health care provider at all times.

Quality can only be assured when clearly defined parameters for practice are applied and associated controls for monitoring are established, maintained, and measured. Quality systems cover details concerning the following:

- Establishment/confirmation of product quality requirements and conformance thereto
- Application of principles in the spirit of GMP
- Quality assurance practices and the responsibilities of stakeholders involved
- Operational plan requirements: quality management and risk management plans

Figure 5 illustrates the relationship between the broad segments of quality systems and how they interact with and operate alongside one another.

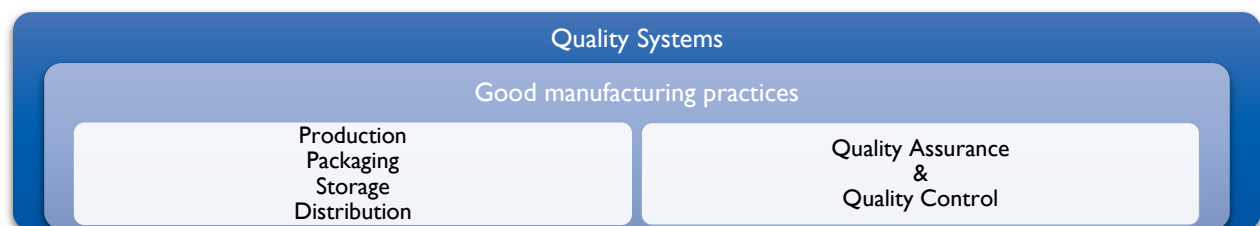


Figure 5: Quality systems framework for medical oxygen (developed from language in WHO, US FDA, and EC's medical oxygen GMP guidance [6, 8, 32])

Quality systems are driven by policy, encompass GMP, QA, and QC, and are governed by regulatory standards.



2.2.1. Regulation of Medical Oxygen

Most countries have an NRA and/or a registration process for medicines whereby local laws and regulations must be followed. However, a gap has been identified where many NRAs do not have a clear framework for the regulation of medical gases, including medical oxygen [5], which would typically cover:

- Control of oxygen as a medicine along the supply chain
- Certification of manufacturers for compliance with GMP
- Enforcement of medical oxygen distributors' and suppliers' compliance with a quality management system, including good distribution practices (GDP) and the application of vigilance principles
- Provision of tools for the application and assessment of QA compliance for medical gases

NRAs without an existing framework for medical oxygen are justified to adapt those of stringent regulatory authorities (SRAs)⁵—regulatory agencies that apply stringent standards of quality, safety, and efficacy in their reviews of medicines, vaccines, and medical devices applying for marketing authorization.

2.2.2. Good Manufacturing Practices and Medical Oxygen

GMP provides oversight and control over the manufacture of medicines for continued safe production and quality output. Compliance with GMP is enforced by regulatory authorities; manufacturers can be audited to ensure good standing.

Normative GMP guidance documents for the manufacture of medical gases, including medical oxygen, exist. However, these documents contain notable caveats that will apply to the manufacture of medical gases in most low- and middle-income countries:

- The European Commission's (EC) GMP recognizes differences between the manufacture⁶ of medicinal gases and that of more traditional pharmaceutical products. [32]
- The manufacture and handling of medicinal gases in hospital (such as with PSA or VSA) falls outside the scope of the WHO's and EC's GMP guidance documents. [6, 32]

Nevertheless, the normative guidance documents suggest that relevant GMP principles be applied to the facility-level manufacture and distribution of medical oxygen. [6, 7, 33]⁷

As with any medicine, the manufacturing process for medical oxygen shall be clearly defined, validated, and systematically reviewed to ensure that it can consistently produce oxygen at the quality required. Thus, application of GMP principles to the production of medical oxygen within a hospital should

⁵ Stringent Regulatory Authorities (SRAs) are those participating in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This includes [65]:

“a) a member of the ICH prior to 23 October 2015, namely the US Food and Drug Administration (FDA), the European Commission, and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or

b) an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or

c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway.

⁶ For medical oxygen, the active pharmaceutical is extracted from ambient air, which is the raw or “starting material.”

Therefore, very little upstream control of the active substance in the starting material exists. Additionally, containers are reused (e.g., bulk storage tanks, high-pressure cylinders).

⁷ EIGA: DOC 99/15 Section 2 – Scope; WHO: Draft GMP guidance Section 2 – Scope; EU: Annex 6 contains guidance for the interpretation of the principles and guidelines of GMP for medicinal products for human use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC.



consider the following: personnel; premises and equipment; source-specific requirements (including on-site production); transportation and storage; documentation and recordkeeping; quality control; complaints and recalls; and self-auditing.

2.2.3. Quality Parameters of Medical Oxygen

Multiple globally recognized pharmacopoeia, such as those of SRAs, have monographs that outline specifications for medical oxygen, both Oxygen 99 and Oxygen 93 (Table I). Additionally, the following parameters for medical oxygen are described:

- **Identity:** Oxygen, in its liquid and gaseous form, is a molecular structure comprising two bonded oxygen atoms, O-O, to make the oxygen molecule (O₂).
- **Relative molecular mass:** 31.998 g/mol
- **Physical Description:** Clear and colorless in its gaseous form, light blue as a liquid. If the air-liquid interface is observed, “boiling off” can be seen.
- **Purity:** Follows a prescribed monograph and is not contaminated with potentially harmful substances.

Table I: Select SRA & WHO pharmacopoeia monographs

Product from ASU (LOX)	Oxygen 99 Requirements		
	Ph. Eur. [16]	USP* [16]	Ph. Int. [34]
oxygen assay	≥ 99.5% V/V	≥ 99.0% V/V	≥ 99.5% V/V
carbon monoxide	≤ 5 ppm V/V	≤ 0.001 % V/V	≤ 5 ppm V/V
carbon dioxide	≤ 300 ppm V/V	≤ 0.03 % V/V	≤ 300 ppm V/V
oil	≤ 0,1 mg/m ³	-/-**	-/-
water	≤ 67 ppm V/V	-/-	≤ 67 ppm V/V
nitric oxide/nitrogen dioxide	≤ 2 ppm V/V	-/-	-/-
sulfur dioxide	≤ 1 ppm V/V	-/-	-/-
Product from oxygen generator plants (PSA & VSA)	Oxygen 93 Requirements		
	Ph. Eur. [16]8	USP [16]	Ph. Int. [34]
oxygen assay ⁹	90.0% - 96.0 % V/V	90.0% - 96.0 % V/V	90.0% - 96.0 % V/V
carbon monoxide	≤ 5 ppm V/V	≤ 0.001 % V/V	≤ 5 ppm V/V
carbon dioxide	≤ 300 ppm V/V	≤ 0.03 % V/V	≤ 300 ppm V/V
oil	≤ 0,1 mg/m ³	-/-	≤ 0.1 mg/m ³
water	≤ 67 ppm V/V	-/-	≤ 67 ppm V/V
nitric oxide/nitrogen dioxide	≤ 2 ppm V/V	-/-	≤ 2 ppm V/V
sulfur dioxide	≤ 1 ppm V/V	-/-	≤ 1 ppm V/V
odor	-/-	No odor	-/-

* Health Canada ascribes to USP

** “-/-” indicates not specified

Where an NRA allows, a mixture of Oxygen 93 and Oxygen 99 may be delivered by a pipeline network; therefore, concentration of the gas can vary between 90% and >99%. [27, 28] No published or draft pharmacopoeia provides a monograph that covers the range across these two products. This blend could result in a purity at the bedside terminal unit (TU) that would be between the monographs for Oxygen 93 and Oxygen 99 of all pharmacopoeias. Medical oxygen is always mixed with air before reaching the lungs. Health facility managers and clinical leads should be aware of the concentration and any changes thereto as it may influence clinical practice.

⁸ European Pharmacopoeia monograph for Oxygen 93 excludes bedside concentrators because they are movable, which can impact the air-intake quality and thus affect product output.

⁹ The remainder consists of mostly argon and nitrogen.



Testing the product is an activity of quality systems that falls under QC. Testing gives an indication of quality at a point in time for a specific parameter, but it does not ensure continued quality and is not comprehensive. For example, if purity testing is done for only CO₂ and CO, other impurities that may be present will not be identified.

With respect to medical oxygen, the following applies:

- **Assay:** A paramagnetic analyzer, which measures the molecule's interaction with magnetic fields, can be used to measure oxygen concentration.
- **Impurities:** Carbon monoxide (CO) and carbon dioxide (CO₂) shall be measured when producing Oxygen 93 (oxygen generator plants should have built-in analyzers for this, see Section 3.2.3). For other impurities, the frequency of testing for oil, nitric oxide, nitrogen dioxide, and sulfur dioxide is to be based on the facility's risk management plan and in line with requirements of the NRA but will have to be done at a pre-identified test facility.
- **Storage:** All storage units and sites shall bear appropriate signage. Specific storage requirements for source type are as follows:
 - Oxygen 93 shall be stored in high-pressure gas cylinders; such container shall have closure systems that comply with local regulations (see details in Section 3.2.4) and shall be used only for medical oxygen. These cylinders shall be stored in a dedicated area accessible only by authorized personnel. This area shall be well-ventilated (at least 50% of the perimeter open if roofed and 30% open if not roofed [35]), protected from direct sun exposure and rain, and have a maximum temperature that never exceeds 52°C. [31]
 - Oxygen 99 in its liquid form shall be stored in a vacuum-insulated bulk storage tank made of stainless steel that is cleaned for medical oxygen service and equipped with unique connection fittings to avoid cross contamination while filling. Tanks shall be situated outside, at a safe minimum distance from nearby buildings, services, or identified hazards, as per NRA guidelines.¹⁰ In Oxygen 99's gaseous form, the requirements for cylinders of Oxygen 93 will apply.

Stored oxygen will be at pressure. Thus, pressures must always be reduced through pressure regulation devices for safe distribution and/or administration to patients.

- **Shelf life:** Oxygen, as a stable element, has been recognized to have a long shelf life; therefore, unless stability-testing indicates otherwise, it has no expiry. [8, 36] However, cylinder valves will require inspection at set intervals, and it accordingly is recommended that the date of last inspection be affixed to cylinders and bulk tanks to ensure that they occur as scheduled.¹¹

¹⁰ Depending on the size of the storage tank, the British Compressed Gases Association has described many considerations for determining safe distances, such as proximity to occupied buildings, public roads, air intakes, and storage of other products. [64]

¹¹ Note that shelf-life refers to stability of oxygen and its efficacy as a medicine. LOX will have a tendency toward gas, and so, if left in a storage vessel with no off-take, will boil and "off-gas." Suppliers and customers shall discuss appropriate configurations for need based on demand estimates—warranties to this effect will be established.



2.2.4. Quality Assurance of Medical Oxygen at Health Facilities

Quality assurance practices along the medical oxygen supply chain play a vital role in ensuring that the medicine remains effective for its purpose and is safe for both the patient and user and that suppliers and end-users alike have confidence that quality requirements are being continuously met.

Quality assurance practices at the health facility will be shared by many cadres of the workforce; however, to verify and accept medicines such as oxygen, that responsibility should be assigned to a specific role. Examples of existing roles or mechanisms that can be leveraged for the purpose are the AP, who is typically the head pharmacist, and/or the quality unit (QU), which is a typical responsible for QA of in-facility medical products. In the case of medical oxygen, the facility biomedical engineer could play a key role establishing and managing QA practices.

Each facility may have a different structure regarding roles and responsibilities for managing QA that reflects its size and staffing. Regardless, the objectives of establishing robust QA practices for medical oxygen (in addition to considering any existing national regulations) are [7, 37]:

- Creating, implementing, maintaining, and monitoring a quality system, including documenting operations and procedures using SOPs and work instructions, which should be strictly followed.
- Ensuring that appropriate and functioning equipment and/or facilities are in place and available to QC personnel for the testing for approval (or rejection) of any medical products, accessories, and ancillary materials, either incoming or produced in-house.
- Approving or rejecting medical products, accessories, and ancillary materials, either incoming or produced in-house. This responsibility includes exercising the authority to review all associated documents and records.
- Approving or rejecting all procedures or specifications of any manufacturer that could impact the identity, quality, and purity of the medicine.
- Conducting internal audits, with all relevant staff, where applicable.

For health facilities with a medical oxygen supply chain that goes beyond the facility, such as those that acquire oxygen from an external supplier, an agreement regarding quality systems shall be in place between any supplier/distributor and the facility's AP and/or QU.¹²

While personnel carrying out QC ideally should remain independent of the production of medical oxygen, such independence may not be possible in facilities with limited personnel and/or complex oxygen systems. In that case, roles and responsibilities must be clearly defined and personnel must be adequately trained and experienced with respect to their QC responsibilities., the imperative is a mechanism that functions for assuring quality up to the point of patient care. [8]

Because QU representatives participate in facility meetings and management reviews, they will manage communications with broader facility personnel and ensure that quality processes remain clear, especially for reporting complaints and/or adverse events.

¹² A written agreement between the external supplier of medical oxygen (LOX or gas) shall be executed. It shall clearly describe the goods and services to be provided to the health facility, inclusive of the quality specifications (those of the NRA, if applicable), PPM services rendered (if applicable), and safety requirements of both parties. It shall also outline the chain of communication, notably the process for reporting product complaints. [8]



2.2.5. Medical Gas Operational Plan—Quality Considerations

A medical gas operational plan is a facility-level manual that should be developed to provide an overview of the facility-specific oxygen system. This plan typically comprises a needs assessment, detailing requisite capacity, source(s), and associated operational protocols, and will indicate quality requirements and personnel needs, along with the personnel's roles and responsibilities. There are significant quality considerations in the operation of a medical gas system; thus, this plan shall include:

- A quality management plan
- A risk management plan

Quality management plan

The quality management plan should encompass principles of GMP as a framework. With predefined requirements for quality, the application of sound QA and QC practices will help facilitate the safe, smooth operation of the system for quality product delivery while minimizing any identified risks.

Where a facility is producing medical oxygen, it will need to define a batch to develop testing protocols, including frequency. Guidelines on how to define a batch can be found in ICH's *Continuous Manufacturing of Drug Substances and Drug Products*; Q13. [38] Third-party testing should only occur when necessary, based on a risk assessment. However, identifying an external accredited laboratory in advance for use should the need arise would be prudent, and contact details for that laboratory should be included in the quality management plan.

A communication protocol for all facility staff should be clearly outlined in this plan. The protocol should include guidance on the facility's mechanism for reporting problems or complaints associated with the use of medical oxygen. Any issue with production or product non-conformance must be recorded and managed through a corrective-action/preventive-action process.

Risk management plan

The risk management plan will include a risk assessment, where potential risks are identified and assessed and preventive controls are determined to mitigate the risk. Most risks can be greatly reduced by having a safe, appropriate system design and qualified and adequately trained personnel carrying out duties, implementing preventive controls, and monitoring the system as per SOPs. [28, 29]

For example, the most common risks associated with on-site oxygen production (both PSA and VSA) are [28]:

- Drop in quality of air at point of intake
- Drop in oxygen product concentration
- Contamination of oxygen product
- Equipment damage stemming from electrical power failure and/or poor-quality power
- Fire in oxygen generator plant/cylinder filling rooms
- Lack of planned preventive maintenance (PPM)

For each of these risks, preventive controls will be identified and implemented. The same approach shall be applied to risks identified along the rest of the supply chain.



