



Zambia Medicines Regulatory Authority

Guidelines For Manufacturing and Distribution of Medical Gases

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1. FOREWORD

The Zambia Medicines Regulatory Authority (ZAMRA) regulates medicines for human and animal use in accordance with the provisions of the Medicines and Allied Substances Act No. 3 of 2013 of the laws of Zambia and the relevant Regulations made thereunder.

These guidelines are issued by the Zambia Medicines Regulatory Authority pursuant to section 68 of the Medicines and Allied Substances Act No. 3 of 2013 of the Laws of Zambia for regulation of manufacturing and distribution of medical gases. The Authority reserves the right to request any additional information to establish the safety, quality and efficacy of a medical gas. ZAMRA may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of premises used for the purpose of manufacture, distribution or storage of medical gases.

Dealers of medical gases are encouraged to familiarize themselves with these guidelines and follow up on all aspects of the manufacture, distribution and post marketing surveillance of their products. Adherence to these guidelines will facilitate efficient and effective regulation by ZAMRA and effective compliance by dealers.

2. PURPOSE AND SCOPE OF GUIDELINES

The purpose of these guidelines is to regulate the manufacturing, distribution, control, importation, exportation and storage of medical gases in order to ensure their quality, safety and efficacy. Medical gases include oxygen, carbon dioxide, nitrous oxide and any other gas or mixture of gases intended for medical use. The guidelines should be read together with other relevant documents such as those on Good Distribution Practices (GDP) as applicable.

The guidelines are intended to be applicable to all dealers (persons and entities) involved in any aspect of the manufacture, importation, exportation, storage and distribution of medical gases. This includes commercial manufacturers, health facilities, wholesalers, distributors, suppliers, government and non-governmental institutions or departments. The document does not cover the production of medical gases using medical devices such as oxygen concentrators in health facilities or at home for personal use. However, the principles contained herein may be applied in those instances to ensure that medical gases generated in such settings are suitable for their intended use.



3. GLOSSARY

The definitions provided below apply to the terms and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents.

Act	means the Medicines and Allied Substances Act No. 3 of 2013 (MASA)
Authority	means the Zambia Medicines Regulatory Authority provided for under section three (3) of the Act
Air Separation	means the separation of atmospheric air into its constituent gases using fractional distillation at cryogenic temperatures.
Batch (or lot)	means a specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.
Bulk Gas	means any gas intended for medical use, which has completed all processing up to but not including final packaging.
Built-In Pressure Regulator	means safety system constituted of pressure regulators integrated with cylinder valves, mainly useful with gases because it avoids the risk of adiabatic compression.
Chemical synthesizers	means synthesizers or processors producing medical gas by chemical reaction (e.g., nitrous oxide by thermal degradation of ammonium nitrate) or by reprocessing feeder gas. Feeder gas is often the waste stream of other industrial manufacturing operations, which is then purified and treated to manufacture a medical gas.
Contract Acceptor	means the person or entity who is providing the medical gas or starting material covered by the contract.
Contract giver	means the person or entity who is receiving the medical gas or starting material covered by the contract.
Cylinder	means a container, usually cylindrical suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature or a transportable, pressure container with a water capacity not exceeding 150 litres. In this document when using the word cylinder, it includes cylinder bundles (or cylinder pack) when appropriate.
Compressed Gas	means a gas which when packaged under pressure is entirely gaseous at -50°C or higher
Container	means a cryogenic vessel, a tank, a tanker, a cylinder, a cylinder bundle or any other package that is in direct contact with the medical gas.
Cryogenic Gas	means gas, which liquefies at 1.103 bar at a temperature below -150°C
Cryogenic Vessel	means a static or mobile thermally insulated container designed to contain liquefied or cryogenic gas. The gas is removed in gaseous or liquid form.



Cylinder Bundle	means an assembly of cylinders which are fastened together in a frame and interconnected by a manifold, transported and used as a unit.
Dedicated	means specific for a gas for medical use
Deal	means to sell or offer for sale or trade by wholesale
Dealer	means a person or entity who sells medical gas(es) or offers to sale or trade by wholesale
Fixed Cryogenic Vessel	means a static thermally insulated container designed to contain liquefied or cryogenic gases. The gas is removed in liquid form.
Fixed Evaporator	means a static thermally insulated container designed to contain liquefied or cryogenic gases.
Gas	means a substance or a mixture of substances that is completely gaseous at 1.013 bar (101.325 kPa) and +15°C or has a vapour pressure exceeding 3 Bar (300 kPa) at +50°C.
Good Distribution Practice (GDP)	means that part of quality assurance that ensures that the quality of medicines and allied substances is maintained by means of adequate control of the numerous activities which occur during the distribution process as well as providing a tool to secure the distribution system from counterfeits, unapproved, illegally imported, stolen, substandard and falsified medicines and allied substances.
Good Manufacturing Practice (GMP)	means that part of quality assurance which ensures that medical gases are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specifications where applicable.
GxP	means good practice guidelines
Hydrostatic pressure test	means a test performed, as required by national or international regulations, in order to ensure that pressure containers are able to withstand pressures up to the container's design pressure.
High Pressure Liquefied Gas	means a gas with a critical temperature between -50 °C and +65 °C.
Liquefied Gas	means a gas which when packaged under pressure is partially liquid (gas over a liquid) at -50°C.
Loop	means spiral metal tube connecting several cylinders.
Low Pressure Liquefied Gas	means a gas with a critical temperature above +65 °C.
Manifold	means equipment or an apparatus designed to enable one or more gas containers to be emptied and filled at the same time.
Manufacture	means any process carried out in the course of making a medical gas, but does not include the process of dissolving or dispensing a medical gas in, or diluting or mixing it with, some other substance for purposes of administering it.

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Manufacturer	means any person or firm that manufactures medical gases, which includes producing, distributing, filling, labelling, mixing, purifying, separating, and transferring.
Medical Gas	means a gas or mixture of gases for human or veterinary use intended to be used or manufactured for use for its therapeutic efficacy or for its pharmacological purpose in the diagnosis, treatment, alleviation, modification or prevention of disease or abnormal physical or mental state or the symptoms of disease in a person or animal
Minimum Pressure Retention Valve	means a valve equipped with a non-return system, which maintains a definite pressure (about 3 to 5 bars over atmospheric pressure) in order to prevent contamination during use.
Mobile Cryogenic Vessel	means a mobile thermally insulated container designed to maintain the contents in a liquid state
Non-Return Valve	means a valve, which permits flow in one direction only.
Packaging	means all the operations, including filling and labelling, that must be undergone by a bulk gas to become a finished product. This includes the repackaging and relabelling of previously packaged and labelled medical gases.
Pharmacopoeia monograph	means the specification and test methods for specific medicinal gases prepared and issued by the European Pharmacopoeia.
Potable Water	water of drinking quality as defined by national and international standards for drinking water.
Pressure Regulator	means a device for pressure reduction
Quality Management System	an appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality
Quarantine	means the status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.
Reference Material	material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process
Refrigerated Liquefied Gas	means gas, which when packaged for storage or transport, is made partially liquid because of a refrigeration system.
Specifications	means a list of detailed requirements (acceptance criteria for the prescribed test procedures) with which the substance or medical gas has to conform to ensure suitable quality
Standard Operating Procedure (SOP)	means an authorised written procedure giving instructions for performing operations both general and specific.



Tank	means a static thermally insulated container designed for the storage of liquefied or cryogenic gas. They are also called "fixed cryogenic vessels"
Tanker	means container fixed on a vehicle for the transport of liquefied or cryogenic gas.
Valve	means a device or object for opening and closing containers or pipes
Valve Outlet Connection	means a screw connector which makes it possible to connect the rubber gas pipe or pressure regulator to the cylinder. It is standardised and ensures fool proofing
Valve Guard	means a device used to protect cylinder valves
Responsible Person	means a pharmacist, veterinary surgeon, veterinary para professional or pharmacy technologist with primary responsibility for ensuring compliance with good practice.
Qualified Person	means a person named within company documentation responsible for release of medical gases prior to supply to patients and performing any duties as may be assigned by the Responsible Person.



4. GENERAL REQUIREMENTS

5.1 DEALERS OF MEDICAL GASES

6.1.1 The following shall fall under the category of medical gas dealers:

- i. Manufacturers including hospitals producing in situ
- ii. Importers/Exporters
- iii. Distributors
- iv. Storage Facilities

6.1.2 All dealers of medical gases shall be required to be registered by the Authority.

6.1.3 Companies who store and distribute medical gas products need to hold a Pharmaceutical Licence issued by the Authority and shall comply with the current Good Distribution Practice guidelines.

6.1.4 GDP requires that medicines are obtained from the licensed supply chain and are consistently stored, transported and handled under suitable conditions, as required by the Marketing Authorisation or product specification where required.

6.1.5 All manufacturers of medical gases shall institute and implement a quality management system which includes:

- i. Appropriate infrastructure or “quality system” encompassing the organizational structure, procedures, processes and the resources; and
- ii. Systematic actions necessary to ensure adequate confidence that a product and documentation will satisfy given requirements for quality.
- iii. A designated person shall be appointed by the manufacturer who shall have defined authority and responsibility for ensuring that a quality management system is implemented and maintained.
- iv. There shall be written procedures and records to ensure traceability of the products produced, imported and distributed.
- v. Where certain duties are delegated or contracted out, the activities shall be documented in contracts and shall be periodically audited and records maintained.
- vi. Dealers of medical gases shall establish safety mechanisms to avoid injuries and deaths.
- vii. Manufacture of the finished product should be done according to good manufacturing practices (GMP) as per requirements provided in section two of these guidelines.



- viii. Importers, exporters, storage facilities and distributors of medical gases should also consult the current guidelines on Good Distribution Practices (GDP) prescribed by the Authority.