Another notable aspect of risk management is to operate using a “permit-to-work” system, whereby any maintenance or repair to oxygen generation, storage, and delivery equipment must follow a strict permit-acquisition process to minimize the impact of any such work on the broader system.

The owner of the operational plan is the AP, though it will require senior management endorsement. As the operational plan reflects a system and its operations, which will likely change over time, it should be reviewed at a set frequency as well as on an ad hoc basis in response to any atypical events. An example of such a document can be found in the UK’s NHS *Medical Gases Health Technical Memorandum 02-01: Medical gas pipeline systems, Part B – Operational Management*. [29]



3. APPLYING QA AND QC TO MEDICAL O₂ SYSTEMS

Quality systems are typically established for a controlled setting (e.g., a closed facility); however, this section of the technical resource will focus on establishing a quality system along the medical oxygen supply chain: acquisition of LOX or production via on-site generator plants (PSA or VSA), transportation and storage, distribution, and some regulation and conditioning, with the aim of assuring the medicine's quality right up to the point of clinical application.

National or local authorities should encourage hospitals producing oxygen to establish and conform to structured quality systems (e.g., GMP and GDP). These authorities should also implement a permitting system analogous to the manufacturing authorization process, whereby hospitals producing oxygen would ideally be certified to do so by the NRA, within the regulatory framework. Considering the recent rapid scale-up in oxygen systems, regulators could initially provide guidance to manufacturers on quality systems practices along the medical oxygen supply chain before they begin enforcement.

Senior facility-level managers should work with the quality unit and head of production to determine the requisite resources (human, financial, materials, facilities, and equipment) to allow for the holistic implementation and maintenance of facility oxygen systems, including their quality management system. These should consider:

- Facility management integration
- Continuous oxygen availability for all wards and services where it could be used
- Oxygen-related training, including refresher training, to be incorporated into any continuous professional development (CPD) program
- The need for assurance that the quality of oxygen delivered is continuously acceptable for patient use

While safety assurance is a practice unto itself, safety is integral to ensuring the continued delivery of quality medical oxygen, given the risk profile of medical oxygen systems. Themes herein will cover relevant and related safety assurance practices. The intrinsic link between safety and quality assurance lies in the resources required for the medical oxygen supply chain—personnel, facilities and equipment, and systematic operations—and that any adverse event resulting from the lack of co-existing safety and quality practices could have a significant impact on the continuity of quality oxygen, safely delivered.

Any known associated and/or specific technical resource or guidance will be referenced where applicable. A more comprehensive package of associated resources and documents can be found in Annex C.

See [Annex C](#) for existing technical resources and guidance related to medical oxygen systems and their quality.

These themes and topics will be addressed from the perspective of quality assurance, the roles and responsibilities of personnel, and activities that are recommended to enhance and maintain quality assurance in these systems.

Note: QA practices will have to be adapted to suit contextual needs. For example, QA and QC needs at a regional referral hospital where oxygen is being produced by an on-site generator plant will differ from those at a secondary hospital relying on oxygen cylinders procured from a nearby oxygen manufacturer.



3.1. PERSONNEL

Personnel are required along the medical oxygen supply chain, beyond the facility and contributing in various capacities. While much of this technical resource will focus on health facility personnel and their role in quality assurance, outside personnel, either individuals or agencies in the broader enabling environment, can also help strengthen the QA of medical oxygen systems. All personnel shall be continuously trained in quality assurance practices as they relate to medical oxygen as well as in other critically important aspects of oxygen, including safety requirements potential hazards to both patients and personnel.

3.1.1. *Entities External to Health Facilities*

The **National Regulatory Agency** for medicines shall ensure that the **Ministry of Health** has oxygen listed as an essential medicine [1] and that requisite standards and specifications are in place. Having an oxygen champion in the Ministry of Health or creating an advocacy group comprising key stakeholders such as national medical associations, pharmacists' councils, and biomedical engineering associations can help support the NRA as it develops, adapts, or enhances policy¹³ related to medical oxygen. An established policy will provide the legal framework from which the NRA can carry out quality-related activities, including:

- Advocating for resources to enhance activities related to regulation of medicines
- Issuing manufacturing and/or marketing authorization
- Issuing certification for hospital production
- Conducting inspections/audits of production facilities via trained inspectors, at their discretion

National associations or **national councils**, including but not limited to medical associations (e.g., pediatrics, neonatology, surgery, and anesthesiology), councils of pharmacology, nursing associations, biomedical engineering associations, and associations for health care administration, that may be involved with oxygen as a medicine—from a clinical, technical, or administrative perspective—should be consulted on the development, revision, or implementation of any policy work. Input from these groups will prove invaluable as they have hands-on experience and can help steer normative guidance from a practical perspective.

NGOs, multilaterals, and donors shall familiarize themselves with the domestic regulatory landscape in the country in which they are working. The procurement of any medicines or medical devices, including donations, shall heed regulatory requirements. Doing so will simplify importation and registration and could enhance a domestic regulatory system by harmonizing requirements toward a global standard of best practice, ultimately leading to more positive patient outcomes.

Suppliers and distributors of LOX shall operate under domestic regulatory requirements and only sell their product for medical application under an NRA-issued marketing authorization or equivalent. Not all markets have a mature regulatory landscape, and suppliers and distributors thus should be able to provide GMP certification (or an indication that the principles thereof have been applied) and facilitate site visits for purchasers. Some geographies will expect GDP when issuing marketing authorization. [39] The supplier/distributor and any purchaser will have an agreement regarding quality systems¹⁴ and, at a minimum, records in the form of a certificate of analysis (CoA) shall be provided at each delivery.

¹³ An example of such a policy was developed by Nigeria's Ministry of Health [63]. That policy is currently under review.

¹⁴ See footnote 12, page 13.



Transporters¹⁵ of medical oxygen, whether suppliers (of private sector LOX or cylinders from a facility PSA) or entities providing third-party logistics, shall have valid driver's licenses (commercial if necessary). They shall undergo induction and refresher trainings on the transport of dangerous goods and the specific risks and hazards associated with medical oxygen. They should drive fit-for-purpose vehicles, be comprehensively trained on any need and/or requirement for the carriage of medical oxygen, and be well-versed in the importance of their role and its associated requirements related to quality assurance of medical products along the supply chain.

See [Annex A6](#) for actionable job-aids for QA activities applicable to oxygen transporters (suppliers/distributors).

Lastly, as these vehicles are moving about on public roads, transporters must operate defensively, always consider the safety of the public, and never carry passengers in or on their vehicles.

3.1.2. *Personnel within Health Facilities*

Health facilities have many different cadres of personnel contributing to aspects of quality in the medical oxygen supply chain in various capacities: medical, technical, and administrative. The list of personnel involved in the production and assurance of oxygen quality includes, but is not limited to, the following:

Medical and paramedical:

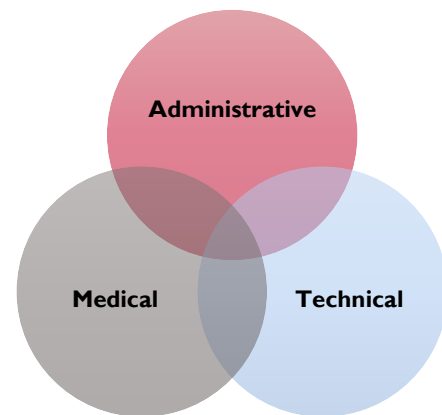
- Pharmacist
- Medical doctor
- Physician assistant
- Anesthetist
- Nurse
- Midwife
- Auxiliary staff
- Medical technician
- Emergency medical teams and first responders

Technical:

- Engineer [biomedical]
- Mechanic
- Electrician
- Driver
- Transporter

Administrative:

- Facility manager
- Facility administrator
- Store manager



All personnel involved in the medical oxygen supply chain, from production through distribution, are to be appropriately qualified, adequately trained, and assessed for competencies regarding medical oxygen, its application and risks, and their roles and responsibilities. No one person shall be overburdened with responsibility in that it could present as a risk to the broader QA efforts. [7]

Each facility shall examine its own needs and requirements with respect to both oxygen and the requisite supportive infrastructure; **senior management** bears responsibility for ensuring ongoing resources to facilitate continuous availability of the essential medicine. This will apply regardless of whether the supply is outsourced or produced on-site and shall consider all associated requirements for

¹⁵ Although this section primarily addresses entities external to health facilities, it is possible that a facility transports medical oxygen, either procured from an outside source or produced in-house, to another facility. This content therefore applies to all transporters, no matter where they are based. See Section 3.4 for more details.



distribution, regulation, and conditioning needed for patient delivery. To that end, senior management is responsible for endorsing a facility's medical gas operational policy.

Senior management shall nominate an **authorized person**, typically the head pharmacist, to be responsible for overall facility-level quality systems as they relate to medicines, including oxygen.

See [Annex A1](#) for actionable job-aids for QA activities applicable to the AP.

The AP, who typically already leads the facility's **quality unit**, will ensure that the quality related to the facility's oxygen system falls within their purview, and will oversee all related training activities.

If oxygen is being produced on-site, the AP will nominate a **head of production** to manage all oxygen production processes and a **head of quality control** to carry out QC functions independent of production. When the medical oxygen supply chain extends beyond the health facility, agreements shall be established between the supplier/distributor and the health facility's QU.¹⁶

Facilities also need **operators/supply managers**, as well as **quality controllers**. Depending on a facility's size and needs, many of the responsibilities associated with those positions can be absorbed by existing personnel with complementary roles. Care should be taken not to over-burden the existing workforce or, conversely, to over-staff or build out a parallel structure. Clear responsibilities for all roles, including time estimates, shall reflect the oxygen system based on facility requirements.

See the following annexes for actionable job-aids for QA activities:

- Applicable to the head of production: [Annex A2](#)
- Applicable to the head of quality control: Annex A4

While the clinical application of medical oxygen is out of scope for this resource, **health care workers** (e.g., doctors, nurses, midwives, anesthetists, and respiratory therapists) must ensure safe and effective clinical application of the medicine and play a role in the quality assurance of the medicine itself. As the primary users of the medicine, health care workers not only influence demand and consumption but are often the first to know if supplies are not meeting needs or if potential quality issues arise. Thus, health care workers will play an integral role in reporting any issues.

Health care facilities may also have a quality improvement team comprising clinical educators and supervisors who implement processes and in-service trainings that will support audit/feedback loops. The level and degree to which this applies will vary from one facility to the next; however, any existing structure to this effect should be leveraged.

An example of in-facility roles for oxygen systems can be seen in Figure 6, which depicts the responsibility hierarchy of the QU (comprising at least the AP), as well as staffing requirements under the head of production and head of QC.

¹⁶ See footnote 12, p. 13.

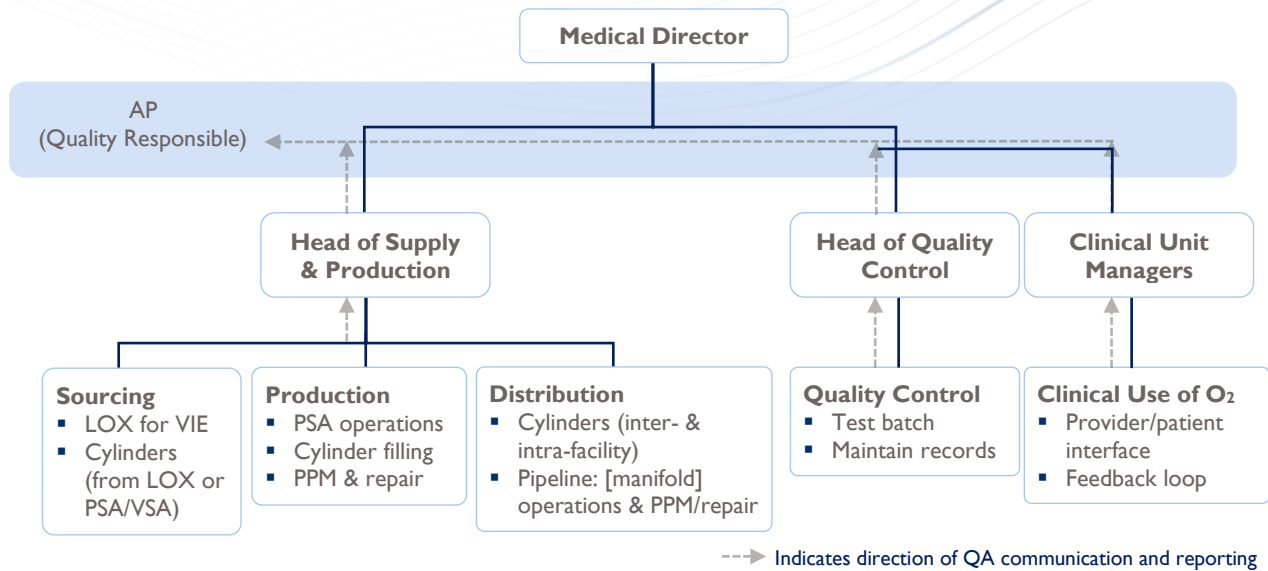


Figure 6: Organigram of QA roles (adapted from EC GMP [7])

3.1.3. Capacity Building

Basic Safety:

- No smoking or naked flames within 5m of any oxygen equipment.
- Tools and accessories used on or with oxygen equipment must be free from oil.
- Personnel working with oxygen equipment must have clean hands, wear work clothing, and don appropriate PPE.

Basic Safety Training Package: EIGA's [Fire hazards of oxygen and oxygen-enriched atmospheres](#). Annex A [40]

Personnel involved in any aspect of the medical oxygen supply chain shall be trained for all work related to their roles (initial and continuing training) and their comprehension shall be verified. The following topics are to be covered, at a minimum:

General—all staff working with oxygen

- Oxygen safety: safe handling, risks and hazards, PPE requirements, emergency contact
- Quality systems principles as they apply to medical products
- Quality requirements of medical oxygen
- Hygiene

Cadre-specific

The following topics are to be covered in training for all staff working in specific areas of the supply chain:

- Health care workers: clinical guidelines and emergency contacts for medical oxygen issues
- Oxygen generator plant operations: daily site-check, power-supply assurance, start up, automatic and manual shutdown, safety checks, PPM, troubleshooting, and repair
- Pipeline distribution network: system and safety checks, secondary supply, and alarms
- Cylinders: properties, risks, management, safety checks and cleaning, and safe handling for loading, unloading, and transport
- VIE system and piping: properties, risks, daily safety checks, PPM, troubleshooting, and repair
- Transport: qualified drivers for vehicle operators, maintenance and upkeep of vehicles, transport of dangerous goods, and GDP of medical products



3.2. PREMISES AND EQUIPMENT

Facilities with oxygen services shall be outfitted with purpose-built equipment and infrastructure that will enable specified operations and support quality assurance activities, complete with features to facilitate safe operations along the oxygen supply chain. Any equipment in contact with the medical oxygen stream must be rated for oxygen use. [33]

3.2.1. General Site Safety

Health facility management shall adequately resource for general safety. Facilities supporting any production, storage, distribution, and delivery of medical oxygen shall have dedicated and designated work areas, accessible only by authorized personnel, which are to be always kept organized and clean.