5. MANUFACTURE OF MEDICAL GASES

6.1 PRINCIPLE

Manufacture of medical gases is normally carried out in closed equipment, and thus, environmental contamination of the product is considered minimal. However, risks of contamination or cross-contamination with other gases may arise, in particular because of the reuse of containers.

6.2 ORGANISATION AND MANAGEMENT

- 6.2.1 There shall be an adequate organisational structure defined with the aid of an organisational chart. The responsibilities, authority and interrelationships of all personnel should be clearly indicated.
- 6.2.2 Duties and responsibilities shall be clearly defined and understood by the individuals concerned and recorded as written job descriptions.
- 6.2.3 Employees should be fully informed and trained in their duties and responsibilities.
- 6.2.4 A designated Responsible Person shall be appointed within the organisation, who has defined authority and responsibility for ensuring that a quality system is implemented and maintained.
- 6.2.5 Managerial and technical personnel must have the authority and resources needed to carry out their duties and to set up and maintain a quality system, as well as to identify and correct deviations from the established quality system.
- 6.2.6 The responsibilities placed on any one individual should not be extensive as to present any risk to product quality.
- 6.2.7 Safety procedures relating to all relevant aspects including the safety of personnel and property, environmental protection and product integrity, should be in place.

6.3 TRAINING AND PERSONNEL

General

- 6.3.1 The correct manufacture of medical products relies upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.
- 6.3.2 Manufacturers of medical gases shall provide training for all the personnel whose duties take them into production areas or laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

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- 6.3.3 Besides the basic training on the theory and practice of GMP relevant to the manufacture of medical gases and company procedures, newly recruited personnel shall receive training appropriate to the duties assigned to them.
- 6.3.4 Continuing training shall also be given, and its practical effectiveness shall be periodically assessed.
- 6.3.5 Training programmes for all personnel and consultants including drivers of tankers and those tasked to transport cylinders, shall be available, approved by either the head of production or the head of quality control, as appropriate. Training records shall be retained.
- 6.3.6 All staff should have the necessary skills and knowledge to carry out their job effectively and safely and shall receive appropriate information, instruction and training, including induction and continuation / refresher training. Such training shall be both theoretical and practical. It is the duty of the employer to ensure their persons are adequately trained and to establish competency. It is recommended that a training programme is carried out under a formalised system where an acceptable level of competency has to be achieved. Records shall be kept of the information, instruction and training provided and of the competence level achieved. The programme shall make provision for periodic competence re-assessment where appropriate.
- 6.3.7 Training shall be based on written standard operating procedures (SOPs).
- 6.3.8 It is recommended that initial basic training for plant technicians and engineers be given at the time of plant installation and commissioning by the manufacturer's installation team. The manufacture should provide complete instruction regarding how to operate the plant, monitor, understand and record the proper performance parameters of the plant, instruction of simple and routine maintenance for the plant according to manufacturer's specification, basic trouble-shooting, and standard operating procedures for acquiring support for service and maintenance when needed.
- 6.3.9 A record of all training, which includes details of subjects covered and participants trained, shall be kept.
- 6.3.10 There shall be an adequate number of competent personnel involved in all aspects of the manufacture of medical gases in order to ensure that the quality of the product is maintained.
- 6.3.11 Visitors or untrained personnel should not be taken into the production and quality control areas. If this is unavoidable, they should be closely supervised and given the appropriate information in advance, particularly about personal hygiene and the prescribed protective clothing.
- 6.3.12 Personnel dealing with hazardous or products presenting special risks of abuse (such as controlled products), fire or explosion shall be given specific training.



- 6.3.13 Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, shall be established and observed. Such procedures shall cover health, hygiene and clothing of personnel.
- 6.3.14 Personnel should receive relevant training on hazards including those associated with pressure and the properties of the various gases used on site.
- 6.3.15 The concept of quality assurance and all the measures capable of improving its understanding and implementation shall be fully discussed as part of the overall training programme during training sessions.
- 6.3.16 For safety reasons every person entering the manufacturing areas shall wear protective garments appropriate to the operations to be carried out.
- 6.3.17 Key personnel involved in critical aspects such as production and quality operations should possess at minimum, a certificate or diploma in key fields such as Chemical Engineering, Process Engineering, Mechanical Engineering, Electrical and Electromechanical Engineering, Biomedical Engineering, Industrial Electronics, Laboratory Technology, Instrumentation and any other related scientific field and a minimum of two years' work experience in a similar setting of manufacturing medical gases.
- 6.3.18 Responsibilities of key personnel involved in production and quality operations should be clearly defined in written job descriptions. The responsibilities include;

Person Responsible for Production

The person responsible for production is generally responsible for:

- 6.3.19 Ensuring that the manufacture of medical gases and the filling of medical gas cylinders follows the authorised procedures detailed on the marketing authorisation, where required, in order to obtain the specified quality.
- 6.3.20 Checking that the maintenance of the equipment and premises under his control are carried out correctly.
- 6.3.21 Ensuring that the appropriate process validations are completed.
- 6.3.22 Ensuring that the required initial and continuing training of personnel under his department is carried out and adapted according to the identified need.
- 6.3.23 Ensuring that any agreed self-inspection programme is completed and that the appropriate actions are taken to correct any identified non-compliances

Person Responsible for Quality Control

The head of the quality control is generally responsible for:

- 6.3.24 Approving or rejecting test results, according to set requirements as specified in compendial or approved methods and the relevant marketing authorisation where applicable, starting materials, packaging materials, and intermediate bulk and finished product.



- 6.3.25 Evaluating batch records.
- 6.3.26 Ensuring that all necessary testing is carried out.
- 6.3.27 Approving specifications, sampling instructions, test methods and other qc procedures.
- 6.3.28 Approving and monitoring any subcontracted qc services.
- 6.3.29 Checking the maintenance of their department, premises and equipment.
- 6.3.30 Ensuring that the appropriate quality control validations are completed.
- 6.3.31 Ensuring that the required initial and continuing training of personnel under his department is carried out and adapted according to the identified need.

Joint Responsibilities

The persons responsible for production and quality control generally have some shared or jointly exercised responsibilities relating to the quality of the medical gases. These responsibilities can include:

- 6.3.32 Authorisation of written procedures and other documents, including amendments.
- 6.3.33 Training.
- 6.3.34 Designation and monitoring of storage and distribution conditions for materials and products.
- 6.3.35 Retention of records.
- 6.3.36 Monitoring of compliance with the requirements of GMP.
- 6.3.37 Control of any changes to procedures or equipment, including any relevant validations.
- 6.3.38 For relatively small facilities, it is generally acceptable for the production and quality control function to be performed by the same individual provided, they are competent to perform these functions and records are well maintained.

The Qualified Person

The qualified person's responsibilities shall include:

- 6.3.39 Ensuring that each batch of bulk medical gas or filled medical gas cylinders has been produced and tested /checked as per set requirements.
- 6.3.40 Release or rejecting each production batch.
- 6.3.41 Approving specifications, sampling instructions, test methods and any other quality control procedures



- 6.3.42 Verifying that the appropriate validations are completed.
- 6.3.43 Verifying that the required initial and continuing training of personnel under their department is carried out and adapted according to the identified needs.
- 6.3.44 Approving and monitoring of suppliers and materials.
- 6.3.45 Approving and monitoring of contract manufacturers and testing facilities.
- 6.3.46 Making the decision to recall potentially defective finished product and to assist, as necessary, in the investigation procedure and any follow-up actions when informed of any product non-conformance
- 6.3.47 The qualified person shall meet the shall possess at minimum, a certificate or diploma in a key field such as Chemical Engineering, Process Engineering, Mechanical Engineering, Electrical and Electromechanical Engineering, Biomedical Engineering, Industrial Electronics, Laboratory Technology, Instrumentation. electrical, mechanical, or biomedical technician or any other related scientific or technical field and have at least a minimum of two years' work experience in the field of manufacturing medical gases.
- 6.3.48 The qualified person shall be registered and certified by a local relevant body such as the Engineering Institution of Zambia, the Health Professions Council of Zambia or any other relevant body as appropriate
- 6.3.49 The qualified person's responsibilities may be delegated to another qualified person with the appropriate experience.
- 6.3.50 The qualified person shall have a thorough knowledge of the production and control of medical gases.
- 6.3.51 The qualified person can also be accepted to act as responsible person if they are eligible

The Responsible Person

The responsibilities of the responsible person shall include:

- 6.3.52 Ensuring that the quality of the product is maintained throughout the distribution process, therefore safeguarding product users against potential hazards arising from poor practices.
- 6.3.53 Be aware and Knowledgeable of the conditions of the license for the site(s) where they are named on the license as a Responsible Person.
- 6.3.54 Understanding the requirements for an effective pharmaceutical quality management system and how it can be implemented, developed and maintained, complete with the importance of effective record keeping.

6.4 PREMISES

General



- 6.4.1 The premises where medical gases are manufactured should be located, designed, constructed and maintained to suit the operations to be carried out.
- 6.4.2 The layout and design of the premises should aim to minimize the risk of errors, mix-ups, contamination and cross-contamination. In addition, it should allow for effective cleaning and maintenance without any adverse effect on the quality of the products.
- 6.4.3 Cylinders and other vessels used for medical gases should be checked, prepared, filled and stored in separate areas from non-medical gases, and there should be no interchanging of cylinders between these areas. However, it could be accepted to check, prepare, fill and store other (non-medical and different types of gases) in the same areas, provided that they comply with the specifications of medical gases and that the manufacturing operations are performed according to GMP standards.
- 6.4.4 Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal articles should not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.
- 6.4.5 Premises should provide sufficient space for manufacturing, testing and storage operations in order to prevent any risk of mix-up. Premises should be designed to provide:
- Separate marked areas for different gases;
 - Clear identification and segregation of cylinders at various stages of processing (e.g. "awaiting filling", "quarantine", "released", "rejected" "prepared deliveries").
- 6.4.6 The method used to achieve these various levels of segregation will depend on the nature, extent and complexity of the overall operation. Marked-out floor areas, partitions, barriers, signs, labels or other appropriate means could be used.
- 6.4.7 Empty cylinders after sorting or maintenance, and filled cylinders should be stored under cover, protected from adverse weather conditions. Filled cylinders should be stored in a manner that ensures that they will be delivered in a clean state, compatible with the environment in which they will be used.