All facility staff shall receive ongoing training on oxygen safety, risks, and hazards. The facility shall have designated assembly points in the event of a fire or explosion, as described in the facility risk management plan, and those points shall be indicated with signage and their locations communicated during training and refresher courses. Locations of fire extinguishing equipment must be similarly indicated and communicated. First-aid protocols shall address any oxygen-related risks.

Where oxygen is being stored and/or produced, an oxygen monitoring system should be present in the room to measure ambient conditions (which must always remain between 19.5 and 23.5% oxygen [28]). The technical team shall always be aware of those conditions to ensure they are never working in a compromised environment.

Specific safety instructions shall be posted where applicable. Examples of such are WHO's [Cylinder Safety poster](#), [Medical Gas Piping System Safety poster](#), and [Medical Oxygen Fire Risk poster](#).

The grounds of the health facility should be entirely smoke-free.

3.2.2. LOX Reception Requirements

Facilities using LOX will need storage vessels. Typically, a vacuum insulated evaporator system comprising a bulk storage tank and passive vaporizers will be installed, but in some cases where volumes are quite low, smaller MicroBulk vessels or LOX cylinders can be used. These vessels are typically owned by the LOX suppliers and thus will be managed and maintained by them. In some cases, the tanks are owned by the facility or another third party and the LOX provider will need to determine whether the hardware aligns with its quality requirements and the fill flanges are compatible with its equipment. In those situations, it would be prudent for the facility to engage the LOX provider in a service level agreement that covers PPM for the VIE system. Daily checks of this equipment, described in Annex A3, shall be carried out by facility staff.

Filling the on-site tanks requires unobstructed access by the LOX tanker truck. When planning tank placement, consideration shall be given to the LOX truck's turning radius as well as approach to the tank(s)—whether drive-through or reverse access. Regardless, direct access will be necessary for transfilling (filling from the tank on the truck to the static tank on site), which should never be done over or through any object. Fencing around the tank site is necessary, as it should not be accessible to

See [Annex A3](#) for actionable job-aids for QA activities applicable to VIE systems.



anyone but authorized personnel. Lastly, the site's proximity to other buildings, their use, and whether the location represents a hazard need to be considered.

3.2.3. Oxygen Generator Plants in Hospitals

Because PSA and VSA oxygen generating plants are medical devices, the QU shall be involved in the procurement of this equipment.

To ensure that the equipment itself is of acceptable quality, the following should be done at time of procurement: apply WHO *Technical specifications for Pressure Swing Adsorption Oxygen Plants* [11], seek out devices with verified regulatory approval/markings from founding members of the International Medical Device Regulators Forum (IMDRF)¹⁷ and associated pressure equipment certifications, and take into consideration contextual conditions (climate and terrain). These units have specific, built-in technical features that must be included to support quality assurance, [28] such as oxygen analyzers, CO and CO₂ analyzers, moisture sensors, alarms, automatic shut-off features, pressure relief valves, and purge valves. Any installation shall include a non-return valve on the final outlet.

In addition to the plant's in-built features, the facility should procure a secondary, hand-held oxygen analyzer, also a medical device, to verify product purity. These hand-held oxygen analyzer units, either ultrasonic or galvanic/electrochemical, are relatively affordable and offer mobility—thus, testing of product purity can occur throughout the system. Each device type and/or sensor technology has different considerations/use cases, so guidance and specifications found in WHO-UNICEF's *Technical specifications and guidance for oxygen therapy devices* [12] should be used when selecting among them.

Oxygen generator plants can come pre-housed in modified shipping containers with all the requisite ventilation and panels for a near seamless installation. Site preparation will still be required, such as positioning the air intake, casting a slab, installing or extending power supply, and providing a roof-type structure over the container to help regulate operating temperatures and protect it from the elements.

Where on-site housing is available or built-for-purpose, consideration should be given to air-intake and its proximity to wards and nearby residential areas, given the associated noise levels. If the site includes a cylinder filling station, ample space should be made for the movement, inspection, sorting, and storage of cylinders. A ramp-type approach rather than a step will be needed so cylinders can be safely wheeled to and from the fill point.

Note that oxygen generator plants shall undergo testing and commissioning post installation. A record of this process should be kept, along with validation that the plant is fit to operate as intended.

For more details, please refer to WHO's *Foundations of medical oxygen systems* [17] or the UK's HTM-02-01: *Medical gas pipeline systems, Part A – Design, installation, validation, and verification* [24].

¹⁷ The IMDRF founding members are the US FDA, Australia's Therapeutic Goods Administration, Japan's Pharmaceutical and Food Safety Bureau, European Union's CE, and Health Canada.



Applying heat shrinking bands **to seal** the valve stem is another way of preventing, or identifying, tampering with cylinder valves after they have been filled. This will require resources to ensure that a continued supply of shrink-wrap plastic to make the seal, a low-heat source (such as a hair dryer), and a power supply are available.

Lastly, there shall be ample space for the filling and management of cylinders. Operators must be able to safely move cylinders around and sort them in compliance with quality assurance practices. Space is also needed to safely store cylinders in their respective categories: empty, full, prepared deliveries, faulty/rejected cylinders, etc.

3.2.5. Pipeline Management

Pipelines facilitate the distribution of oxygen from either an oxygen generator plant, a VIE system, or a cylinder manifold. The personnel responsible for distribution shall be familiar with the network layout, carry out their daily checks and requisite maintenance duties, and ensure that the (preferably digital) drawings of the network remain accurate by keeping them up to date. Those personnel also shall brief any work-person on site about the whereabouts of the network to avoid a pipeline breach that could result in both a service disruption and an oxygen enriched environment (see Annex A3).

The pipeline network itself shall be color coded and clearly labelled for oxygen use, right up to and including the bedside TUs.

See [Annex A3](#) for actionable job-aids for QA activities applicable to operators managing pipelines.

If for any reason the pipeline network is not in use, it shall be kept at pressure to maintain the identity and integrity of the pipeline, minimizing risks associated with contamination or particulate matter within the distribution system. This shall be done with medical air¹⁸ and the network shall be purged with oxygen and tested before use. [24, 30]

3.2.6. Pipeline and Cylinder Accessory Sets

Quality assurance activities associated with cylinder accessory sets comprising pressure regulators, flowmeters, and humidifiers, as well as pipeline TU accessory sets comprising flowmeters and humidifiers, are limited yet important. These accessory sets must be cleaned for medical oxygen use and always have a connection compatible with the cylinders with which they will be used or with the TU to which they will be connected. Details on cylinder accessory sets and TUs can be found in WHO-UNICEF's *Technical specifications and guidance for oxygen therapy devices* [12] and WHO's *Foundations of medical oxygen systems* [17] respectively.

During use, connections shall be handled gently. For cylinder sets, they shall be tightened only by hand, not using a tool. Forcing or overtightening the connection points could permanently damage connection fittings, rendering them useless or, even worse, resulting in a leak that may not be seen. A leak will make operations more inefficient (and therefore more expensive) and could put many people at risk by generating an oxygen-enriched environment.

¹⁸ Medical air is mainly used in respiratory therapy as a power source for patient ventilators and for blending with oxygen. It is also a driving gas for nebulizers. It is typically supplied from a compressed air plant that includes high-quality drying and filtration equipment; alternatively, medical oxygen and medical nitrogen can be blended to generate medical air. Medical air is considered a medicine and thus must comply with quality requirements of the nationally recognized pharmacopoeia.



No staff member noticing a loose connection or a leak with any of these devices shall resort to an ad-hoc solution, such as tightly winding examination gloves around the leak or other such “field fixes,” as doing so could prove to make a dangerous situation even more so. Instead, either or both components of the connection shall be swapped out with a new accessory set from the maintenance department, which will then address the broken equipment appropriately.

Humidifiers need to have their water filled or changed daily, using either distilled water or water that has been boiled and then cooled. [21] While humidifiers are typically sterilizable, it is only necessary to clean and disinfect them, which must be done on a weekly basis. For details, see WHO’s *Decontamination and reprocessing of medical devices for healthcare facilities* [46] and WHO’s *Medical equipment related to oxygen therapy – Cleaning – task sequence checklist* for use in infectious settings. [47]

3.2.7. Maintenance and Repair

Maintenance is critical for the safe, continued operation of equipment to facilitate quality product output, and it should be taken into consideration to ensure continued quality operations. All maintenance and repairs must follow a “permit-to-work” system—an established procedure in the facility’s risk management plan that requires all work on a facility’s medical gas infrastructure to be formally authorized by the AP to minimize risks, especially those associated with patient care. As part of this system, a permit document must be completed describing the scope, location, and duration of the planned work; wards or departments that will be isolated from service; all potential hazards (including disruption to patient care) and potential consequences, as well as pre-emptive precautions taken; and proposed mitigative measures in case of an adverse event. [29, 48]¹⁹

One aspect of quality is continuity of supply, which relies on adherence to a strict PPM schedule. At a minimum, the PPM schedule recommended by any equipment manufacturer shall be respected, and all preventive control parameters, as identified in the facility risk management plan (Section 2.2.5), shall be checked at prescribed intervals. The facility shall have a secondary and/or emergency supply of oxygen available to facilitate PPM or any critical repairs that require taking the primary supply offline. These alternate sources shall be checked frequently to ensure they are in working order and yield oxygen of acceptable quality.

Equipment spares and consumables shall always be available, or quickly attainable, to facilitate the PPM schedule. “Fast moving” spares and consumables (for example, compressor filters, O-rings, medical grade tubing, oil-free soap, or pressure regulators) shall be stocked so they will be on-hand at all times, while a system shall be in place for the rapid sourcing of any other spares parts needed in the event of a break-down.

For an **oxygen generator plant** (PSA or VSA), checks will be made and results recorded at every maintenance interval for functionality of visible and audible alarms as well as the automatic shut-down function. These alarms must activate when the following quality-related parameters are not met (adapted from EIGA Doc I95/20 [28]):

- Oxygen concentration must remain $\geq 90\%$
- Carbon monoxide and carbon dioxide must not exceed levels indicated in NRA pharmacopoeia

¹⁹ Permit-to-work authorization is not needed for LOX transfilling, changing cylinders on a distribution manifold, or any emergency isolation of gas supply undertaken by a health care provider. [29]



- Moisture must be absent from the outlet stream
- System temperature must remain within a predetermined operating range
- Differential pressure across the filtration unit must remain constant
- Continuity of supply must be maintained

In addition to testing alarm functions for quality-related parameters, the switchover function of the secondary/emergency reserve supply (where applicable) shall be tested to ensure that it remains functional.

If any maintenance or repairs to the **pipeline network** are needed, they should be conducted under a “permit to work” authorization process. If work requires welding, assurance must be made that the service provider grounds its equipment to minimize the risks associated with alternating currents from nearby electrical sources. [30]

Color-coded **cylinder** paint should be maintained to facilitate ease of sorting and minimize any potential cross-contamination. Repainting of the white shoulders should be carried out as soon as a cylinder’s identity is no longer apparent. Additionally, hydrostatic (pressure) testing must take place for each cylinder every 10 years. [45]

Equipment should be cleaned and purged following any maintenance and/or repair.

For safety, an oxygen monitoring system should be in place in any room where oxygen is being produced or cylinders are being filled to ensure that the room air does not become oxygen deficient or enriched, as either situation could put the team and facility at risk. Cells in the analyzers of this equipment shall be checked and calibrated regularly and replaced as needed. [28]

LOX storage vessels (e.g., bulk tanks, MicroBulk tanks, and LOX cylinders) shall be checked with regularity. These include simple visual inspections to ensure continued, dependable operations, which involve determining the vessel pressure and the LOX level (via their respective gauge and indicator) and to ensure that all pressure relief devices remain ice-free (see Annex A3). More comprehensive maintenance requirements are typically carried out by a qualified third party.

As for the premises, technicians must have a clean, well-lit, spacious environment to carry out their work. The regular workshop can be used if the above conditions are met and the technicians have access to clean drop sheets as well as the ability to work with clean (oil-free, lint-free) hands and clothing.

3.3. SOURCE-SPECIFIC REQUIREMENTS: PRODUCTION OR PROCUREMENT

As described in Section 2.1.1, two types of oxygen are available for medical application: Oxygen 99 and Oxygen 93. Clear standard operating procedures (SOPs) and work instructions, tailored to facility and context, shall be developed for facility-specific source(s), whether on-site production or procured oxygen, to minimize risks to product quality and to any personnel along the oxygen supply chain. These shall cover:

- Outsourcing—procuring oxygen in the form of:
 - LOX
 - High-pressure oxygen gas cylinders from oxygen produced outside of the facility
- Producing oxygen (PSA/VSA plant) on site, at the hospital

Quality assurance practices shall be clearly indicated on the SOPs where appropriate and applicable.



3.3.1. LOX: Quality Assurance When Procuring Medical Oxygen

LOX (or Oxygen 99) will be manufactured off-site, typically by a third party, and be supplied either in liquid form or as a gas in high-pressure cylinders. The responsibility for quality, safety, and efficacy of LOX as a medicine lies with the manufacturer. Typically, an NRA will grant a manufacturer a license to produce LOX and, if the manufacturer is in compliance with GMP, marketing authorization to sell its product for medical purposes. [28] This type of domestic licensing will indicate the NRA's pharmacopoeial requirements, as well as information regarding the safe clinical application of the product. Thus, in the acquisition of LOX:

- The composition of oxygen shall meet the need of the clinical application and the standards set by the NRA. When the NRA does not specify the standards, well-resourced regulatory authorities such as SRA²⁰ standards, along with the specifications of an internationally recognized pharmacopoeia (e.g., USP, Ph. Eur., BP²¹, or Ph. Int.), may be justified.
- It must have been manufactured using GMP and ideally have a valid GMP certificate issued by the relevant NRA. In the absence thereof, a valid GMP certificate issued by a well-resourced recognized NRA, e.g., from a country participating in the Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme (PIC/S), will suffice.

NRAs for many jurisdictions may not recognize LOX as a medical product, and those jurisdictions may not have a formal system in place to validate and certify GMP. In any case, the LOX manufacturer shall produce oxygen that meets the NRA's pharmacopoeial requirements and have an established functional quality system in place that allows it to demonstrate that its production follows the principles of GMP. [6, 7, 33] In such situations, it may be necessary for the purchaser to carry out site inspections to ensure that acceptable quality systems are firmly in place and being implemented.²² Regardless of its formal GMP status, the supplier shall furnish each delivery with a CoA to indicate its compliance with the standards, which shall be handed over to the QU that has authority to approve (or reject) the batch before the transfilling process begins.

See [Annex B](#) for recordkeeping examples.

Records of all CoAs that come from LOX suppliers for filling on-site tanks or delivering cylinders, provided they are complete (with information on date, batch, purity, and impurities), are considered records of quality of product and shall be kept on file (see Annex B for examples). These products do not have to be systematically re-tested.