Location

- 6.4.8 The premises shall be located away from sites or activities or any other place where safety, quality, efficacy and performance of the products can be compromised.
- 6.4.9 The premises shall be required to address among other issues, the fire prevention facilities.
- 6.4.10 Location and infrastructure requirements of the filling plant

The area where the filling operation is to take place shall:

- be an external area or inside a structure which has been assessed to assure there is a high ventilation rate. Filling shall not take place in an enclosed area.
- be constructed primarily of non-flammable materials;



- iii. be constructed using compatible materials, for example, when filling with oxygen avoid the use of oil, greases and bitumen products;
- iv. have fire-fighting equipment / facilities as required by the local competent authorities
- v. have adequate lighting;
- vi. have no other hazardous products stored within the filling area;
- vii. consider human factors in the design of the filling equipment and the operations around it;
- viii. be ergonomically designed and laid out, for example, to ensure visibility of pressure gauges and access to valves;
- ix. be subject to regular housekeeping, including the collection and removal of all combustible products, such as packaging, which are no longer required;
- x. have multiple independent escape routes available.

Building(s)

- 6.4.12 Buildings must be of permanent construction and address and should be located at a site approved by relevant local authorities such as the local council.
- 6.4.13 The finishing of walls, ceiling and floors shall be such that, they are easy to clean and non-combustible. Buildings shall be kept clean and maintained.
- 6.4.14 Sufficient lighting and ventilation shall be provided to enable all operations to be carried out.
- 6.4.15 Buildings should protect products from contamination and deterioration, including protection from excessive heat or undue exposure to direct sunlight.
- 6.4.16 Buildings should have sufficient security to prevent unauthorized access and misappropriation of the products.
- 6.4.17 Building should be constructed, serviced and maintained regularly to protect stored products, from all potentially harmful influences such as undue variations of temperature and humidity.
- 6.4.18 Receiving and dispatch bays shall protect products from the extreme climate conditions. They shall be designed and equipped to allow containers of incoming products to be cleaned.
- 6.4.19 Steps shall be taken to prevent the entry of unauthorised people to production, cylinder filling, storage and quality control areas, which shall not be used as a right of way by personnel who do not work in them.
- 6.4.20 The surrounding should be maintained so as to minimize dust, soil and other contamination to enter the building.
- 6.4.21 Residential houses shall not be used for manufacturer of medical gases.
- 6.4.22 Manufacturing premises shall also be required to comply with premises requirements as prescribed in these guidelines.



Layout

- 6.4.23 Premises used for the filling of medical gas cylinders should preferably be laid out in such a manner as to allow a flow through the area, with cylinder filling steps taking place in areas connected in a logical order corresponding to the sequence of the cylinder filling operations. Cylinder filling areas shall be of a sufficient size and have an orderly layout, providing separately marked areas for different gases and, where applicable, different cylinder sizes.

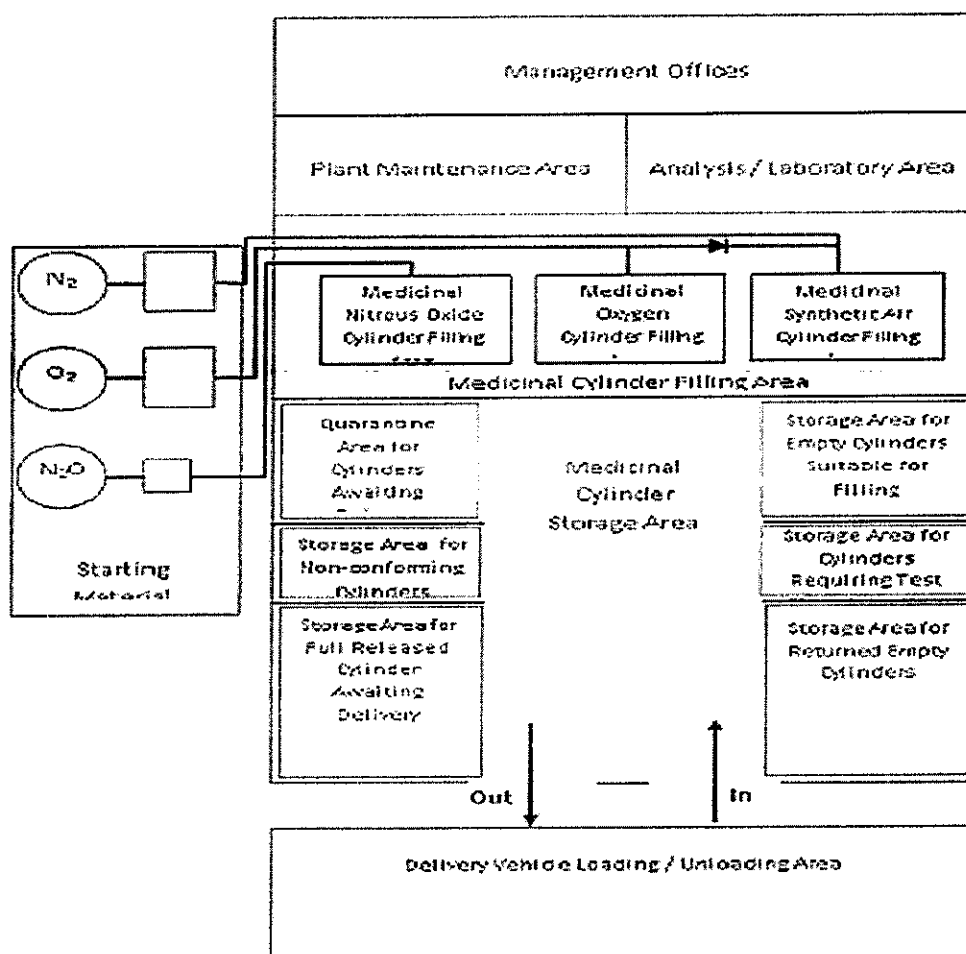


Fig 1 Layout of a Typical Medicinal Cylinder Filling Plant

An example of a typical cylinder filling plant layout. Source: EIGA

Sanitation

- 6.4.24 In order to maintain hygienic working conditions, premises shall have good supply of potable water, proper sink for hand washing and accessible toilets. Toilets should not communicate directly with production and filling areas.
- 6.4.25 Washing and toilet areas, as well as facilities for changing clothes shall be easily accessible and designed for the appropriate number of users. These toilet facilities



shall not have direct access with production, cylinder filling, quality control or storage areas.

6.5 EQUIPMENT

- 6.5.1 The manufacture of medical gases and the filling of medical gas cylinders is carried out in closed pipework, containers and tanks. Consequently, environmental contamination of the product is minimal, provided that the equipment is suitably commissioned and maintained in an operational condition. However, there could be a risk of cross-contamination with other gases if the pipework allows for interconnections between different gases without any suitable backflow protection and the appropriate, validated procedures are not followed correctly.
- 6.5.2 Equipment and utilities should be selected, located, constructed and maintained to suit the operations to be carried out.
- 6.5.3 Pressure gauges and weighing scales used for the filling of gas cylinders shall be properly maintained and regularly calibrated in-line with the quality management system. To reduce operator error, it is recommended that pressure gauges and weighing scales display the same units as those stamped on the cylinders being filled i.e. bar and kg.
- 6.5.4 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.
- 6.5.5 A list of equipment with their respective unique identification numbers should be maintained and each equipment should bear this identification.
- 6.5.6 The layout, design, installation and use of equipment and utilities should aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.
- 6.5.7 Equipment shall be cleaned and maintained regularly according to a documented preventative maintenance programme. The repair and maintenance operations shall ensure that they do not present any hazard to the quality of the medical gas, and be carried out according to detailed written procedures.
- 6.5.8 Repair and maintenance operations (including cleaning and purging) of equipment, should not adversely affect the quality of medical gases. In particular, procedures should describe the measures to be taken after repair and maintenance operations involving breaches of the system's integrity. Specifically, it should be demonstrated that the equipment is free from any contamination that may adversely affect the quality of the finished product before releasing it for use. Records should be maintained.
- 6.5.9 There should be a documented preventative maintenance programme to ensure regular and effective maintenance of equipment.



- 6.5.10 Equipment should be designed to ensure that the correct gas is filled into the correct cylinder or container.
- 6.5.11 There should normally be no cross connections between piping carrying different gases.
- 6.5.12 If cross connections are needed (e.g. filling equipment of mixtures), qualification should be performed to ensure that there is no risk of cross contamination between the different gases. In addition, the manifolds should be equipped with specific connections.
- 6.5.13 Tanks and tankers should be dedicated to a single and defined quality of gas. Where non-dedicated tanks and tankers are used, risks of contamination should be assessed and controlled. This may include applying the same good practices such as those on Good Manufacturing Practice in production and having the same quality specification for industrial and medical gas.
- 6.5.14 Tanks and tankers should be dedicated to a single and defined quality of gas. Where non-dedicated tanks and tankers are used, risks of contamination should be assessed and controlled by ensuring that all the quality of non-medical gases is at least equal to the quality of the medical gas and that GMP standards are maintained. In such cases, quality risk management should be applied and documented.
- 6.5.15 A common system supplying gas to medical and non-medical gas manifolds is only acceptable if there is a validated method to prevent backflow from the non- medical gas line to the medical gas line.
- 6.5.16 Attempts should be made to ensure that filling manifolds are dedicated to a single medical gas. In exceptional cases, filling gases used for other medical purposes on manifolds dedicated to a particular medical gas may be acceptable if justified and performed under control. In these cases, the quality of the non-medical gas should be at least equal to the required quality of the medical gas and GMP standards should be maintained. Filling should then be carried out by campaigns.
- 6.5.17 Critical instruments used for measuring, weighing, recording and controlling equipment shall have specific calibration periods using appropriate validated methods. All critical instruments shall be calibrated and checked at the prescribed intervals. Detailed records of all of the calibration tests, including the 'as found' and the 'post calibration' values shall be maintained.
- 6.5.18 Defective equipment shall be clearly labelled as defective and, if possible, be removed as soon as possible from the manufacturing, production or laboratory areas.
- 6.5.19 It is acceptable to manufacture non-medical gases and medical gases concurrently, such as in an air separation unit (ASU), provided that the quality of the non-medical gas is at least equal to the quality of the medical gas.
- 6.5.20 In an ASU, where atmospheric air is used as a raw material, it shall be filtered at the inlet point to restrict the intake of particulate matter into the plant.



6.5.21 Cylinders in medical gas service shall be dedicated to that service. The cylinders should have the appropriate technical characteristics, according to international or national regulations. Cylinders shall be labelled and painted correctly, according to the national standards and to comply with the relevant marketing authorisation, where applicable.

6.5.22 In exceptional circumstances, where it is impracticable to have a dedicated medical gas cylinder filling facility. The principle of campaign filling may be used to allow medical gas cylinders to be filled on non-dedicated cylinder filling equipment. In these circumstances, the area shall be dedicated to medical gas cylinder filling during the campaign and appropriate tests and procedures carried out to ensure that the product is not contaminated with non-medical gas and the cylinders filled comply with the relevant specifications. GMP standards shall be maintained during the campaign filling process.

6.6 TRANSFERS AND DELIVERIES OF GASES

6.6.1 Measures should be employed to prevent any cross-contamination resulting from backflows during transfers. This may be attained through use of non-return valves or other suitable alternatives.

6.6.2 Flexible connections, coupling hoses and connectors should be flushed with the relevant gas before use. The transfer hoses used to fill tanks and tankers should be equipped with product-specific connections.

6.6.3 The use of adaptors allowing the connection of tanks and tankers not dedicated to the same gases should be adequately controlled and the method of control should be documented and validated.

6.6.4 Deliveries of gases may be added to tanks containing the same defined quality of gas provided that a sample is tested to ensure that the quality of the delivered gas is acceptable. This sample may be taken from the gas to be delivered or from the receiving tank after delivery.

6.6.5 Cryogenic liquefied medical gases may be transported in the same tankers as non-medical gases. This may only be permitted provided that the quality of the non-medical gas is at least equal to the quality of the medical gas. There shall also be a validated backflow protection device fitted to prevent back feeding of non-medical product from the customer's storage tank into the tanker when product is being transferred.

6.6.6 Where tankers are used for delivering medical liquefiable gases also to non-medical customers, where a two-hose filling system is used to balance the pressure between the tanker and the storage tank, then either:

- i. The deliveries of medical gases shall be made before any non-medical deliveries are made, to ensure that there is no cross contamination between medical and non-medical customer storage tanks.



- ii. The assay of the gas being delivered to a medical customer is monitored prior to the tanker offloading any product. The testing procedure needs to consider the likely contaminants that could be present to confirm that there has been no degradation of the product.

6.7 CYLINDER FILLING AND LABELLING

General

- 6.7.1 Before filling cylinders, a batch of gas or batch es of gases should be determined, controlled according to defined specifications and approved for filling.
- 6.7.2 In the case of continuous processes, there should be adequate in-process controls to ensure that the gas complies with set specifications.
- 6.7.3 Cylinders, vessels (tanks, tankers) and valves should conform to the appropriate technical specifications and any relevant requirements.
- 6.7.4 Cylinders, vessels and valves should be dedicated to a single medical gas or to a given mixture of medical gases.
- 6.7.5 Cylinders should preferably be fitted with minimum pressure retention valves with a non-return mechanism in order to provide adequate protection against contamination.
- 6.7.6 Cylinders, vessels and valves should be checked before first use in production, and should be properly maintained according to defined written procedures. Where accessories are used, the maintenance should address the manufacturer's instructions
- 6.7.7 Checks and maintenance operations should not affect the quality and the safety of the medical gas product.
- 6.7.8 The water used for hydrostatic pressure testing carried out on cylinders should be at least of drinking quality (potable).
- 6.7.9 As part of the checks and maintenance operations, cylinders should be subjected to an internal visual inspection before valve fitting, to make sure they are not contaminated with water or other contaminants. The checks should be done in the following instances:
 - i. when they are new and initially put into medical gas service;
 - ii. following any hydrostatic pressure test or equivalent test
 - iii. where the valve is removed;
 - iv. whenever the valve is replaced.
- 6.7.10 Maintenance, including preventive maintenance and repair operations of cylinders, vessels and valves are the responsibility of the manufacturer of the medical gas. If subcontracted, they should only be carried out by approved subcontractors, and contracts including technical agreements should be established. Subcontractors should be audited to ensure that appropriate standards are maintained.



- 6.7.11 There should be a system to ensure the traceability of cylinders and valves.
- 6.7.12 There should be a defined system of performing cylinder checks before filling operations. These include:
- i. positive residual pressure check in each cylinder;
 - ii. that all previous batch labels have been removed;
 - iii. that any damaged product labels have been removed and replaced;
 - iv. visual external inspection of each cylinder and valve for dents, arc burns, debris, other damage and contamination with oil or grease; cleaning should be done if necessary;
 - v. check of each cylinder outlet connection to determine that it is the proper type for the particular gas involved;
 - vi. A check of the date of the next test to be performed on the valve (in the case of valves that need to be periodically tested);
 - vii. A check of the cylinders to ensure that any tests required by national or international regulations (e.g. hydrostatic pressure test or equivalent for cylinders) have been conducted and are still valid; and
 - viii. A check to determine that each cylinder is color-coded.
- 6.7.13 Cylinders that have been returned for refilling should be prepared with care in order to minimize the risks of contamination, in line with the pre-defined procedures. Procedures, which should include evacuation and/or purging operations, should be validated. There should be appropriate checks to ensure that each cylinder has been properly filled.
- 6.7.14 Each filled cylinder should be tested for leaks using an appropriate validated method, prior to fitting the tamper evident seal. The test method should not introduce any contaminant into the valve outlet and, if applicable, should be performed after any quality sample is taken. Each cylinder should be properly labelled.

Cylinder Selection

- 6.7.15 A suitable cylinder shall be selected for the intended product. Such selection will be made on criteria including size, material of construction, test period, valve type, and previous service history.
- 6.7.16 The cylinder and its accessories shall conform with the requirements shall be in conformance to the current ZABS standards for medical gas cylinders.
- 6.7.17 The pressure rating of the cylinder shall be matched to the filling parameters.
- 6.7.18 The material and type of cylinder shall be compatible with the gas(es) being filled.
- 6.7.19 The material and type of valve, including the valve outlet connection, shall be compatible and appropriate for the gas(es) being filled.
- 6.7.20 The cylinder shall be in-date for its periodic inspection and test.



- 6.7.21 Filling sites are often presented with cylinders for filling that are owned by customers or other third-party organisations. In such cases the filling site shall follow a sequence of checks before filling the cylinder(s) to ensure product quality and safety of the filling personnel and that the cylinder is safe for eventual use by the end user.
- 6.7.22 The customers or other third-party organisations have a duty of care to inform the fillers of the nature and the mechanical integrity of the cylinders presented for filling.
- 6.7.23 Where a cylinder does not meet the acceptance criteria then it shall not be filled. These cylinders shall either be disposed, or sent for further inspection and tests.

Cylinder Pre-fill Inspection

- 6.7.24 There shall be written procedure for carrying out pre-fill inspection of cylinders. The pre-fill inspection shall ensure the absence of any damage that might affect safety and that the gas cylinder is in a safe condition to fill.
- 6.7.25 Information permanently stamped onto the shoulder of each gas cylinder, for example, the date of periodic test, the fill pressure or the serial number, should be clearly visible
- 6.7.26 The cylinder shall be internally free of any residual or contaminant gas that would affect the filling operation or the product quality. Any gas removed from the cylinder shall be disposed of safely.

Filling process

- 6.7.27 There shall be a written procedure for carrying out filling operations considering the filling parameters, each piece of equipment and the filling methods being used. This shall be based on the manufacturers' instructions and on a risk assessment. The standard operating procedure shall be approved by appropriate competent persons and be periodically reviewed.
- 6.7.28 Filling shall normally be carried out either by pressure or by weight. Pressure filling involves high pressure process equipment, and has the advantage that different sizes of cylinder can be filled at the same time. Liquefied gases are usually filled individually by weight, always establish the tare weight before commencing filling.
- 6.7.29 At any time, at any filling manifold, only one product should be in the process of being filled.
- 6.7.30 Some gases and gas mixtures require very detailed procedures that shall be tailor-made for the product being filled. Such procedures may need to address issues such as material compatibility, cylinder preparation, corrosion, interaction between substances, safe concentration limits, product disposal, product handling and personnel exposure.
- 6.7.31 Cylinders shall not be filled with a substance different from that which they have previously contained unless the specific operations necessary for a change of gas



service have been carried out. A change of gas service shall be carried out under the control of the QMS.