3.3.2. Oxygen Generator Plants: Quality Assurance When Producing in Hospitals

Oxygen 93 is a medicine produced from an oxygen generator plant, typically by facility staff. The quality, safety, and efficacy of the product falls under the responsibility of the AP. NRAs shall strive to certify oxygen generator plants for medical application. To achieve and maintain this certification, the AP would have to ensure that operations of these units fall within their broader quality systems and that the principles of GMP are applied [7] just as they are to any other medical

See [Annex A3](#) for actionable job-aids for QA activities applicable to operators of on-site oxygen generator plants.

²⁰ See footnote 5, p. 10.

²¹ The British Pharmacopoeia (BP) is a member of the European Pharmacopoeia (Ph. Eur.) and continues to reproduce Ph. Eur. Text. WHO, which publishes the Ph. Int., is not a regulatory body, but its pharmacopoeia aligns with those of SRAs.

²² PIC/S has developed a site inspection "cheat sheet" that summarizes requirements of the EC's GMP, Annex 6 – Manufacture of Medicinal Gases. [66]



product prepared in pharmacies, such as those described by the PIC/S. [9] This type of framework will help ensure that production of the medicine is controlled, the product will meet the monograph specifications of the jurisdiction's pharmacopoeia, and, ultimately, its ongoing safety and quality for patient use is assured.

The facility's head of production, along with its operator(s), shall ensure that the plant configuration is reflected in the SOPs that are developed and follows the plant manufacturer's recommendations. The operator on shift is responsible for carrying out duties, as per the SOPs, and for documenting activities accordingly. The operator shall carry out day-to-day operations, including system checks and routine maintenance, and ensure that the controllers note product quality at the frequency that defines the production unit's batch (see Section 2.2.5). While the QU will sign-off on the product, coordination of these activities shall be seamless.

See [Annex A5](#) for actionable job-aids for QA activities applicable to quality controllers.

The operator shall always ensure that if any issue arises with quality and/or the operation of the oxygen generator plant, the secondary supply is activated immediately, the QU is notified, and a plan is devised for managing the issue.

The production room shall always be kept clean, and any tools and/or equipment shall be rated and/or cleaned for use with oxygen service. No unrelated tools or equipment are to enter or be stored in the production room.

3.3.3. Cylinder Filling

Cylinder filling shall follow all applicable regulations of pressure system legislation and adhere to a structured quality systems framework. [28]

Cylinder identification is an important aspect of quality assurance. Only cylinders rated for and dedicated to medical oxygen service shall be accepted at health facilities and filled by hospital cylinder filling stations. These cylinders are typically easily identifiable by their coloring, which may vary depending on geography (see WHO's *Foundations of medical oxygen systems* [17] for more details), and, equally important, by the valves that are used. The proper valves are required for both filling station connection points and for accessory sets for regulation and conditioning before oxygen can be delivered to patients.

See [Annex A3](#) for actionable job-aids for QA activities applicable to operators filling cylinders.

Cylinder filling involves working with high-purity oxygen at high pressure. A known potential safety risk associated with filling is adiabatic compression, also known as “gas hammer”—a phenomenon where, for an instant, the pressure downstream of the valve is higher than the pressure within the cylinder and the temperature becomes elevated, which in-turn can cause a fire if any foreign object is present. [49] Thus, cylinder valves always must be opened slowly to ensure that gas is not released quickly enough to cause this phenomenon and work always must be done under clean conditions with equipment certified for oxygen use.

Another often overlooked safety risk is the potential for the cylinders themselves to inflict bodily harm. Large cylinders have a tare weight of upwards of 70 kg; if they fall on personnel or a patient, they can cause severe trauma.



Thus, the **handling and management** of cylinders is an important activity for quality assurance, including safety (content herein adapted from EIGA DOC 209/17: *Quality of delivered product from medicinal gas cylinders* [50], except where otherwise noted).

Cylinders are to be checked, prepared, filled, and stored appropriately, with oxygen cylinders kept separate from other medical gases. Adequate space shall be available to move cylinders about, and a labeling system shall be employed. For example: cylinders could be labeled “awaiting checking,” “awaiting filling,” “full,” “prepared deliveries,” “fail/rejected,” etc. Cylinders shall be physically segregated according to these labels, either by marked floor areas or physical barriers with signage.

For the **check**, all cylinders shall be visually examined prior to filling, both for appropriate color coding and valves and for any obvious damage. While complete failure of cylinders themselves (e.g., rupture) is very rare, pre-emptively removing any notably damaged cylinder from circulation is advised. As part of this visual examination, each cylinder should be checked to ensure that it had a hydrostatic test within the previous 10 years [45]. This can be tracked multiple ways, including with barcoding, QR codes, or neck-rings. During the check, any previous batch labels (e.g., stickers) shall be removed, as appropriate.

To mitigate the potential for contamination, cylinders shall be **prepared** for filling following one of the following three standardized processes to ensure they are empty: the cylinder valve stem has a built-in RPV, whereby a nominal above-atmosphere pressure will remain in the cylinder to prevent ingress of any foreign material; the filling station has a purge/vacuum pump, with which any remaining content in the cylinders can be “sucked” out prior to filling; or a protocol for uniform, nominal pressurization and release is applied.

For **filling**, only medical oxygen cylinders with valves that are compatible with the connections on the filling ramp can be filled. The recommendation is to avoid using adapters; however, under exceptional circumstances and only after consulting with the ramp manufacturer, an adapter can be used. [8] During the process, the operator shall check to see if cylinders are filling properly by quickly touching them; a rise in a cylinder’s temperature indicates that it is filling. If a cylinder remains cool, the cause should be investigated.

A less common fill practice is cascading, i.e., filling one cylinder from another. In addition to stringent technical operating procedures, key considerations related to quality (and safety) for this process are two-fold: valves must be handled carefully and opened slowly, and a safe final temperature for cylinders is set and must be reached prior to disconnecting.

After filling, a mild, oil-free soap solution shall be applied to the valves to check for leaks, which are indicated by bubbling. Depending on the facility’s quality management plan, at least one cylinder from each batch shall be **tested** by a quality controller. All cylinder filling details (production batch, cylinder ID, etc.) shall be **recorded** and maintained to ensure traceability (see Annex B).

See [Annex B](#) for recordkeeping examples.

Further details can be found in EIGA’s DOC 209/17: *Quality of delivered product from medicinal gas cylinders*. [50]



3.4. TRANSPORTATION AND STORAGE

Good distribution practices are a necessity when transport is part of the medical product supply chain, including with respect to medical oxygen. GDP follow the same principles of GMP: personnel, premises and equipment, operations (instead of production and transport in GMP), documentation, complaints and recall, and self-inspection/auditing. Clear SOPs and work instructions, tailored to facility and context, shall be developed to minimize risk to the quality of the product and to any personnel working along the oxygen supply chain. These shall cover (see Annex A6 for more details):

See [Annex A6](#) for actionable job-aids for QA activities applicable to oxygen transporters (suppliers/ distributors).

- Transport and transfer of oxygen
- Storage of oxygen, including fit-for-purpose and labelled containers/vessels

Compliance with local regulation takes precedence; in the absence thereof, international norms such as the EU's *Guidelines on Good Distribution Practice of medicinal products for human use* [51] or WHO's *Good storage and distribution practices for medical products* [52] shall be used.²³ Additionally, these shall be complemented by the US DOT's requirements [43] under the US Code of Federal Regulations or the UN's *Recommendations on the Transport of Dangerous Goods* to develop local regulations that incorporate the risks associated with oxygen into GDP.

All drivers must have a valid driver's license (commercial, if necessary) and be comprehensively trained on their vehicle, the transport of dangerous goods, and the specifics for carrying oxygen.

Vehicles transporting oxygen, as well as vessels filled with oxygen, are to be properly classified, certified, labelled, and identified to do so; they must bear a symbol indicating that they contain an oxidizer (Figure 8). Other information specified in the UN's *Recommendations on the Transport of Dangerous Goods, Model Regulations—Volume 1*, as per Table 2, must also be clear:



Figure 8: Globally Harmonized System (GHS) Symbol [53]

Table 2: UN transport product classification for oxygen [54]

Oxygen, compressed gas	Oxygen, cryogenic liquid
<ul style="list-style-type: none">■ Product name: oxygen, compressed■ Safety conditions: oxidizing substance, non-flammable gas■ UN ID Number: UN1072■ Risk identification/hazard class: 2.2	<ul style="list-style-type: none">■ Product name: oxygen, refrigerated liquid■ Safety conditions: oxidizer, non-flammable gas■ UN ID Number: UN1073■ Risk identification/hazard class: 2.2

The vehicle must meet national and local regulations and be up to date with respect to service (electrically and mechanically), which shall follow SOPs and be conducted and documented by trained, qualified personnel.

²³ GDP typically would be covered under marketing authorization. If a marketing authorization structure is in place for the manufacture and distribution of oxygen, checking to see whether GDP is covered would be prudent.



For enhancing the safety of delivery, all vehicles transporting oxygen shall have the following (adapted from EIGA Doc I28/21 [55]):

- A vehicle reverse alarm feature
- A secondary locking device to prevent rolling when parked (such as wheel chocks)
- A charged fire extinguisher in the driver's cab
- "No smoking" signs in the cab and on the back of the vehicle
- A vehicle safety equipment kit, comprising two safety cones (pylons), a torch/flashlight, and a reflective jacket
- A first-aid kit

The vehicle engine must be turned off during loading/off-loading and must be kept clean.

3.4.1. Bulk Liquid Oxygen

Road conditions must allow for the safe passage of fully loaded LOX tanker trucks. They must be sealed (having one of the following surface treatments: asphalt concrete, bitumen, tarmac, or chipseal) and in passable condition.

Transfilling, or shifting LOX from one tank to another, will happen at multiple points along the LOX supply chain—for example, from point of manufacture to a LOX tanker truck, then to a bulk LOX storage point, back onto a LOX tanker truck, and finally to one or more facility LOX storage vessels. And so, while many transfer points need to be managed, all transfers upstream of the final on-site fill, from a QA perspective, will be managed as part of the chain-of-custody and thus will be reflected in one CoA, which will be handed over upon delivery of bulk LOX at the health facility.

See [Annex A3](#) for actionable job-aids for QA activities applicable to operators managing VIE systems.

Quality practices will be required for the final transfer of LOX to the facility storage vessel(s), which remain the responsibility of the LOX supplier. In addition to the safety points listed above:

- The transport tanker will be pressurized slightly higher than the recipient vessel(s) and a non-return valve will be located downstream of the transfer pump. Both features serve to ensure that no oxygen back-flows from the on-site storage vessel into the tanker truck.
- A CoA for the LOX in the tanker shall be handed over from the driver to the QU representative. A formal acceptance process must take place prior to transfilling the facility storage vessel(s). This document is essential recordkeeping.
- No vehicles shall block the entrance or exit of the LOX tanker truck.
- Only authorized persons shall be allowed near the tanker truck or VIE tank; to avoid oxygen enrichment, personnel involved in the process shall not stand near oxygen vents.
- Transfilling shall not take place over, under, or through anything.
- The operator responsible for transfilling shall wear appropriate PPE.



3.4.2. High-Pressure Gas Cylinders

The transport and transfer of oxygen cylinders require general transport considerations, and good practices for loading, offloading, and handling shall be established by the transporter and shared with recipient facilities to avoid any damage or injury that can be caused by dragging or falling cylinders.

In addition, the following cylinder-specific practices shall be implemented (adapted from EIGA DOC I28/21 [55]):

- The cargo area shall have ample ventilation (total free area shall be $\geq 600 \text{ cm}^2$ across a minimum of two vents—one at the top near the cab and one at the rear by the floor) and shall always be separate from the cab.
- Vehicle loading:
 - Lifting devices shall be used where available (e.g., hydraulic liftgate, forklift); otherwise, a ramp shall be used with a trolley.
 - Vehicle payload capacity shall never be exceeded. Consider the weight of empty cylinders being returned—do not overload with empty cylinders.
 - Imbalances should always be avoided as they could pose a risk during transport.
 - Cylinders shall be upright and restrained so they cannot move during transport.
 - Vents shall never be blocked by cylinders, trollies, or any other ancillary equipment.
 - Cylinders shall always be transported with valve protection (e.g., valve cap or valve guard) in place to ensure that the integrity of the valve and valve stem remains intact.
 - Unrelated cargo shall never be loaded on vehicles transporting oxygen. If a spare tire is in the cargo area, it must be in a separate compartment.
 - **Never transport people in the cargo area**—not staff, not civilians.

Disinfecting the interior of the vehicle, both cab and cargo area, may be necessary following the collection of very dirty cylinders or cylinders suspected of contamination.

Because vehicles transporting oxygen cylinders may also carry other gases for other uses, oxygen cylinders must be clearly marked to avoid any mix-up upon delivery.

3.4.3. Facility Reception Point QA Considerations

A facility receiving oxygen cylinders must have a clearly defined offloading area to ensure controlled and safe operations. The area must bear signage prohibiting the parking (or standing) of any other vehicle and restricting entry during loading/offloading to authorized personnel. Additional requirements include establishing a fire safety point, complete with a charged fire extinguisher.

Localized facility-level transport shall be by cylinder trolley. In cases where cylinders need to be shifted only a short distance, they can be carefully rolled on the rim of the bottom edge. Under no circumstances shall cylinders themselves be rolled horizontally.

A pressure regulator and flowmeter assembly shall only be mounted onto a cylinder intended for bedside use and only after that cylinder has been placed in its final bedside position.



3.5. DOCUMENTATION AND RECORDKEEPING

Documentation and recordkeeping practices are critical aspects of quality management systems and shall be established and maintained as they will support quality assurance across the medical oxygen supply chain. Content herein has been adapted from EIGA DOC 99/15 [33] & EU [7, 32])

The **quality management plan** and **risk management plan** are foundational documents for the facility's acquisition or production of medical oxygen, as well as that oxygen's storage, distribution, regulation, and delivery.

There will be multiple established procedures along the supply chain, with many responsibilities to be carried out, to ensure that only quality product reaches the patient. Having all these **procedures documented, in applicable SOP format**, will help ensure that personnel are appropriately qualified and/or trained to carry out their duties. SOPs must reflect each facility's unique oxygen ecosystem; all previous chapters in Section 3 cover topics to be documented, and Annex A provides role-specific job aids to make sure quality-related responsibilities are considered.

Documentation needs are detailed in [Annex A](#) alongside role-specific job-aids for QA activities.

For production, most procedural **activities carried out along the oxygen supply chain will require real-time recordkeeping**. Production using an oxygen generator plant will require the defining of a "batch" (done during the development of the quality and risk management plans). At the established testing frequency, the analysis results and process-control parameters, as well as relevant operational details, will be recorded. Deviations in process or product (or any otherwise abnormal event), as well as details regarding the ensuing investigation and outcome, are also to be recorded. This will facilitate traceability if a recall is necessitated by an adverse event.