Post-fill inspection and settling

- 6.7.32 A check shall be carried out to ensure that the filling was completed as intended. This shall involve:
- a check in accordance with your QMS of the finished product to ensure compliance with the desired specification;
 - ensure that sufficient settling time is allowed in accordance with your QMS.
 - providing the correct identification of the product, e.g. marking and labelling;
 - a check of the pressure / weight. The cylinder shall be within its safe operating limits. It shall not be overfilled or over pressurised. Any excess gas shall be removed in a safe manner and the cylinder checked for continued fitness for service.
- 6.7.33 For liquefied gases the weight of the cylinder shall not exceed the total weight allowed for the cylinder and contents combination;
- a check that the outlet valve is closed;
 - a leak check;
 - a visual inspection of the gas cylinder for any obvious problems, including security of attachments.
- 6.7.34 Procedures should exist for dealing with cylinders that have been filled incorrectly or are not fit for continued use.
- 6.7.35 Once a filled cylinder has been assessed as serviceable then appropriate protective covers and / or valve caps should be fitted around the valve. These can help to prevent
- 6.7.36 damage to the valve and to minimise contamination of the valve outlet.
- 6.7.37 Filling records shall be maintained in accordance with your QMS. These are to identify:
- when a cylinder was filled;
 - the product with which it was filled;
 - batch / lot identification;
 - quality control checks and results

6.8 QUALITY CONTROL

- 6.8.1 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.
- 6.8.2 The quality controller, or his nominated deputy, shall be responsible for ensuring that the manufacturing and release procedures have been carried out correctly and any specified tests have been completed, having satisfactory results. All starting materials

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and pre-mixes shall not be released for use, and no finished products released for sale or supply, until their quality has been judged satisfactory.

- 6.8.3 Each batch of medical gas shall be tested and released according to its specifications. In addition, it shall also be tested according to relevant pharmacopoeia requirements at sufficient frequency to assure ongoing compliance.
- 6.8.4 Reference gases for calibration purposes and indicator tubes for testing should be marked with an expiry date and not used after the stated time.
- 6.8.5 Each batch of medical gas or mixture of gases (cylinders, mobile cryogenic vessels, hospital tanks) should be tested in accordance with the requirements (using applicable recognised compendial methods and standards) and certified. The sampling plan and the analysis to be performed should comply, in the case of cylinders, with the following requirements.
- 6.8.6 In the case of a single medical gas filled into cylinders via a multi-cylinder manifold, the gas from at least one cylinder from each manifold filling cycle should be tested for identity and assay each time the cylinders are changed on the manifold.
- 6.8.7 In the case of a single medical gas filled into cylinders one at a time, the gas from at least one cylinder of each uninterrupted filling cycle should be tested for identity and assay. An example of an uninterrupted filling cycle is one shift's production using the same personnel, equipment, and batch of gas to be filled.
- 6.8.8 Testing for moisture content should be performed unless otherwise justified. Other sampling and testing procedures that provide at least equivalent level of quality assurance may be justified.

6.9 HANDLING AND TRANSPORTATION OF PACKAGED GASES

Safety When Moving and Handling Gas Cylinder

- 6.9.1 Gases supplied in cylinders can be in compressed, liquefied or dissolved form. The cylinders vary in weight, size and shape. These physical characteristics present potential manual handling hazards.
- 6.9.2 Appropriate risk assessment, competence and handling aids are required. The minimum requirements for the movement and handling of gas cylinders are:
- all personnel shall wear appropriate personal protective equipment
 - mechanical handling equipment, such as serviceable purpose-designed trolleys, should be used for moving cylinders, wherever practicable;
 - subject to risk assessment, for moving over even, level floors and only for short distances, by competent operators, the 'churning' method may be considered;
 - cylinders shall not be rolled horizontally along the ground; this may damage or even open the valve and will also damage identifying labels, marks and symbols;
 - a cylinder shall not be moved with the valve open. A valve should be opened only at the location and time that the cylinder is being emptied or filled;



where provided, valve protection caps should be fitted before moving a cylinder.

- 6.9.3 Cylinders shall not be lifted by using the valve protection device unless they have been designed for that purpose.

Security

- 6.9.4 Gas cylinders and the gases they contain are hazardous. Whilst in storage (before and after the filling process) they should be located in a secure area.
- 6.9.5 During the filling process gas cylinders should be traceable and be subject to routine management checks.

6.10 DOCUMENTATION

General

- 6.10.1 Good documentation is an essential part of any system used for the manufacturing of medical gases and the filling of medical gas cylinders. Clearly written documentation prevents errors and permits the tracing of batch history. Specifications, standard operating procedures and related documents, work instructions and records for the manufacture, control, storage, and distribution of medical gases, shall be available to all of the relevant personnel either in written or electronic format. The documentation should be established and implemented.
- 6.10.2 Principles of good date and records management should be applied.
- 6.10.3 Data included in the records for each batch of cylinders must ensure that each filled container is traceable to significant aspects of the relevant filling operations. As appropriate, the following should be entered:
- name of the product;
 - batch number;
 - date and time of the filling operation;
 - identification of the person(s) carrying out each significant step (e.g. line clearance, receipt, preparation before filling, filling etc.);
 - batch (es) reference(s) for the gas (es) used for the filling operation;
 - equipment used e.g. filling manifold; quantity of cylinders before filling, including individual identification references and water capacit(ies);
 - pre-filling operations performed;
 - key parameters that are needed to ensure correct filling at standard conditions;
 - results of appropriate checks to ensure the cylinders have been filled;
 - a sample of the batch label;
 - specifications of the finished product and results of quality control tests;
 - quantity of rejected cylinders with individual identification references and reasons for rejections;
 - details of any problems or unusual events, and signed authorization for any deviation from filling instructions; and
 - release statement by the qualified person, date and signature.

Specifications



There shall be appropriately authorised and dated specifications for all starting materials, including bulk products, packaging materials and finished medical gases. These specifications shall serve as the basis for all quality evaluations in the quality control system used to control any starting materials, bulk and final product. These shall include, as appropriate:

6.10.4 Specifications for Starting and Packaging Materials

- i. description of all of the starting and packaging materials;
- ii. chemical formulae and designated name or reference code of the starting material;
- iii. relevant pharmacopoeia monograph of the starting material, where specified;
- iv. original manufacturer and the approved suppliers of the materials;
- v. detailed sampling and testing methods, including any specified analytical procedures and equipment;
- vi. qualitative and quantitative testing requirements with the acceptance limits; and
- vii. storage conditions and special precautions.

6.10.5 Specifications for Medical Gas Cylinders

Specifications for medical gases cylinders used for storage and distribution of compressed or liquefied gases or refrigerated liquefied gases shall include:

- i. a list of approved suppliers
- ii. where the manufacturer does not perform checks in-house, a list of subcontracted retesting facilities
- iii. water capacity of the cylinder and the volumetric content for the appropriate medical gases;
- iv. design code, design pressure and maximum working pressure of the cylinder;
- v. material of construction of the cylinder;
- vi. colour coding for its intended gas service;
- vii. physical dimensions of the cylinder, where required;
- viii. any internal cleanliness requirements, including the method of cleaning and the acceptance limits for both new and re-tested cylinders;

6.10.6 Specifications for Medical Gas Cylinder Valves

Specifications for cylinder valves fitted to medical gases cylinders for storage and distribution of compressed, liquefied or refrigerated liquefied medical gases shall include:

- i. List of approved suppliers
- ii. Where the manufacturer does not perform checks in-house, a list of subcontracted retesting facilities.
- iii. materials of construction - of the cylinder valve, with specific reference to the compatibility of materials used in its manufacture with the Medical gases for its intended service;
- iv. design pressure and maximum working pressure of the cylinder valve;



- v. testing criteria and any maintenance requirements for approving the valve for use;
- vi. inlet and outlet connections (as appropriate) with reference to the appropriate valve outlet standards (where specified by national or international standards);
- vii. approved method of operation

6.10.7 Specifications for Medical Gas Cylinder Labels

Specifications for printed cylinder labels shall include:

- i. printed text details and
- ii. list of approved suppliers.

6.10.8 Specification for Medical Gas Storage Tanks

Specification for the medical gas storage tanks for storage and distribution of refrigerated liquefied gases shall include:

- i. volumetric capacity / water capacity of the storage tank appropriate for the medical gases;
- ii. design code, design pressure and the maximum working pressure of the storage tank;
- iii. materials of construction, physical dimensions; and
- iv. any internal cleanliness requirements, the acceptance limits for both new and re-tested storage tanks statutory periodic inspection requirements.

Procedures

6.10.9 All medical gas dealers shall have in particular the following records:

- i. complaints handling book or register;
- ii. out of specification products register (in the case of manufacturers);
- iii. controlled gases(products) register;
- iv. recall register;
- v. expired products register
- vi. final invoices with corresponding import permits;
- vii. copies of delivery notes;
- viii. sales invoices with batch/lot numbers.
- ix. disposal register

6.10.10 There shall be written procedures for production, receiving, storage, dispatch, transportation, recalled, returned, expired, complaints, substandard, falsified products and adverse drug reactions.

6.10.11 Documented methods of production and detailed standard operating procedures shall be available for bulk gases and filling of cylinders. These procedures shall include:

- i. product name, with reference to its specification and pharmaceutical form;
- ii. a list of all starting materials and their relevant specifications;
- iii. a list of the principle equipment to be used;
- iv. a statement of expected yield from the plant, where appropriate; and
- v. the analytical limits of acceptance for the product quality.
- vi. the documented method of production and the detailed procedures shall be available for the filling of cylinders for each medical gas.



6.10.12 Medical Gas Cylinders Filling Procedures

There shall be approved procedures for the filling of medical gas cylinders. Cylinder type and size should be taken into consideration. These procedures shall normally include:

- i. name of the medical gases;
- ii. size of the cylinder to be filled, expressed either as a reference code or as the volumetric or weight content of the filled cylinder
- iii. precautions to be observed, including initial purging of the cylinder filling line to ensure that the gas used for cylinder filling will meet the filled cylinder specification;
- iv. any in-process quality control checks, with the appropriate acceptance limits;
- v. any post-filling quality control tests, with the appropriate acceptance limits;
- vi. a description of the final packaging operations, including fitting of tamper evident seals.