Similar recordkeeping will be kept for cylinder filling. For the reception of LOX, the supplier will provide all relevant information as part of the CoA. (see Annex B for sample record forms).

See [Annex B](#) for recordkeeping examples.

For equipment, all **PPM shall follow SOPs**, as per manufacturers' recommendations (and adapted to context where necessary), and activities performed shall be recorded in a pre-defined template. For on-site oxygen generator plants, maintenance must be carried out at intervals set by the plant's operations manual or established by the head of production (some details can be found in WHO's *Foundations of medical oxygen systems* [17]). VIE systems will typically be managed by the LOX supplier, but, if they are not, SOPs set out by the manufacturer shall be closely followed. Pipeline distribution networks are static in nature and require minimal maintenance, but they do need frequent checks, as prescribed by the facility quality management plan. Cylinders themselves shall bear a stamp or label indicating the date of last hydrostatic test. [45]

Recordkeeping for stock management of cylinders shall leverage the pharmacy's existing system where applicable, as the physical cylinder follows the notion of stock movement "in" and "out" (even though cylinders cannot be physically stored in the pharmacy). With respect to oxygen gas moving in pipelines, quantifying the product used in specific wards will be challenging. A few approaches can be applied; for example: tracking consumption over a period via patient charts or estimating consumption using UNICEF's *Oxygen System Planning Tool* [18] and facility-specific input data.



Recording staff training, including refresher courses and any comprehensive assessments, is another important aspect of quality systems. Doing so will serve to reinforce content and ultimately ensure that the oxygen systems function as safely and efficiently as possible.

Recording non-conformance of product, anomalies in production, or other mishaps that occur along the supply chain is mandatory. This information will support any investigation that will be needed to determine corrective and preventive actions (CAPA) in the event of a complaint and/or a recall, should one be deemed necessary.

All **documents shall be permanent in nature**. Any changes to process or procedure shall go through a formal (and documented!) process justifying those changes. All records shall be kept electronically; where doing so is not possible, they shall be kept in ink in a pre-defined format. All documents and records are to be kept for a minimum of five (5) years. [28]

3.6. QUALITY CONTROL

Quality control is an activity under quality systems that is complementary to quality assurance and comprises the testing of production processes as well as batch testing of product to indicate whether a medical product meets pharmacopoeial specification or in-house standards at a specific point in time. [33] This point-in-time data also informs quality systems functionality, and a positive outcome supports quality assurance. Statements in monographs constitute mandatory requirements. This does not imply that a manufacturer must perform all of the tests described in a monograph when assessing compliance with the specified standards before release. The manufacturer may obtain assurance that a product is of quality on the basis of its design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process. With the agreement of the responsible authority, alternative analytical procedures may be used for control purposes, provided they enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official procedures were used. In the event of doubt or dispute, however, the analytical procedures of the applicable pharmacopoeia are alone authoritative (see, e.g., USP or Ph. Eur.). Results are to be recorded on batch-specific CoA before the product can be released for use. Personnel involved in quality control must be independent from those involved in production. [7]

3.6.1. *Test Methods and Equipment*

Methods for testing will follow those that have been prescribed by the NRA, as indicated in the pharmacopoeia monograph, as well as those required for manufacturing authorization (if applicable). Where methods or assays have not been indicated, those of an SRA can be adopted.

Test equipment is critical for quality control; the equipment itself shall be regularly maintained and calibrated, per the manufacturer's instructions, and its functioning shall be validated. Specific to medical oxygen analyzers, depending on the technology of the sensor, frequent calibration may be required or the sensor may need to be replaced after a predetermined period. The QU shall be familiar with its testing equipment, and the quality controllers shall ensure that their equipment is always in working condition.

Testing capacity and capability will vary from one context to the next and even between facilities. Depending on pre-existing laboratory capacity, facilities may or may not have broader analytical capabilities.



Regardless, in addition to facility level QC, the QU could consider third-party testing as part of its quality management plan. Another option to explore could be a site visit from the manufacturer or distributor of the oxygen generator plant to carry out tests and checks with a pre-established frequency. Any such third-party testing would require a contract clearly delineating the roles and responsibilities of involved parties.

3.6.2. Sampling

Testing the product is essential to ensure that it is meeting specifications required for safe and effective patient use. While the required specifications will be defined by the NRA, the process to test shall be clearly defined in the facility quality management plan (see Section 2.2.5).

Production of medical oxygen (both LOX and PSA/VSA) is continuous in nature, and testing of the product therefore will not come from a sample of a clearly identifiable batch. A framework for defining a batch can be found in ICH's *Continuous Manufacturing of Drug Substances and Drug Products*; Q13. [38] This batch definition will determine the frequency with which to test and document.

- For LOX, testing frequency shall be established and indicated in the facility's master file as part of its overall quality system. Production monitoring will typically be continuous in nature, so trending can be observed. Additionally:
 - For tanker filling, the product purity at the time of fill will be indicated on the transport documentation, which will be included on the fill-specific CoA, whether it be from the ASU site or from a LOX storage hub.
 - For cylinder filling from LOX, *at least one* cylinder from each batch will be tested, and all parameters for the fill batch will be documented as the batch's CoA.
- For an oxygen generator plant, the team responsible for quality control (nominated by the AP) shall test according to the set schedule indicated in the facility's quality management plan, and records of the results shall be diligently kept. These units will have a built-in analyzer that should align with the assay specifications as set out in the specified pharmacopoeial standard, which will be testing the output continuously. Additionally, a sampling port should be located just downstream of the oxygen generator plant with which the recommended hand-held analyzer can be used by a quality controller to test the output purity, validating the result from the built-in analyzer.
- For at-facility cylinder-filling, in addition to QC of the source output (oxygen generator plant or bulk LOX), *at least one* cylinder from each fill batch shall be tested, and all parameters for the fill batch will be documented as the batch's CoA. Quality of packaging and storage applies to the cylinder (see Section 3.2.4); all checks prior to and after filling of cylinders shall be reviewed by a controller.

Any test result that could affect the quality, safety, or efficacy of the medical gas must be reported, reviewed, and thoroughly assessed. This includes any non-conformances, malfunctions, or errors, including those related to premises, equipment, sanitation, and testing. [10] All test results, both passing and out-of-specification, are considered valid and shall be recorded by the quality controller. [10] The QU will authorize the records and make the ultimate decision on whether to release the product for use.

All records shall be kept, including the CoA from the supplier/distributor and results from in-facility production and cylinder filling. Any anomaly in the quality of the product will be deemed an irregularity, and action shall be taken according to the quality management plan. See Annex B for sample recordkeeping forms.



3.6.3. Product Release

The QU has the authority to approve or reject all product. Any product with test results that do not conform to specifications will need to be investigated and undergo a CAPA process. QC will flag these results to QU, and the procedure indicated in the facility risk management plan will be followed.

For any product from an external supplier/distributor, agreements shall be in place with the health facility QU regarding the supplier's/distributor's quality system.²⁴ Additionally, any delivery will come with a CoA reflecting the batch to be offloaded. The QU again has the authority to release the batch, either by accepting or rejecting it.

To maintain the required level of quality, it is also important to examine all returned medical gases. [10]

3.7. COMPLAINTS AND RECALL

A channel for complaints shall be in place through which any person (e.g., personnel on the oxygen supply chain, caregivers, or patients) experiencing an issue with medical oxygen can request that it be examined for any abnormalities in quality, which in turn could potentially trigger a recall. All complaints shall be taken seriously, as they are indicators of problems related to quality.

A process shall be established and outlined in the facility quality management plan for the management of complaints, covering their reception, steps for investigation to determine cause, resolution via necessary corrective measures (inclusive of recall), and all necessary reporting (both internally and to the original complainant). [7, 33] A recall process for use when a compromise in quality necessitates that the product to be withdrawn from supply shall be clearly described.

The following information will be needed for the review process (adapted from [7, 10]):

- Product name (e.g., Oxygen 99 or Oxygen 93)
- Pharmacopoeia (that of an NRA or one adopted from an SRA)
- Manufacturer/distributor
- Batch number
- Complainant's name and contact information
- Date of complaint
- Description of complaint

The information above should be enough to identify the product's place and date of production so all records from the batch can be reviewed and the product can be traced along the supply chain, including through transportation and distribution. Records of all testing done should also be reviewed.

To manage a complaint, it shall be reviewed with the intention of establishing a cause and determining a resolution according to a CAPA process to avoid future issues. Once the cause has been identified, the QU will work with necessary teams to implement CAPAs. Requisite re-testing shall be carried out to ensure quality of product.

²⁴ See footnote 12, p. 13.



QU will also determine whether the complaint was related to or resulted in an adverse event and, if so, open an investigation to identify trends or patterns. [8]

If there is any indication that the product in question could present a health risk to anyone, a voluntary recall should be initiated. This will entail tracing the batch, communicating (verbally or in writing) with whomever may have (or have had) the product, and removing any remaining product from supply. The recall process will be documented in the facility quality management plan; agreements between supplier/distributor and end-user will also contain these details.

All activities related to complaints and recall shall be recorded, including the original complaint, CAPA process, and follow-up communication with the complainant. Any recall shall be communicated to the NRA.

3.8. SELF-AUDIT/INSPECTION

Self-audits, conducted with a frequency established in the facility quality management plan, serve to ensure that the whole manufacturing process is being carried out under the applied quality framework (such as GMP), appropriate QC is taking place, and assurance in the quality of the medical oxygen being used ultimately remains. While scrutinizing, self-audits are to be regarded as an opportunity for growth and improvement.

These reviews shall be carried out by personnel appropriately trained regarding the quality standards and quality system requirements and shall be independent of operations. Before a self-audit begins, the audit team will develop an audit plan. This will typically cover, but not be limited to (adapted from EIGA Doc 195/20 [28]):

- Any previous audit and associated resulting activities (if applicable)
- Production data, metrics, trends
- Review of specifications, application, appropriateness
- Equipment status
- Efficacy of in-process controls
- Non-conformance events, associated investigations, efficacy of CAPA processes
- Contract review (if applicable), e.g., PPM, quality agreements with external entities

Any findings resulting in proposals for corrective measures shall be noted and managed through a change control system. This will involve documentation, evaluation, and approval by the head of the QU. Changes made to processes or to the system may require re-validation. [10]

A comprehensive report shall be generated from the self-audit and include trends, non-conformance, complaints, adverse events, CAPA processes, and any proposals for recommended system or process changes. [28]

It is common that for LOX manufacturers producing medical oxygen, internal audits are conducted every six months, with a focus on purity and contaminant monitoring.



ANNEX A: ROLE-SPECIFIC QA SUPPLEMENTS

The following tables can serve as job-aids, outlining role-specific quality assurance activities along the medical oxygen supply chain. Entities in such roles, or facilities with personnel in roles with these responsibilities, can use these job-aids to supplement their operational plans, SOPs, and work instructions with regard to quality assurance activities related to medical oxygen systems.

A National Regulatory Authority is responsible for ensuring that medical products (pharmaceuticals, biological products, medical devices) released for public distribution are evaluated and deemed to be of an acceptable standard of quality, safety, and efficacy. Typically, a NRA will have established a regulatory framework within which requirements for medical gases, inclusive of medical oxygen, will be outlined.

Examples of activities under the purview of NRAs would be ensuring compliance with specified standards, such as pharmacopeial specifications and requirements for specific medical products, inclusive of medical oxygen. NRAs are responsible for issuing product marketing authorizations for commercial vendors of medical products and conducting requisite inspections to ensure compliance with GxPs²⁵ (GMP, GDP, GSP, and GPP). NRAs also play a key role in vigilance practices across all medical products—medicines and medical devices alike.

While specific details regarding the role and responsibilities of NRAs as they relate to medical oxygen are beyond the scope of this document, it is important to note that any NRA requirements will take precedence over, and underpin the application of, QA practices, inclusive of these job-aids. Thus, these job-aids should be adapted accordingly.

Note:

- These job-aids are not to be interpreted as prescriptive; rather, they are to be used as a tool that can be adapted to suit the user's context.
- QA practices will have to be adapted to suit contextual needs. For example, QA and QC needs at a regional referral hospital where oxygen is being produced by an on-site oxygen generator plant will differ from those at a secondary hospital relying on oxygen cylinders procured from a nearby oxygen manufacturer.
- Establishing QA and QC needs and revisiting them at a set interval (e.g., annually) would be a prudent approach.

²⁵ "GxP" is the acronym for good [anything] practice—in this case, good manufacturing practice (GMP), good distribution practice (GDP), good storage practice (GSP), and good pharmacy practice (GPP).



AI: JOB-AID FOR AUTHORIZED PERSON (TYPICALLY HEAD PHARMACIST)

Description: The role of the AP is to take overall responsibility for the quality of oxygen in a health care facility—the production of Oxygen 93 and/or the acquisition of oxygen from an external source: LOX, cylinders from LOX, or cylinders from an external PSA/VSA. The AP must have a comprehensive understanding of the clinical application of oxygen and the monograph requirements under the nationally recognized pharmacopoeia. This role shall be nominated, but it is typically assigned to head pharmacists, who also head the quality units.

Qualifications: Licensed pharmacist (B.Sc., has passed the pharmacy board exams and is licensed through a relevant professional association).

Tasks related to medical oxygen QA adapted from EIGA Doc I 95/20 [28]:

Activity	Details	Frequency	Documentation
Establish and fill QA and QC roles that correspond with facility oxygen services	As responsible for overall quality, ensure that all roles and responsibilities of QA and QC respectively are covered, and that personnel have appropriate training and experience. Nominees may require a deputy to ensure comprehensive and continuous coverage.	Once, at outset of system implementation/in absence of QA practice	Nominees to be provided with detailed descriptions of duties and responsibilities for O ₂ QA; facility-level QA organigram to be developed
Lead development of facility-specific medical gas operational policy	Details of facility-specific system, comprising needs assessment, capacity, operational protocols, quality requirements, and personnel roles and responsibilities. Includes: <ul style="list-style-type: none">quality management planrisk management plan	Once, at outset of system implementation/in absence of QA practice *Revisit at specified interval (e.g., every 5 years and with any adverse event or source change)	
Ensure that the oxygen meets quality requirements of the nationally recognized pharmacopoeia	<input type="checkbox"/> Sign off on oxygen: <ul style="list-style-type: none">on-site production (PSA/VSA), as per testing protocol in operational policyLOX delivered, as per CoAcylinders delivered, as per CoA <input type="checkbox"/> Notify health care providers in the event of an Oxygen 93 and Oxygen 99 blend	As needed	Signatory on QC documents
QA during procurement of oxygen generator plants	<input type="checkbox"/> Involve technical team in procurement <input type="checkbox"/> Ensure that product meets nationally accepted regulatory requirements for medical devices.	As needed	Follow internal procurement processes, ensure vendors provide appropriate quality-related documentation
Lead training program	<input type="checkbox"/> Develop and/or adapt training content with department or activity leads <input type="checkbox"/> Ensure all staff who work with oxygen have been trained on oxygen safety and risks, safe equipment operations and handling, and equipment maintenance (where applicable) <input type="checkbox"/> Manage trainers administering specific modules <input type="checkbox"/> Ensure O ₂ content incorporated into CPD	Set into CPD cadence after onboarding	Maintain a training log, to be revisited every year (or at a frequency set out in facility operational plan)



Activity	Details	Frequency	Documentation
Manage CAPA processes	With quality unit, investigate any off-specification oxygen and/or any (reported) adverse events, taking: <input type="checkbox"/> corrective action <input type="checkbox"/> preventive action	As needed	Thorough documentation of event and CAPA
Authorize “permit to work”	Provide sign-off on “permit-to-work” applications	Prior to any PPM and repairs as needed	Strict documentation in line with facility risk management plan
Lead internal audits	Review, at a minimum: <input type="checkbox"/> Previous audit and associated resulting activities (if applicable) <input type="checkbox"/> Production data, metrics, trends <input type="checkbox"/> Specifications, application, appropriateness <input type="checkbox"/> Equipment status <input type="checkbox"/> Efficacy of in-process controls <input type="checkbox"/> Non-conformance events, associated investigations, efficacy of CAPA <input type="checkbox"/> Existing contracts (if applicable), e.g., PPM, quality agreements with external entities	Annually, unless otherwise triggered by significant adverse event.	Audit reports, inclusive of trends, adverse events; plans for required system or process change
Report adverse events to NRA	Part of vigilance practice as per national requirements, ensure facility management is informed	As needed	Stringent recordkeeping of any adverse event



A2: JOB-AID FOR HEAD OF PRODUCTION

Description: A necessary member of the team for ensuring quality medical oxygen systems, the head of production has oversight of all activities related to the production of medical oxygen when an on-site oxygen generator plant is used. Will liaise with the AP for quality control if/where needed.

Qualifications/requirements/experience: Engineer (civil, mechanical, biomedical, electrical) with project management skills and work experience in the health care sector.

Tasks related to medical oxygen QA adapted from EIGA Doc I95/20 [28] and EIGA Doc I49/22 [56]:

Activity	Details	Frequency	Documentation
Develop and finalize facility-specific SOPs for production	Working with production team, base operational SOPs on manufacturer's instructions and have final SOPs approved by AP; flag all QA requirements	Once, but revisit if/when needed	Documented, part of facility quality management plan
Ensure production in accord with SOPs	Review all records to ensure that production team is consistently following SOPs and recording necessary information	Quarterly	Review of records
Ensure continuity of supply	Ensure that secondary supply has been established for facility, that it remains adequate, and that it is activated appropriately	Once, but revisit if/when needed	Documented, part of facility quality management plan
Ensure thorough and timely PPM program	Review all records to ensure that PPM is conducted according to plan and necessary records are created	Quarterly	Review of records
Validate the on-site oxygen generator plant, alongside the AP	Equipment tested for functionality, safety, and performance, and to ensure that it operates in line with specifications	Typically, following installation and after any major repair or other work	To record, with AP, if indicated with PPM
Validate cylinder filling, analysis, and release process, alongside AP	Equipment tested for functionality, safety, and performance, and to ensure that it operates in line with specifications	Typically, following installation and after any major repair or other work	To record, with AP, if indicated with PPM
Validate any monitoring and measuring equipment, ensure calibration process is established and clear	Validation will take place upon commissioning; however, after any major work, equipment shall be tested for functionality, safety, and performance and to ensure that it operates in line with specifications; additionally, calibration protocols—if/when indicated—shall be clearly established based off manufacturer's guidance	Validation as needed, typically after major repair; calibration as indicated by manufacturer of measuring device	To record, with AP, if indicated with PPM
Facilitate technical trainings, alongside AP	Deliver any technical modules covered in a training cycle, at the request of AP; can deputize for capacity building, if appropriate	At intervals set in quality management plan	To record, with AP
Conduct periodic review of operational log for preventive control parameters	Monitor purity, flow, temperature, pressures, vibrations, power, capacity, and any other variable established in the risk management plan as preventive control parameters	Quarterly	Review of records
Manage "permit-to-work" system applications	Responsible for the execution of technical work, and thus shall manage all activities under "permit to work," including any third-party contractors (AP has the ultimate responsibility)	Prior to all PPM events, and as needed in case of repairs	Record via "permit to work" application process
Participate in internal audit	At the request, and under the guidance, of the AP	Annually, unless otherwise triggered by a significant adverse event	Audit report, inclusive of trends, adverse events; plans for required system or process change
Support CAPA processes	With quality unit, investigate (reported) adverse events, taking <input type="checkbox"/> corrective action and <input type="checkbox"/> preventive action	As needed	To record, with AP



A3: JOB-AIDS FOR OPERATORS

Description: Day-to-day operations of medical oxygen systems must be carried out with great care to ensure continued quality outputs. Operators shall be dutiful with regard to task, meticulous with regard to recordkeeping, and fastidious with regard to cleanliness.

Qualifications/requirements/experience: To operate on-site oxygen generator plants, fill cylinders, and manage pipeline distribution networks and VIE systems, operators can be technicians of the following disciplines: biomedical technician, mechanic, electrician, builder/contractor. They shall also have experience in the health care sector, and shall have received training from the oxygen generator plant manufacturer.

The following QA requirements have been developed for specific components of the system. An operator of a specific unit is assumed to be capable of and responsible for the cleaning and maintenance of said component.

On-site oxygen generator plant operations

Tasks related to medical oxygen QA adapted from EIGA Doc I 95/20 [28], unless otherwise indicated:

Activity	Details	Frequency	Documentation
Provide input to head of production on SOPs and work instructions, noting QA activities	All activities for start-up and operation of the complete unit shall be made; activity to be carried out with the head of production and manufacturer/distributor of plant	Once, prior to commissioning of the unit *Refine as needed	SOPs to be documented in facility quality management plan, a form developed enabling recordkeeping of procedures followed and any notable parameters
Conduct facility check (Adapted from: EIGA Doc I 49/22 [56])	Ensure the following: <input type="checkbox"/> Fire safety system and fire suppression equipment are present and functional <input type="checkbox"/> Room O ₂ levels are between 19.5% and 23.5% at all times <input type="checkbox"/> Ambient air conditioned to manufacturer-specified operating conditions <input type="checkbox"/> Monitor and maintain air intake, notify HP of any risks (acute: fire; protracted: new construction nearby) <input type="checkbox"/> No unauthorized or unrelated work in oxygen generator plant and cylinder filling room <input type="checkbox"/> Production room remains clean at all times	Daily * It must be ensured that staff are working in a safe environment and that external contamination risks are minimized and/or mitigated	Record all details in a standardized format
Operate the unit per SOPs	<input type="checkbox"/> Adherence to established SOPs <input type="checkbox"/> Follow work instructions (where applicable) <input type="checkbox"/> Carry out QA activities and make records	Every time the unit is operational (e.g., start-up, operations, shut-down)	Record operations in template, indicate procedures followed and any notable parameters
Trigger secondary and/or emergency source in the event of unresolvable issue	Notify head of production in the event of any deviation in established operational values	During PPM or under abnormal conditions/adverse event	Record the start-up of the secondary and/or emergency source, including justification



Activity	Details	Frequency	Documentation
Carry out PPM and repairs (or accompany third party and support recordkeeping in the case of a service level agreement) (Adapted from EIGA Doc 149/22 [56] and EIGA Doc 33/18 [57])	<input type="checkbox"/> Complete request for “permit-to-work” authorization with head of production <input type="checkbox"/> Carry out all work as per manufacturer recommendation <input type="checkbox"/> Use only parts or spares labelled “Clean for oxygen service” and include inspection documentation and cleaning certificates ²⁶ <input type="checkbox"/> Ensure materials used/connected to system are clean of mill scale, rust, dirt, weld slag, flux, oils, greases, and any other organic or inorganic particulates and solvents before recommissioning *Ensure adequate spares availability	As per PPM schedule, recommended by manufacturer and outlined in the quality management plan	Record all details in a standardized format
Oxygen purity analyzer maintenance (both in-built and secondary hand-held)	<input type="checkbox"/> Calibrate periodically as per manufacturer’s instructions ²⁷ <input type="checkbox"/> Conduct PPM as per manufacturer’s instructions <input type="checkbox"/> Replace sensor at frequency set by manufacturer	As per PPM schedule, recommended by manufacturer and outlined in the quality management plan	Record all details in a standardized format

Cylinder filling

Tasks related to medical oxygen QA adapted from EIGA Doc 209/17 [50]:

Activity	Details	Frequency	Documentation
Determine “batch” definition, with AP (see ICH Q13 [38])	Based on filling station size (filling ramp/manifold connection points): <input type="checkbox"/> Determine how many cylinders filled comprise a batch <input type="checkbox"/> Determine number of cylinders from a batch need testing <input type="checkbox"/> Establish nomenclature to indicate batch number and cylinder within batch to facilitate batch tracing <input type="checkbox"/> Develop template for recordkeeping of each batch filled	Once, prior to commissioning of the station, refined if any physical changes are made to hardware	Definition to be documented in quality management plan, record template to be used during operations
Establish SOPs and work instructions for filling, alongside the head of production and based on specs from manufacturer of cylinders	These SOPs shall cover: Checks: <input type="checkbox"/> Cylinder color-coding paint intact <input type="checkbox"/> Cylinder valves for oxygen service <input type="checkbox"/> Visual checks: valve for cleanliness and damage, shell for damage <input type="checkbox"/> Cylinder up to date on testing (last hydrostatic test, test ring intact) Preparation: <input type="checkbox"/> Cylinder purge (cylinders may/may not have residual pressure valve; SOP specific to type of cylinder valve and requisite purge shall be developed) Fill and post fill: <input type="checkbox"/> Fill schedule <input type="checkbox"/> Fill pressure requirements <input type="checkbox"/> Valves leak-tested and closed <input type="checkbox"/> Batch labelling <input type="checkbox"/> Coordinate with QC for batch testing	Every batch filled	Record all details in a standardized format

²⁶ Non-metallic materials—gaskets, valve packing, insulation, and lubricants—shall be certified for oxygen service. Consult the supplier before using these materials.

²⁷ Calibration gases may be difficult to acquire. Consider when selecting analyzer sensor type during procurement.



Activity	Details	Frequency	Documentation
Manage cylinders	<input type="checkbox"/> Keep cylinders sorted by categories, for example: empty, full, prepared deliveries, faulty/rejected cylinders, etc. (if needed, can use chalk or crayon to make a temporary marking) <input type="checkbox"/> Safely maneuver cylinders using a trolley or forklift (for pallets) <input type="checkbox"/> Maintain product rotation (e.g., first-in, first-out)	Continuous	Follow pharmacists' stock-management recordkeeping
Booster compressor PPM	<input type="checkbox"/> Liaise with plant operator <input type="checkbox"/> Carry out all work as per manufacturer recommendation <input type="checkbox"/> Use only parts or spares labelled "Clean for oxygen service" and include inspection documentation and cleaning certificates ²⁸ *Ensure adequate spares availability	Every 1,000 hours of operations and earlier, if context indicates	Record all details in a standardized format
Facilitate for testing	Batch labeling to be completed to facilitate testing by quality controllers (different personnel)	Every batch filled	Record all details in a standardized format

Pipeline management

Tasks related to medical oxygen QA adapted from EIGA Doc I3/20 [30], unless otherwise indicated:

Activity	Details	Frequency	Documentation
SOPs and work instructions development	Develop written procedures, alongside head of production, for: <input type="checkbox"/> system shutdown/start-up <input type="checkbox"/> PPM <input type="checkbox"/> Planning for repairs ("permit to work")	Once, when system is installed, and updated when/if needed	Documented templates for use when/as needed
Operations check	<input type="checkbox"/> Manifold alarms and change-over functioning <input type="checkbox"/> Monitoring of alarms (master/ward)	Continuous	Record when normal, flag if/when deviation occurs
PPM: Broad system check	Conduct a full walk of pipeline system (See PPM checklist in EIGA 013/20 Appendix F [30]), visually check for the following: <input type="checkbox"/> Any abnormal/accidental interference with damage to system <input type="checkbox"/> System signage and markings remain intact	Daily, no need for "permit to work"	Record all checks on a standardized template
PPM: Targeted checks	<input type="checkbox"/> Leak test all exposed fittings and flanges <input type="checkbox"/> Test cathodic protection system (if applicable) <input type="checkbox"/> Full pipeline pressure check	Every 3 months Every 3 months Every 6 months	Record all checks on a standardized template
Repair work preparation (accompany third party and support recordkeeping)	<input type="checkbox"/> All personnel must be trained in oxygen safety and work safety for oxygen pipelines <input type="checkbox"/> Solicit for authorization under "permit to work" with head of production; only decommission necessary areas <input type="checkbox"/> All parts or spares used in oxygen systems must come labeled "Clean for oxygen service" and include inspection documentation and cleaning certificates [57] <input type="checkbox"/> If piping is to be opened, ensure depressurization and purging with air [56] <input type="checkbox"/> Establish provisional grounding if any welding will be conducted	As needed	All work intended to be carried out shall be recorded by "permit to work" process

²⁸ Non-metallic materials—gaskets, valve packing, insulation, and lubricants—shall be certified for oxygen service. Consult the supplier before using these materials.



Activity	Details	Frequency	Documentation
System start-up	<input type="checkbox"/> Ensure materials used/connected to system are clean of mill scale, rust, dirt, weld slag, flux, oils, greases, and any other organic or inorganic particulates and solvents before recommissioning [56, 57] <input type="checkbox"/> Purge with oxygen to remove working shield gas (air or nitrogen) and test all outlets to ensure working purity achieved <input type="checkbox"/> Conduct leak test upon re-start after prolonged shut-down <input type="checkbox"/> Coordinate with QC to test purity at recommissioned bedside terminal units	As needed, typically after major repair	All work completed, inclusive of confirmation of final purge and leak test, shall be recorded by “permit to work” process
System drawings	Maintaining a current “redline” of the system drawings will ensure that any future works are carried out most efficaciously Also, those undertaking any adjacent work must know where pipelines run to avoid any breach	Whenever changes are made to original pipeline network	Drawing directly onto a “live” copy of the original system drawings in a notable color

VIE and LOX cryo-cylinder management

Each tank is unique and has its own “databook”—a comprehensive dossier including plans, process and instrumentation diagrams, certifications, and operating instructions. The databook must stay with the tank and its owner and be updated when any significant repairs or changes are made to the tanks, piping, valves, etc., that warrant validation by an NRA-recognized third-party authorized inspection agency (AIA).