6.10.13 Bulk Medical Gas Supply Procedures

Documented methods and detailed procedures shall be available for the supply of bulk medical gases. These procedures for each medical gas shall include:

- i. product name, with reference to its specification, pharmacopoeia monograph and pharmaceutical form;
- ii. specification of the approved bulk medical gas;
- iii. statement of the approved bulk medical gas loading location and details of the equipment to be used; and
- iv. finished product analytical testing methods with their acceptance limits.
- v. the precautions to be observed when loading and discharging the tanker, including the initial purging of the tanker and tanker filling line for tanker loading and the delivery hose purging for tanker off loading, in order to ensure that the bulk medical gas meets the finished product specification when supplied as a starting material into the storage tank at the cylinder filling site or into the customer's storage tank;
- vi. details of any in-process quality control checks, with the appropriate acceptance limits; and
- vii. details of any post-fill checks

6.10.14 Batch Manufacturing Records

Batch records shall provide a history of each batch of bulk medical gases produced or batch of medical gas cylinders filled. These batch records should include all details pertinent to the quality of the final product.

- i. Batch records shall be designed such that all significant recordable activities involved in either the manufacture of medical gases or the filling of medical gas cylinders permit the traceability of each defined batch. All batch records shall be dated and signed.
- ii. This documentation shall also include any other relevant original data such as laboratory notebooks or production records.
- iii. Bulk medical gases are usually produced continuously and their quality continuously monitored. This does not comply with the normal batch philosophy used for the



manufacture of pharmaceutical products. A batch of bulk medical gases may be defined as:

- a) product produced into a bulk storage tank, where the product is defined as being a homogeneous batch;
- b) product transferred from a bulk cryogenic storage tank into a bulk cryogenic tanker, where the contents of the tanker is defined as being a homogeneous batch; and
- c) a continuous production process within a defined time period.
- iv. For continuous production, the batch record shall only reference the in-process quality control checks made. Where the bulk product is produced in defined batches, a batch record shall be kept for each batch processed.

The batch record shall be based on the relevant parts of the currently approved manufacturing procedure and processing instructions. The method of preparation of such records shall be designed to avoid transcription errors. The batch identity number shall be recorded on the batch record.

6.10.15 Batch Distribution Records

Records shall be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary. A system should be in place ensuring traceability of cylinders and valves as well as for the bulk medical gases and the filled medical gas cylinders.

6.10.16 Transfer Operations

- i. All the transfer operations, including controls before transfers, of liquefied gases from primary storage shall be in accordance with written procedures designed to avoid any contamination. The transfer line shall be equipped with a validated back-flow prevention device. Particular attention shall be paid to purging the flexible connections and to coupling hoses and connectors.

6.10.17 Electronic Data

- i. Where data is recorded electronically, detailed procedures relating to the validation of the system shall be available. If data is recorded electronically, only authorised persons shall be able to enter or modify data in the computer and changes or deletions shall be recorded. Access to the system shall be restricted by passwords or other means and the results of entry of any data critical to the correct performance of the plant shall be independently checked by appropriate authorised person to ensure that the plant is in control.
- ii. Electronically stored batch records shall be protected by a reliable back-up system. It is particularly important that all data is readily available throughout the period that batch records need to be retained.
- iii. A written detailed description of the system should be produced (including diagrams as appropriate) and kept up to date. It should describe the principles, objectives, security measures and scope of the system and the main features of the way in which the computer is used and how it interacts with other systems and procedures.



- a) Only authorized personnel should be allowed to enter or modify data in the computer.
- b) Access should be restricted by passwords or other means. User should have a unique identifier (User ID) for their personal and sole use so that activities can subsequently be traced to a specific individual.
- iv. There should be a record of changes and deletions. Any alteration to an entry of critical data should be authorized and recorded with the reason for the change. Consideration should be given to the system creating a complete record of all entries and amendments (an “audit trail”)
- v. Records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper or other means, at regular intervals. It is particularly important that the data including audit trail, are readily available throughout the period of retention. Back - up data should be stored as long as necessary at a separate and secure location.
- vi. All documents shall be completed, approved, signed (as required) and dated by an appropriate authorised person(s) and shall not be changed without the necessary authorisation.
- vii. The records referred above shall be kept and maintained within the premises for a period of not less than two (two) years from the date of product expiry.

6. OTHER REQUIREMENTS

7.1. HANDLING OF MEDICAL GASES

- 7.1.1 Handling of medical gases shall be in such a manner as to prevent contamination, deterioration and damage. For importers/distributors, attention shall be paid to manufacturer’s instructions.
- 7.1.2 Medical gases shall be received and examined for correctness against an order (where applicable).
- 7.1.3 All products received shall be verified and certified against delivery note and in particular the physical quantities, batch number/serial number, unit of issue, package size, weight and expiry date (where applicable).
- 7.1.4 Products shall be stored in accordance with manufacturer’s instructions and relevant guidelines and shall be arranged in a logical manner

7.2. STORAGE AREAS

- 7.3.1 Precautions must be taken to prevent unauthorised persons from entering storage areas.
- 7.3.2 Storage areas shall be clean, well ventilated, dry and free from accumulated waste, spillage, vermin and pests. There shall be a written sanitation and pest control



program indicating the frequency of cleaning and methods to be used to clean the premises and storage area.

- 7.3.3 Floors should be even and not present any hazard to the product packaging.
- 7.3.4 Gases shall be stored in a dedicated area that is subject to appropriate additional safety and security measures.
- 7.3.5 Where controlled environmental storage conditions such as temperature and humidity are required, these conditions should be regularly monitored at defined periods and documented. The monitoring should be done at least twice per day.
- 7.3.6 Appropriate actions, on the premise, equipment and/or materials should be taken when the storage conditions are not met. As far as possible, the actual storage temperature should be expressed quantitatively by the manufacturer.

7.3. TRANSPORTATION AND DELIVERIES TO CUSTOMERS

- 7.3.1 Products shall be transported in such a way that:
 - i. their identification is not lost e.g. Label
 - ii. they do not contaminate and are not contaminated by other products or materials.
 - iii. adequate precautions are taken against spillage, breakage, or theft.
 - iv. they are secured and not subjected to any adverse influence.
- 7.3.2 All cylinders shall be transported vertically.
- 7.3.3 Medical gases requiring controlled temperature storage should be transported by appropriate or specialized means e.g. liquid gases.

7.4. HANDLING OF RETURNED PRODUCTS

- 7.4.1 For the purposes of this guidance, gas(es) remaining in high-pressure cylinders or cryogenic containers that are returned for refilling are not considered to be returned medical gases.
- 7.4.2 For a medical gas that is returned, it is recommended that the container be vented.
- 7.4.3 Medical gases that have been improperly stored must not be salvaged and returned to the market.
- 7.4.4 All returned products should be quarantined to prevent redistribution until a decision has been reached regarding their disposal following an investigation.
- 7.4.5 Products returned from the market may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure.



- 7.4.6 The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be considered in this assessment.
- 7.4.7 Medical gases should only be returned to saleable stock if:-
- i. they are in their original cylinders and in good condition;
 - ii. it is established that they have been stored and handled under proper conditions and the remaining shelf life period is acceptable.
 - iii. The products have been examined and assessed by appropriate personnel.
- 7.4.8 The returned products should be formally released to saleable stock by the qualified person following a documented satisfactory quality re-evaluation.
- 7.4.9 Reconditioning, re-packaging or re-labelling of the products shall not be carried out by any distributor or manufacturer different from the original manufacturer unless they hold a license for such activity issued by the authority and have a written agreement with the original manufacturer.

7.5. SUBSTANDARD AND FALSIFIED PRODUCTS

- 7.5.1 If there is a suspected substandard or falsified product, the Market Authorization holder, manufacturer and ZAMRA should be informed immediately and the distribution chain shall be halted and the product should be clearly labelled.
- 7.5.2 Upon confirmation of the products to be substandard/ falsified, recall procedures should be instituted and followed as set out in the ZAMRA current guidelines on recalls.

7.6. RECALLS

- 7.6.1 There shall be a system, which includes a written procedure, to effectively and promptly recall medical gases known or suspected to be defective or counterfeit, with a designated person(s) responsible for recalls. The system shall comply with the current guidance issued by the Authority. This procedure shall be checked regularly and updated as necessary.
- 7.6.2 The recall procedure shall include the need to designate a person as responsible for the execution and co-ordination of the recall. The nominated person shall be given adequate resources to handle all the aspects of the recalls with the appropriate degree of urgency. The nominated person should normally be independent of the sales and marketing organisation.
- 7.6.3 The distribution records shall be readily available to the person(s) responsible for recalls and they shall contain sufficient information related to the product, e.g. quantities, product name, manufacturer, manufacture and expiry dates and batch/lot/serial number. Information on the customers who received the potentially



- defective product including their addresses and contact details should also be made available.
- 7.6.4 If the nominated person is not the Responsible Person, he shall be made aware of any decisions to recall potentially defective finished product.
- 7.6.5 The original manufacturer or marketing authorization holder shall be informed in the event of a recall. Where a recall is instituted by an entity other than the original manufacturer or marketing authorization holder, consultation with the original manufacturer or marketing authorization holder shall, where possible, take place 24 before the recall is instituted. Information on a recall shall be shared with the Authority. If a recall of the original product is necessary because of a counterfeited product which is not easily distinguishable from the original product, the manufacturer of the original product and the Authority shall be informed.
- 7.6.6 The Authority shall be notified promptly if a recall is considered to be necessary. The notification should include sufficient information such as; quantity, common name, manufacturer, manufacture and expiry dates and batch/lot/serial number.
- 7.6.7 In case of product recall initiated by the manufacturer himself, the Authority shall be notified on the reason for recall.
- 7.6.8 All recalled medical gases should be appropriately labelled and quarantined separately until further actions are agreed. For bulk cryogenic gas, due to the nature of the product, it is probable that any recalled batch will not be reused for medical purposes. An action would be to carry out specific analytical checks on the product to determine whether there was any defect with the gas and whether the complaint was justified
- 7.6.9 Upon completion of the recall, a final report shall be issued to the Authority, which shall include a reconciliation between the delivered and recovered quantities of cylinders or bulk medical gas from the suspect batch.
- 7.6.10 The documented recall system shall be routinely reviewed to evaluate its effectiveness and the system revised to reflect any shortcomings. The recall procedure should be capable of being initiated promptly and at any time.

7.7. COMPLAINTS

- 7.7.1 There should be a system of receiving, evaluating and classifying complaints. Complaints relating to the manufacturers own activity shall be evaluated and measures taken, where appropriate to prevent their recurrence.
- 7.7.2 There shall be a written procedure in place for the handling of complaints.
- 7.7.3 All complaints and other information concerning potentially defective and potentially substandard and falsified products shall be reported to the marketing authorization holder and the authority.



- 7.7.4 Any complaints concerning a product defect shall be recorded and thoroughly investigated to identify the origin or the reason for complaint (e.g. repackaging procedure, original manufacturing process, etc.).
- 7.7.5 Any complaints from users regarding adverse reaction to medical gases event/incident shall be documented in the respective form(s) and should be reported to the Authority through the pharmacovigilance system.
- 7.7.6 Complaint should be reported to the Authority using telephone, email or letter by describing its type, nature and adverse event.
- 7.7.7 Adverse events regarding the products can also be reported through ZAMRA electronic system for reporting Adverse Drug reactions (ADRs) via the following methods:

Online reporting: Complete and submit the report using the online reporting platform available MedSafety App

Email: Download and fill in appropriate form (see link above), complete all required sections of the form and send via email to: ZAMRA at npvu@zamra.co.zm and pharmacy@zamra.co.zm

Post: Download and print appropriate form at www.zamra.co.zm and complete all required sections of the form and send via post to: ZAMRA at Box 31890

7.8. DISPOSAL OF PRODUCTS

- 7.8.1 Disposal of expired, damaged, substandard, falsified or any other unwanted products shall be done in accordance with the current guidelines on disposal issued by the Authority
- 7.8.2 Expired, damaged, substandard, falsified products awaiting conclusion of investigations or disposal, shall be quarantined in the designated area to avoid mix ups

7.9. SELF-INSPECTION

- 7.9.1 The quality system shall include self-inspections. Self-inspection of the various distribution activities at a site may be divided into several individual self-inspections of limited scope. However, the self-inspection programme should ensure that all of the significant distribution activities at the site are covered annually. Self-inspections shall be conducted to monitor implementation and compliance with the principles of GMP and, if necessary, to trigger corrective and preventive measures.
- 7.9.2 Self-inspections shall be conducted in an independent and detailed way by designated competent person(s).
- 7.9.3 The results of all self-inspections shall be recorded. Reports shall contain all observations made during the inspection and, where applicable, proposals for corrective measures. There shall be an effective follow-up programme. Management shall evaluate the inspection report and the records of any corrective actions taken



7.10. CONTRACTS

- 7.10.1 Contract manufacture and analysis of medical gases shall be formally agreed, correctly specified and controlled by means of a contract. The contract conditions shall ensure that the contracted arrangements are carried out correctly and that there are no misunderstandings which could lead to product or work of unsatisfactory quality.
- 7.10.2 There shall be a written contract between the contract giver and the contract acceptor which clearly establishes the duties and responsibilities of each party.
- 7.10.3 The contract shall clearly state, the way in which the qualified person shall release each batch of product to exercise their full responsibility.
- 7.10.4 This section deals with the responsibilities of medical gas manufacturers towards the Authority with respect to the granting of marketing authorisation and manufacturing licence. It is not intended to affect the respective liability of contract acceptors and givers to consumers.
- 7.10.5 There shall be a written contract between the contract giver and the contract acceptor covering the manufacture, product quality control and supply of any medical gases or starting materials by another supplier. The written contract shall include any specific technical arrangements or product specifications, including its container, in connection with the contracted service.
- 7.10.6 All of the arrangements in connection with either the contract manufacture or analysis shall be in accordance with the details specified in the relevant marketing authorisation, where required. Any proposed changes to the method of manufacture or analysis shall be agreed prior to the change and be in accordance with the marketing authorisation for the product concerned.
- 7.10.7 The contract giver shall be responsible for assessing the competence of the contract acceptor to carry out successfully the manufacture, product quality control and supply of any medical gases or starting materials by another supplier required and for ensuring, by means of the contract, that the principles and guidelines of Good Manufacturing Practice (GMP) with respect to medical gases are followed.
- 7.10.8 The contract giver shall provide the contract acceptor with all the information, including the specification and specified methods of manufacture or analysis, in order to comply with the marketing authorisation and any other legal requirements.
- 7.10.9 The contract giver shall ensure that the contract acceptor is fully aware of any associated problems with the product manufacture or analysis which could cause a risk to their personnel, premises, equipment and other processes that could be involved.
- 7.10.10 The contract giver shall ensure that all manufactured medical gases or bulk gases for use in the manufacturing process delivered to him by the contract acceptor comply with the specification detailed in the marketing authorisation, where required by the



national authorities. For finished product, the contract giver shall ensure that the medical gases have been formally released, using a qualified person.

- 7.10.11 The contract acceptor shall have suitable premises and equipment to manufacture or analyse medical gases or starting materials to the appropriate specification. They shall also have sufficient competent personnel with adequate knowledge and experience to carry out the contracted work satisfactorily. Contract manufacture of medical gases shall only be undertaken by a holder of a manufacturing licence issued by the authority and covering the manufacture of the medical gas covered by the contract.

REFERENCES

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5. FDA Current Good Manufacturing Practice for Medical Gases I Guidance for Industry
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ANNEXES

Annex 1: MANUFACTURE OF MEDICAL GASES AT HEALTH FACILITIES

1.1. General

- 1.1.1 Any health facility that wishes to manufacture medical gases must obtain Authorisation from the Authority by applying for a Pharmaceutical Licence
- 1.1.2 Health facilities shall be required to operate a quality management system which complies with the basic principles and practices of Good Manufacturing Practice (GMP) for medical gases.
- 1.1.3 Where manufacturing of medical gases is subcontracted, written agreements shall be in place and the minimum requirements under of this guideline under 'contracts' shall be met. The subcontracted manufacturer shall possess a valid Pharmaceutical Licence issued by the Authority.
- 1.1.4 Medical gases generated at health facilities shall not be required to have Marketing Authorisation (product licence) from the Authority.
- 1.1.5 Medical gas generation and distribution shall be under the supervision of the pharmacy.
- 1.1.6 There shall be a written and approved organisation chart and job descriptions clearly outlining responsibilities for manufacture and distribution of medical gases at the health facility
- 1.1.7 The health facility pharmacy, shall be responsible for overseeing the distribution activities of medical gases manufactured at the facility including medical gas cylinders or bulk gases procured from external suppliers.
- 1.1.8 Some equipment, such as medical gas regulators, demand valves and medical gas flow meters, that are associated with the administration of medical gases, are classified as



medical devices and must therefore comply with the relevant guidelines on medical devices. This includes oxygen concentrators

- 1.1.9 Access to manufacturing and filling areas shall be restricted to authorised persons
- 1.1.10 Production equipment for medical gases shall be qualified on installation and requalified at defined intervals and records of qualification works maintained.
- 1.1.11 Maintenance and preventive maintenance activities shall be carried out on production and testing equipment and records shall be maintained. Where maintenance works are outsourced, there shall be a written agreement in place
- 1.1.12 Equipment and measuring devices shall be calibrated and records maintained
- 1.1.13 The gas manufacturing system should preferably be inspected on a daily basis and for parameters such as pressure control and other critical parameters
- 1.1.14 Storage areas such as those used for cylinders shall be kept in a tidy and hygienic condition
- 1.1.15 Manufacturing areas should not have direct communication with toilet facilities and eating areas
- 1.1.16 Pipelines and storage tanks normally do not require cleaning. However, where any critical cleaning measures are carried out, they should be validated.

1.2. Medical (Compressed) Air

Medical (compressed) air systems should be suitably installed and maintained in such a way as to generate medical air of appropriate quality. The following aspects should be considered:

- 1.2.1 The source of medical air should be free from environmental contaminants.
- 1.2.2 The compressor room should be maintained in a state of hygiene, have appropriate ventilation. Temperature should be monitored and recorded at regular intervals.
- 1.2.3 Pipelines should preferably be colour coded based on an approved written procedure.
- 1.2.4 Purging of pipelines should be based on approved written procedures.
- 1.2.5 Filters used should be of the appropriate material and porosity and should be regularly maintained to prevent contamination.
- 1.2.6 The design, sizing and sequence of filters should be suitable. Filter integrity checks and changes should be routinely carried out based on approved written procedures. Records should be maintained.

1.3. Bulk Medical Gases

For health facilities making use of bulk medical gases, the following requirements should be met:



- 1.3.1 Records of ownership and equipment history for storage tanks and evaporator units should be maintained.
- 1.3.2 Measures should be put in place where a non-dedicated mobile tank is used.
- 1.3.3 The health facility shall maintain records such as the certificate of analysis from the manufacturer which should be obtained upon delivery of the bulk gas.
- 1.3.4 There shall be a written procedure for filling. The medical gas shall be released by the qualified person before commencement of the filling operation.
- 1.3.5 There should be a validated method of backflow prevention in the line supplying the health facility to prevent contamination of the storage tank / evaporator unit.