Tasks related to medical oxygen QA adapted from EIGA Doc 127/20 [58] and EIGA Doc 128/21 [55] and EIGA Doc 224/20 [59]

Activity	Details	Frequency	Documentation
Site check	<input type="checkbox"/> VIE area is clean, clear, and free from any obstruction <input type="checkbox"/> Access to site remains unobstructed, open for LOX delivery tanker truck	Daily	Report any abnormal conditions
Operations check	<input type="checkbox"/> tank pressure <input type="checkbox"/> LOX level* <input type="checkbox"/> pressure gauge* <input type="checkbox"/> ensure outer shell and pressure relief devices are ice-free** <input type="checkbox"/> if bursting discs rupture, CAPA (incl. replacement)	Daily	Report any abnormal conditions: pressure drop, leakage, off-gassing, to the QU to ensure secondary/back-up option can be ready
Inspection of storage tank and vaporizer***	<input type="checkbox"/> Intact (visual, no deterioration) <input type="checkbox"/> Functionality of all pressure relief devices and gauges <input type="checkbox"/> Slab integrity (visual) <input type="checkbox"/> Fencing and signage integrity (visual)	Every 12 months, in consultation with tank manufacturer, LOX provider, and NRA, if applicable	Record and retain results alongside databook
Maintenance of storage tank***	PPM in oil-free environment: <input type="checkbox"/> Liquid level measurement system <input type="checkbox"/> Overfill protection system <input type="checkbox"/> Emergency shutoff valve (if applicable) *Ensure adequate spares availability	Every 24 months, in consultation with tank manufacturer, LOX provider, and NRA, if applicable	Record and retain details of any work done alongside databook
Safety valve check	<input type="checkbox"/> Establish a “service period,” typically three years <input type="checkbox"/> Test for functionality <input type="checkbox"/> If bursting discs used, replace at this interval	Every three years, unless otherwise required by tank manufacturer, LOX provider, and/or NRA	Record and document, if necessary, in databook



Activity	Details	Frequency	Documentation
Solicit for and manage repairs by approved entity	Original spares to be used Conducted by approved maintenance facilities/personnel Reclean for oxygen service if indicated Final inspection by an AIA	As needed, and as per tank manufacturer, LOX provider, or NRA	Record details of work done, include in databook with requisite test certificates issued by AIA

* The LOX level and pressure gauges do not need to be calibrated, as their values are indicative only—accuracy is not critical.

** Water should not be used to de-ice pressure relief devices/valves. If ice build-up is continuous, employ mitigative measures as ice can inhibit valves from functioning properly or altogether block lines. Consideration shall be made to insulating problematic lines or heating them to prevent any further ice build-up.

*** Excludes inner tank and annular space as periodic inspection is not considered necessary. Taking the tank out of service and exposing the inner tank and/or annular space when not indicated will pose additional risks to the system, and thus it will only be taken out of service for repair on an as-needed bases.



A4: JOB-AID FOR HEAD OF QUALITY CONTROL

Description: Responsible for all quality control activities as they relate to production of medical oxygen within the health facility. Liaises with AP.

Qualifications/requirements/experience: Technical or clinical background with experience in the health care sector. Can be a facility pharmacist, though typically not the AP.

Tasks related to medical oxygen QA adapted from EIGA Doc 195/20 [28]:

Activity	Details	Frequency	Documentation
Develop quality control processes	With AP, develop quality control processes: <input type="checkbox"/> In-line with facility quality management plan <input type="checkbox"/> Complementary to risk management plan <input type="checkbox"/> Monitoring all preventive controls <input type="checkbox"/> Monitoring to ensure compliance with pharmacopoeia <input type="checkbox"/> Escalation of quality issues (develop communication ladder)	After initial development, revisit with frequency indicated in operational plan	Documents to be included in the facility medical gas operational policy, templates to be used for daily activities
Manage QC team	<input type="checkbox"/> Support team in activities if/when needed <input type="checkbox"/> Work to troubleshoot when any issues arise	As needed	Record if troubleshooting uncovers quality issue
Verify quality control processes	Ensure that QC processes support QA of facility oxygen; review: <input type="checkbox"/> QC records for completion <input type="checkbox"/> QC records for conformance to specifications	Annually, unless otherwise triggered by a significant adverse event	Record in facility audit
Equipment maintenance and calibration	With QU, ensure that operational and QC teams maintain and calibrate equipment as per manufacturer recommendations	PPM as per manufacturer instruction	Record all details in a standardized format
Equipment validation	Ensure that equipment for manufacture of medical oxygen has been validated according to NRA requirements	As needed, typically after major repair	Record all details in a standardized format
Facilitate trainings alongside AP	Support AP in administration of training	At intervals set in quality management plan	Record, with AP
Participates in internal audit	At the request and under the guidance of the AP	Annually, unless otherwise triggered by a significant adverse event	Generate audit report, inclusive of trends, adverse events; plans for required system or process change
Support CAPA processes	With quality unit, investigate (reported) adverse events, taking: <input type="checkbox"/> corrective action and <input type="checkbox"/> preventive action	As needed	Record, with AP



A5: JOB-AID FOR QUALITY CONTROLLERS

Description: Carries out quality control activities as they relate to medical oxygen within the health facility.

Qualifications/requirements/experience: Technical or clinical background with experience in the health care sector. Important to distinguish QC role and that controller be experienced and adequately trained.

Tasks related to medical oxygen QA adapted from EIGA DOC I 95/20 [28]

Activity	Details	Frequency	Documentation
Calibrate monitoring and measuring equipment	Ensure that all equipment used in monitoring and measuring is calibrated as per manufacturer requirements	At each calibration interval, as indicated by device manufacturer	Record all details in a standardized format
Test quality of product	Test the following: <input type="checkbox"/> On-site oxygen generator plant output, as per batch definition in the facility quality management plan (record values from oxygen generator plant AND from secondary hand-held analyzer) <input type="checkbox"/> Cylinder filling, minimum one per batch, to be released by AP	Daily, for each batch as defined in the quality management plan	Standard QC record template; prepare CoA for QU if any are to be sent elsewhere; non-conformance reported and flagged to QU
Test secondary systems	Ensure automatic switch-over to secondary supply (where applicable) if: <ul style="list-style-type: none">▪ Main power supply outage affects primary source▪ Pressure or purity drops from primary source	PPM, to be carried out as scheduled with plant operator	Record all details in a standardized format
Test monitoring and alarm systems	All alarms and controls shall be tested for operating limits (e.g., pressure, oxygen concentration, CO, CO ₂ , automatic shut-off, vent valves) <ul style="list-style-type: none">▪ Test one function at a time▪ Observe that audio, visual, and—where applicable—operational control is activated	PPM, to be carried out as scheduled with plant operator	Record all details in a standardized format



A6: JOB-AID FOR TRANSPORTER (AND DISTRIBUTOR, IF APPLICABLE)

Description: Any vehicle operator or transporter of medical oxygen, either LOX or high-pressure gas cylinders.

Qualifications/requirements/experience: Personnel shall be trained in all the technical characteristics of oxygen and its risks and hazards, as well as in the quality requirements of medical oxygen and the sensitivities associated with working for and in proximity to patients. They shall have a valid driver's license (commercial, if deemed necessary). Any inspection, examination, and/or maintenance of any vehicle (including tanker truck) shall be performed by personnel trained and qualified in auto mechanic work.

Tasks related to medical oxygen QA and transport adapted from EIGA Doc I28/2I [55]

Activity	Details	Frequency	Documentation
Develop, verify, and validate SOPs	All protocols/SOPs shall be developed and tailored to each vehicle to ensure that nuances are captured	At time of acquisition of vehicle, to be re-visited if vehicle is modified/changed	Documented as part of GDP; templates for records developed
Conduct vehicular check	<ul style="list-style-type: none"><input type="checkbox"/> Tire condition and pressure<input type="checkbox"/> Safety kit available/complete and not expired<input type="checkbox"/> Vehicle and driver documents present<input type="checkbox"/> Vehicle fueled up<input type="checkbox"/> Brakes functioning<input type="checkbox"/> No obvious issues/damage	Every trip	Record all details in a standardized format
Observe loading protocol	<ul style="list-style-type: none"><input type="checkbox"/> Engine off and parking brake engaged<input type="checkbox"/> Maximum number of cylinders never exceeded²⁹<input type="checkbox"/> Verify load distribution<input type="checkbox"/> Ensure load is secured<input type="checkbox"/> Valve guards or caps fitted<input type="checkbox"/> Full and empty cylinders segregated<input type="checkbox"/> Accessories stored separately: regulators, flowmeters, trollies, etc. (if applicable)<input type="checkbox"/> Safely maneuver cylinders using a trolley or forklift (for pallets)	Every leg of every trip	Record all details in a standardized format
Maintain vehicle	Follow appropriate maintenance schedule based on mileage. Additionally, ensure: <ul style="list-style-type: none"><input type="checkbox"/> Cargo compartment structure is sound (floor smooth)<input type="checkbox"/> Vents are adequate, unobstructed<input type="checkbox"/> Load securing system is intact<input type="checkbox"/> Doors/gates open smoothly<input type="checkbox"/> Lift is functional (if applicable) *Smoking prohibited in garage ** Oils, greases, solvents to be kept away from vehicle	As per Ministry of Transportation and/or Ministry of Industry requirements (e.g., at a pre-set number of kilometers on odometer)	Record all details in a standardized format

²⁹ Cylinders come in many sizes, each with its own specifications. The transporter (distributor, if applicable) shall establish equivalents in their SOPs and heed a uniform and conservative estimate for each size—e.g., large cylinders have tare weights of upwards of 70 kg.



Activity	Details	Frequency	Documentation
LOX-specific transfilling	<ul style="list-style-type: none"><input type="checkbox"/> Mitigate potential for contamination:<ul style="list-style-type: none">▪ Maintain required pressure differential between truck and receiving tank▪ Purge transfer hose prior to filling▪ Ensure non-return valves are functional▪ Use only compatible connection fittings<input type="checkbox"/> Filler to wear PPE (goggles, face shield, long sleeves, heavy duty gloves); receiving attendant, too, if assisting<input type="checkbox"/> Filler to stay present for whole fill	At every LOX drop, all details noted by receiver	Record all details in a standardized format
LOX-specific maintenance	<p>Vehicle maintenance is the responsibility of the provider; the transfilling equipment and process can affect quality of LOX delivered:</p> <ul style="list-style-type: none"><input type="checkbox"/> No obvious issues with vehicle<input type="checkbox"/> No visible damage or corrosion on:<ul style="list-style-type: none">▪ Fittings on truck and hose▪ LOX transfer hose <p><i>Anything damaged shall be decommissioned immediately</i></p>	At every LOX drop, all details noted by receiver	Record all details in a standardized format
LOX truck cryogenic tank	<ul style="list-style-type: none"><input type="checkbox"/> Check status of vacuum	Every 6 months	Record status in standardized format



ANNEX B: RECORDKEEPING

ON-SITE OXYGEN GENERATOR PLANT

The following is recorded for each batch cycle (adapted from EC's Good Manufacturing Practice, Medical Gases [32]):

TEMPLATE

Detail	Value
Product name	
Batch number	
Date, time, address of production operations	
Operator responsible	
Operations room inspection	
Air intake inspection	
Time of system start-up	
System checks status	
Time purity reached	
Specification results (O ₂ , CO ₂ , CO)	
Test method, equipment, and ID; date of last calibration	
QC tester	
Batch certification, QU representative	

EXAMPLE

Detail	Value
Product name	Oxygen 93
Batch number	PSA0011228899
Date, time, address of production operations	10 March 2021, morning shift Friendship RRH 123 Ruby Road
Operator responsible	Cecilia
Operations room inspection	Normal
Air intake inspection	Clear
Time of system start-up	7:26 am
System checks status	Normal
Time purity reached	8:24 am (0:58 min)
Specification results (O ₂ , CO ₂ , CO)	O ₂ : 93.6% CO ₂ : <300 ppm V/V CO: < 5 ppm V/V
Test method, equipment, and ID; date of last calibration	Inbuilt paramagnetic, ID PSA123 Maxtec 'MaxO ₂ +A' galvanic ID HH
QC tester	Cecilia Jones, <i>Cecilia Jones</i>
Batch certification, QU representative	Peter Paul, 10 March 2021, 3:45pm <i>Peter Paul</i>

Note: Depending on the size of the oxygen generator plant, the system can take over an hour to reach purity. During this start-up time, the operator will be conducting necessary checks, recording all details and findings, and getting documentation prepared for clearance by QU.



CYLINDER FILLING

All cylinders in a batch will have been inspected and cleared for filling. The following is recorded for each batch filled (adapted from EC's Good Manufacturing Practice, Medical Gases [32]):

TEMPLATE

Detail	Value
Product name	
Batch number	
Date, time, address of filling operation	
Personnel involved; duties performed	Inspection: Preparation: Fill: Leak test:
Batch reference for fill gas	
Fill equipment and ID	
Fill pressure	
Reference temperature	
Specification results (O ₂ , CO ₂ , CO)	
Cylinder serial numbers	
Test method, equipment, and ID; date of last calibration	
Quantity of rejected cylinders, reason	
QC tester	
Batch certification, QU representative	

EXAMPLE

Detail	Value
Product name	Oxygen 93
Batch number	CYL0011228899
Date, time, address of filling operation	10 March 2021, morning shift Friendship RRH 123 Ruby Road
Personnel involved; duties performed	Inspection: Jerry Preparation: Jerry Fill: Jerry Leak test: Cecilia
Batch reference for fill gas	CYL0011228899 from Friendship RRH PSA
Fill equipment and ID	Friendship RRH PSA fill ramp B
Fill pressure	140 bar
Reference temperature	60°C
Specification results (O ₂ , CO ₂ , CO)	O ₂ : 93.6% CO ₂ : <300 ppm V/V CO: < 5 ppm V/V
Cylinder serial numbers	(insert all SNs of cylinders in batch)
Test method, equipment, and ID; date of last calibration	Maxtec 'MaxO ₂ +A' galvanic ID HH Maxtec calibrated same day Inbuilt infrared, ID PSA456
Quantity of rejected cylinders, reason	0, N/A
QC tester	Cecilia Jones, <i>Cecilia Jones</i>
Batch certification, QU representative	Peter Paul, 10 March 2021, 3:45pm <i>Peter Paul</i>

*If cylinders leave one facility to go to another, the above information shall be included in a CoA. However, it is important to double check cylinders and their SNs in the CoA (e.g., multiple CoAs may be needed for a given delivery).



LOX RECEPTION

The following is recorded for each LOX batch delivered (adapted from US FDA's Current Good Manufacturing Practice for Medical Gases [8] and EC's Good Manufacturing Practice, Medical Gases [32]):

TEMPLATE

Detail	Value
Product name	
Batch number	
Date, time, address of transfilling operation	
Personnel involved; duties performed	
Vehicle license	
Vehicle size	
Product specification results	
Test method, equipment, and ID; date of last calibration	
Date of last calibration	
QC tester	
CoA provided	
QU decision	

EXAMPLE

Detail	Value
Product name	Oxygen 99
Batch number	ASU9988221100
Date, time, address of transfilling operation	24 March 2022, 10:23 am Orchid RRH 783 Prosper Boulevard
Personnel involved; duties performed	Samson, LOX lorry driver & transfiller; Bruce, Facility BME
Vehicle license	AZ23HG
Vehicle size	23 Tonnes
Product specification results	99.9%
Test method, equipment, and ID; date of last calibration	Siemens paramagnetic analyzer IDAmeASU2345
Date of last calibration	June 12, 2021
QC tester	Bruce
CoA provided	Yes
QU decision	Patricia George, Head pharmacist <i>Patricia George</i>



SAMPLE COA

The following template has been developed as an adaptation from multiple sources [60, 61, 62]:

<div style="border: 1px dashed black; padding: 10px; text-align: center;">LOGO Name manufacturer Address manufacturer</div>	<div style="display: flex; justify-content: space-between;"><div>Medical oxygen DIN: _____ Pharmacopoeial Standard: _____ Produced by: _____</div><div>Form No.: _____ Date: _____ Time: _____ Page: _____</div></div>												
CERTIFICATE OF ANALYSIS													
<div style="display: flex; justify-content: space-between;"><div>Batch number: _____ Lot number: _____</div><div>Vehicle plates: _____ Driver: _____ Volume loaded: _____</div></div>													
Analysis report:	<table border="1" style="width: 100%; border-collapse: collapse;"><thead><tr><th>Test</th><th>Method of analysis</th><th>Specification</th><th>Results</th></tr></thead><tbody><tr><td>Oxygen assay</td><td>Paramagnetic analyzer (Analyzer SN: _____)</td><td>≥ 99.5%</td><td></td></tr><tr><td>Odor</td><td>Organoleptic (nasal/smell)</td><td>None</td><td></td></tr></tbody></table> <div style="margin-top: 10px;"><div>Is additional testing needed? <input type="checkbox"/> Yes <input type="checkbox"/> No</div><div>Is product in compliance with specification? <input type="checkbox"/> Yes <input type="checkbox"/> No</div><div style="display: flex; justify-content: space-between; margin-top: 10px;"><div>Analyzed by (name): _____</div><div>Signature: _____ Date: _____</div></div><div style="display: flex; justify-content: space-between; margin-top: 10px;"><div>Witnessed by (name): _____</div><div>Signature: _____ Date: _____</div></div></div>	Test	Method of analysis	Specification	Results	Oxygen assay	Paramagnetic analyzer (Analyzer SN: _____)	≥ 99.5%		Odor	Organoleptic (nasal/smell)	None	
Test	Method of analysis	Specification	Results										
Oxygen assay	Paramagnetic analyzer (Analyzer SN: _____)	≥ 99.5%											
Odor	Organoleptic (nasal/smell)	None											
Fill report:	<div style="margin-bottom: 10px;"><div>Was product loaded as indicated on this CoA? <input type="checkbox"/> Yes <input type="checkbox"/> No</div><div>Was correct fill procedure followed? <input type="checkbox"/> Yes <input type="checkbox"/> No</div></div> <div style="display: flex; justify-content: space-between;"><div>Fill responsible (name): _____</div><div>Signature: _____ Date: _____</div></div>												
<p><i>Form must be completed when LOX tanker truck is filled. A copy of the form shall be handed over to the facility where LOX is being offloaded, the above to be filled in.</i></p>													
<div>Drop location 1: _____ Time: _____ Address 1: _____ Address 2: _____</div>	<div>Drop location 2: _____ Time: _____ Address 1: _____ Address 2: _____</div>												



ANNEX C: RESOURCES

The following are established resources relating to medical oxygen systems and the management thereof. Each has been provided with a hyperlink and a brief description of its utility in the context of striving toward quality assurance along the medical oxygen supply chain.

Resource and hyperlink	Description
EIGA's DOC 152/18 - Comparison of European, US & Japanese pharmacopoeia monographs for medical gases	To provide a cross reference between the three sets of published monographs to enable a comparison of the requirements for each method.
EIGA's Fire hazards of oxygen and oxygen-enriched atmospheres	<i>"Essential information necessary and the relevant protective measures that should be taken to prevent fire hazards resulting from handling oxygen. An appendix provides a summary of the information in the publication that can be reproduced as a pamphlet to be handed to those involved in daily operations involving oxygen or be used as a supplement to safety presentations..."</i>
EU' GMP for Manufacture of Medicinal Gases	<i>"Gases which fulfil the definition of medicinal product of Directive 2001/83/EC or Directive 2001/82/EC (hereinafter, medicinal gases) are subject to the requirements laid down in these Directives, including the requirements on manufacturing. In this regard, this Annex deals with the manufacture of active substance gases and with the manufacture of medicinal gases."</i>
FHI360 Epic oxygen assessment tools	<i>"This collection of tools is a resource to support meaningful assessments and better target effective interventions for those who are building the oxygen ecosystem. A key element of this work is partnership across sectors and groups to optimize opportunities for collaboration, and a recognition that oxygen by itself does not save lives, without knowledge and additional capacity. The tools collected here can be used individually for specific areas or together, as the first section focuses on liquid oxygen at the national level, then an assessment at the hospital level and, finally, the primary care level. By improving the understanding of the gaps and resources related to medical oxygen supply and effective delivery, the goal is for more patients to receive the treatment they need."</i>
ISO 7396-1: Medical gas pipeline systems – Part 1: Pipeline systems for compressed medical gases and vacuum	*Fee* <i>"This part of ISO 7396 specifies requirements for pipeline systems for gases for medicinal use, medical device gases, gases for driving surgical tools and vacuum. It is intended for use by those persons involved in the design, construction, inspection and operation of health care facilities treating human beings. Those persons involved in the design, manufacture and testing of equipment intended to be connected to these pipeline systems should also be aware of the contents of this part of ISO 7396."</i> <i>This part of ISO 7396 seeks to ensure that medical gas pipelines contain only the specific gas (or vacuum) intended to be supplied. For this reason, gas-specific components are used for terminal units and for other connectors which are intended to be used by the operator. In addition, each system is tested and certified to contain only the specific gas (or vacuum).</i>
NFPA 99: Health Care Facilities Code	*Fee* for downloadable/print version (Free online-only version if registered). <i>"The scope of this document is broad. Where medical oxygen is concerned, this code outlines minimum criteria for levels of health care services or systems based on risk to the patients, staff, or visitors in health care facilities for gas and vacuum systems. It covers performance, maintenance, installation, and testing of medical gas systems, portable compressed gas systems, and ancillary gas equipment in health care facilities."</i>



Resource and hyperlink	Description
Open Critical Care The hub for critical care education tools	<p><i>“OpenCriticalCare.org (beta) was launched in August 2020 as a repository for reliable, open-access critical care learning tools with relevance to resource-variable settings. In response to COVID-19, we have built an open-access Resource Library of critical care educational resources for medical educators and learners as well as a COVID19 Guidelines Dashboard, and the Oxygen Calculator. Our resource library includes curated and original content that can be used for training at various levels and multiple healthcare cadres, and are suited for independent learning and as well as integration into institutional training programs and curricula. ...In 2023, OCC has begun to transition from urgent content creation and dissemination for COVID19 and is now focusing on the creation of novel tools and content to advance education with an emphasis on learners and educators in resource-variable and resource-denied settings.</i></p>
PATH Oxygen delivery toolkit Oxygen generation and storage Oxygen business models	<p>The oxygen delivery toolkit <i>“provides materials to help decision-makers, implementers, and advocates plan, manage, and communicate the value of scaling up oxygen delivery systems and access to oxygen and pulse oximetry.”</i></p> <p>The oxygen business models brief <i>“introduces the oxygen ecosystem that business models operate within and then outlines four types of business models: bulk supply agreements, cash-and-carry filling stations, direct equipment purchases, and equipment leasing.”</i></p> <p>The Oxygen Generation and Storage brief <i>“is intended to be a concise primer for decision-makers who govern, lead, support, or manage health systems and their associated facilities. Providing an overview of the key elements that define each technology—as well as key considerations related to COVID-19—it can establish a starting point for understanding the solutions available to meet a health system’s need for medical oxygen and its delivery. It should serve alongside a broader suite of planning and analytical requirements necessary for the implementation of medical oxygen solutions.”</i></p>
PIC/S Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme “Aide-Memoire” Inspection of Medicinal Gases	<p>Purpose: <i>“This Aide-Memoire was prepared to enable the effective planning and conducting of GMP inspections of manufacturing of medicinal gases, in particular from the point of view of optimal use of limited inspection time and from the point of view of optimal evaluation of GMP compliance.</i></p> <p>Scope: <i>“This document describes three different types of manufacturing of medicinal gases: air separation units, filling stations and manufacturing of medicinal gases in hospitals which should be covered during inspections and which should be evaluated from the point of view of GMP compliance. This document focuses on the special needs for inspecting the manufacturing of medicinal gases.</i></p>
UK National Health System—Department of Health’s Health Technical Memoranda (HTM) catalogue: <ul style="list-style-type: none"> Medical Gases HTM 02-01: Medical gas pipeline systems Part A: Design, installation, validation, and verification Medical Gases HTM 02-01: Medical gas pipeline systems Part B: Operational management 	<p><i>“This guidance applies to all medical gas pipeline systems installed in health care premises. It is aimed at health care estates services to help them ensure medical gas pipeline systems are managed effectively. The guidance contains:</i></p> <ul style="list-style-type: none"> <i>guidance on the design, installation, validation and verification</i> <i>management of medical gas pipeline systems</i> <i>guidance on dental compressed air and vacuum systems</i>
UN’s Recommendations on the Transport of Dangerous Goods – Model Regulations 21st revised ed.	<p><i>“These Recommendations have been developed by the United Nations Economic and Social Council’s Committee of Experts on the Transport of Dangerous Goods in the light of technical progress, the advent of new substances and materials, the exigencies of modern transport systems and, above all, the requirement to ensure the safety of people, property and the environment. They are addressed to governments and international organizations concerned with the regulation of the transport of dangerous goods. They do not apply to the bulk transport of dangerous goods in sea-going or inland navigation bulk carriers or tank-vessels, which is subject to special international or national regulations.</i></p>



Resource and hyperlink	Description
UNICEF Oxygen System Planning Tool	<p>“The Oxygen System Planning Tool (OSPT) ... can be used to support high-level health care budgeting and planning needs related to oxygen, including health and procurement specialists and oxygen technology stakeholders.</p> <p>The tool uses health facility-level input data and customizable country input parameters to calculate oxygen needs. With the relevant data from users, the Oxygen System Planning Tool recommends an oxygen source to meet those needs ... can help users develop multiple scenarios of oxygen infrastructure to compare CAPEX/OPEX cost, demand, resource re-allocation, and other key outcomes</p>
US FDA’s Current Good Manufacturing Practice for Medical Gases - Draft Guidance for Industry	<p>“This guidance is intended to assist manufacturers of medical gases in complying with applicable current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211). Medical gases are generally regulated as finished pharmaceuticals and are subject to CGMP requirements regardless of the processing stage. Compliance with applicable CGMP requirements helps to ensure the safety, identity, strength, quality, and purity of medical gases. Medical gases that are not manufactured, processed, packed, or held according to applicable CGMP requirements can cause serious injury or death.</p>
WHO initiatives’ “Access to Oxygen Initiative” webpage	<p>WHO’s centralized repository of oxygen-related resources and references, both internal and external.</p> <p>“Medical oxygen is a life-saving medicine that is used to treat many conditions throughout the care continuum. Despite the clinical importance of medical oxygen and inclusion on the WHO Essential Medicines List, it remains a hard to access resource in health care settings.</p> <p>The COVID-19 pandemic highlighted inequities in availability and access to this life-saving medicine and the inherent challenges in the process of generation, distribution, and delivery of oxygen to patients.</p> <p>The WHO Access to Oxygen Initiative provides technical and operational support to Member States. This includes identifying and implementing holistic solutions to enable a resilient oxygen ecosystem.</p>
WHO Posters: <ul style="list-style-type: none"> ▪ Medical Oxygen Fire Risk – Mitigation Measures ▪ Oxygen Cylinder Safety ▪ Medical Gas Piping System Safety 	<p>“This poster is intended for health workers and other personnel on the safety and mitigation measures that need to be adhered to when dealing with medical oxygen. Medical oxygen, either in liquid or gas form, is an oxidizing agent that can result in a fire or explosion if not handled properly.</p>
WHO-UNICEF Technical specifications and guidance for oxygen therapy devices	<p>“In order to meet the growing demand from countries to increase the availability of good quality, affordable, safe and appropriate oxygen therapy systems, the purpose of this interagency publication is to provide harmonized product specifications for a wide range of oxygen products, and to provide guidance on the selection, procurement, use and maintenance of these products.</p>
WHO’s Decontamination and reprocessing of medical devices for health care facilities	<p>“Following recent threats caused by widespread epidemics and increasing awareness about the spread of antimicrobial resistance, several countries are paying more attention and investing resources to strengthening IPC infrastructures and improving practices. In this context, this manual is a very important instrument to provide guidance to health managers and health workers on required infrastructures and standard procedures for effective sterilization, and decontamination reprocessing of medical devices. This edition of the manual represents a thorough revision and update of the Sterilization Manual for Health Centers issued by the Pan American Health Organization in 2009 and it is the result of a close collaboration between the IPC Global Unit at the Headquarters of the World Health Organization, the Pan American Health Organization, and a group on international experts.</p>
WHO’s GMP for medicinal gases	<p>“Arising from an increased demand for medicinal gases, in particular the use of oxygen in the treatment of patients with coronavirus disease 2019 (COVID-19), the World Health Organization (WHO) Health Products Policy and Standards Department (formerly Essential Medicines and Health Products) and other departments involved in the supply of oxygen and the inspection of production sites of medicinal gases raised the urgency for the preparation of the WHO good manufacturing practices for medicinal gases guidance text.</p>
WHO’s Guidance for post-market surveillance and market surveillance of medical devices, including in-vitro diagnostics	<p>“... This document pertains to the objectives and processes for post-market surveillance for medical devices conducted by manufacturers with the assistance of their economic operators, as well as market surveillance conducted by regulators, and the role of other stakeholders in these processes. It describes the measures taken to ensure the ongoing compliance of medical devices with the requirements for safety, quality, and performance after they are placed on the market.</p>



Resource and hyperlink	Description
WHO's Medical equipment maintenance program overview	<i>"A maintenance strategy includes procedures for inspection, as well as preventive and corrective maintenance. Performance inspections ensure that equipment is operating correctly, safety inspections ensure the equipment is safe for both patients and operators, and preventive maintenance (PM) aims to extend the life of the equipment and reduce failure rates.</i>
WHO's Oxygen Sources & distribution for Covid-19 treatment centers	<i>"This interim guidance on oxygen sources and distribution strategies for COVID-19 treatment has been adapted from WHO and UNICEF's technical specifications and guidance for oxygen therapy devices, which is part of the WHO medical device technical series. This guidance is intended for health facility administrators, clinical decision-makers, procurement officers, planning officers, biomedical engineers, infrastructure engineers and policy-makers. It describes how to quantify oxygen demand, identify oxygen sources that are available, and select appropriate surge sources to best respond to COVID-19 patients' needs, especially in low-and-middle income countries.</i>
WHO's Technical specifications for Pressure Swing Adsorption (PSA) Oxygen Plants	<i>"Oxygen is an essential medicine required at all levels of the health care system; only high quality, medical-grade oxygen should be given to patients. Pressure swing adsorption (PSA) oxygen generating plants are a source of medical-grade oxygen. This document provides technical specifications as the minimum requirements that a PSA Oxygen Plant must meet for use for the administration of medical-grade oxygen.</i>



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