Annex II: REQUIREMENTS FOR A SITE MASTER FILE (SMF)

1.1. General

- 1.1.1 This section aims at guiding the manufacturer of medical gases in the preparation of a Site Master File (SMF) that is useful to the Authority in planning and conducting GMP inspections. It includes guidance on the preparation and content of the SMF.
- 1.1.2 The SMF is prepared by the medical gas manufacturer and should contain specific information about the quality management policies and activities of the site, the production and/or quality control of medical gas manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. It forms part of documentation belonging to the quality management system of the manufacturer and kept updated accordingly
- 1.1.3 If only part of a gas manufacturing operations is carried out on the site, an SMF need only describe those operations, e.g. testing, filling, etc.
- 1.1.4 When submitted to the Authority, the SMF should provide clear information on the manufacturer's good manufacturing practices (GMP)-related activities that can be useful in general supervision and in the efficient planning and undertaking of GMP inspections.
- 1.1.5 An SMF should contain adequate information but, need not contain long narratives. Simple plans, outline drawings or schematic layouts are preferred instead of narratives. The SMF, including appendices, should be readable when printed on A4 paper sheets
- 1.1.6 The SMF shall contain the following information;

1.2. General information on the manufacturer

1.2.1 Contact information on the manufacturer

- i. name and official address of the manufacturer;
- ii. names and street addresses of the site, buildings and production units located on the site;
- iii. contact information of the manufacturer including 24-hour telephone
- iv. number of the contact personnel in the case of product defects or recalls; and

1.2.2 Authorized medical gas manufacturing activities of the site

- i. copy of the valid manufacturing licence issued by the Authority in Annex 1 of the SMF;
- ii. brief description of manufacture, import, export, distribution and other activities as authorized by the Authority including foreign authorities with authorised products



- iii. type of products currently manufactured on-site (list in Annex 2 of SMF) where not covered by Annex 1; and
- iv. list of GMP inspections of the site within the last five years; including
- v. dates and name/country of the competent agency having performed the inspection.
- vi. A copy of the current GMP certificate or clearance letter (in Annex 3 of SMF)
- vii. description of non-medical gas manufacturing activities on site, if any.

1.3. Quality Management System

1.3.1 Quality Management System of manufacturer

- i. brief description of the quality management systems run by the company and reference to the standards used;

1.3.2 Release procedure of finished products

- ii. responsibilities related to the maintaining of the quality system including
- iii. senior management; and
- iv. information on activities for which the site is accredited and certified, including dates and contents of accreditations, and names of accrediting bodies, if any.
- v. detailed description of qualification requirements (education and work experience) of the qualified person(s) responsible for product release procedures;
- vi. general description of product release procedure;
- vii. role of qualified person in quarantine and release of finished products and in assessment of compliance with the marketing authorization, where applicable;

1.3.3 Management of suppliers and contractors

- i. a brief description of the qualification system of contractors
- ii. measures adopted where substandard/spurious/false-labelled/falsified/counterfeit medical gases are suspected or identified;
- iii. use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
- iv. list of contract manufacturers and laboratories including the addresses and contact information for outsourced manufacturing and testing activities, e.g. should be presented in Annex 4; and
- v. brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with the marketing authorization and GMP requirements

1.3.4 Quality risk management

- i. brief description of quality risk management (QRM) methodologies
- ii. used by the manufacturer; and scope and focus of QRM including brief description of any activities
- iii. which are performed at corporate level, and those which are performed locally. Any application of the QRM system to assess continuity of supply should be mentioned.

1.3.5 Product quality reviews

brief description of methodologies used.

1.4. Personnel

- i. organization chart showing the arrangements for quality management, production and quality control positions/titles (in Annex 5), including senior management and qualified person(s);
- ii. and number of employees engaged in the quality management, production, quality control, storage and distribution, respectively with respect to the medical gas manufacturing activity



1.5. Premises and equipment

1.5.1 Premises

- i. short description of plant: size of the site and list of buildings.
- ii. simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings are not required);
- iii. layouts and flowcharts of the production areas (in Annex 6) indicating the production activities (i.e.
- iv. cylinder checking, filling, testing storage, packaging, etc.) in the rooms;
- v. layouts of warehouses and storage areas; and
- vi. brief description of specific storage conditions if applicable, but not indicated on the layouts.
- vii. Brief description of environmental conditions defining temperature, humidity, where required
- viii. Brief description of any other applicable utilities employed in medical gas manufacturing

1.5.2 Equipment

- i. List of major production and control laboratory equipment with critical pieces of equipment identified should be provided in Annex 7. A list of mobile oxygen plants should be included in Annex 8, where they exist.
- ii. brief description of cleaning and sanitation methods where this is undertaken
- iii. brief description of GMP critical computerized systems (excluding equipment specific programmable logic controllers (PLCs)).

1.6. Documentation

- i. description of documentation system (i.e. electronic, manual); and
- ii. when documents and records are stored or archived off-site (including pharmacovigilance data, when applicable): list of types of documents/records; name and address of storage site; and an estimate of time required to retrieve documents from the off-site archive.

1.7. Production

- i. type of products manufactured including (references to Annex 1 or 2 can be made)
- ii. toxic or hazardous substances; product types manufactured in a dedicated facility or on a campaign basis, if applicable;
- iii. brief description of general policy for process validation;
- iv. arrangements for the handling of starting materials, packaging materials, bulk and finished products including sampling, quarantine, release and storage; and
- v. arrangements for the handling of rejected materials and products.

1.8. Quality control

- i. description of the testing activities carried out on the site

1.9. Distribution, complaints, product defects and recalls

- i. description of the system used to verify that each customer/recipient is legally entitled to receive medical products from the manufacturer;
- ii. arrangements for product distribution and methods by which product traceability is maintained; and
- iii. measures taken to prevent manufacturers' products entering into the illegal supply chain.
- iv. brief description of the system for handling complaints, product defects and recalls.

1.10. Self-inspections

- i. short description of the self-inspection system with focus on criteria used for selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities.



Annex III: SAFETY SYMBOLS OF MEDICAL GASES

The signage should be displayed in a manner that it is visible to all persons concerned.

Text Example	Symbol Example
No Smoking No smoking shall be allowed in areas used for manufacturing, storage and in vehicles when carrying gas cylinders. Ignition of a flammable gas following a leak could be catastrophic. Some medical gases have oxidizing properties and will therefore strongly support combustion.	
Ventilation Ideally, gases should be transported in an open vehicle. If this is not possible, make sure you have good ventilation to maintain a suitable environment inside the vehicle. The best way to improve ventilation is to open a window.	
Cryogenic liquefied gases Take extra care with cryogenic liquefied gas containers. They continually vent cold gas (even when not in use) and could leak liquid if not kept upright.	
Fire Manufacturing and storage facilities including transporting vehicles should contain firefighting equipment. Personnel, including drivers should be trained in their use. A 2 kg dry powder extinguisher is the minimum requirement for a cylinder transporting vehicle. Strongly recommended for personal use.	
Secure Cylinder Storage Cylinders are to be securely stowed, preferably in the luggage area during transportation.	
All valves are to be closed Ensure the valves are closed on all cylinders. Check that there are no leaks. Disconnect and remove any ancillary equipment	



Flammable Gas	
Oxidising Gas	
Toxic Gas	
Non-flammable, non-toxic gas	
Danger if inhaled	

Annex IV: COMMON OXYGEN PLANTS IN ZAMBIA

Plant Type	General Expectations
Air Separation Units	Air separation units use fractional distillation to produce cryogenic or liquid oxygen of purity not less than 99%, which is often described as Oxygen 99%. These units use ambient air by cryogenic distillation of gases and more than one gas can be extracted from this type of plant.
Pressure Swing Adsorption and Vacuum Swing Adsorption Plants	This type of plant uses ambient air by pressure swing adsorption (PSA) or vacuum swing adsorption (VSA) technologies to generate 90% to 96% purity of oxygen, which is often described as Oxygen 93%. PSA plants are the most commonly employed oxygen generating plants in hospitals.
Oxygen concentrators¹ (Bedside and potable)	These devices work on the same principal as that of PSA plants and are capable of producing oxygen with purity between 82% and 96%.



**Annex V: MEDICAL GAS CYLINDER COLOUR IDENTIFICATION (CODING)**

Each individual gas cylinder has to have a label which identifies its contents, it also provides basic safety information on the hazard(s) associated with the product. The label is the primary method of identifying the contents. The label will contain mandatory information as required in this guideline and marketing authorisation guidelines. It is the responsibility of the person filling the gas cylinder to affix a label. Cylinders are commonly colour coded based on the following international standards:

1. British Standard Colour Coding System (BS EN 1089-3 [2])
2. BS EN 1089 – 3 [2] Transportable gas cylinders. Gas cylinder identification.
3. EN 1089-3 [2] standards (EIGA)

Annex VI: EXAMPLE OF COMMON CYLINDER SIZES

Cylinder size	D	E	F	G	J
Nominal content/oxygen capacity (L)	340	680	1360	3400	6800
Water capacity (L)	2.3	4.7	9.4	23.6	47.2
Dimensions (height × diameter) (mm)	535 × 102	865 × 102	930 × 140	1320 × 178	1520 × 229
Approximate full weight (kg)	3.9	6.5	17	39	78
Valve outlet connection (and specification)	Pin index (ISO 407)	Pin index (ISO 407)	Bullnose (BS 341)	Bullnose (BS 341)	Pin index side spindle (ISO 407)
Nominal service pressure (kPa/bar/psi)	13 700 kPa (137 bar/1987 psi)	13 700 kPa (137 bar/1987 psi)	13 700 kPa (137 bar/1987 psi)	13 700 kPa (137 bar/1987 psi)	13 700 kPa (137 bar/1987 psi)



Cylinder size	D	E	F	G	J
Health facility use	Emergency and ambulance transport	Emergency and ambulance transport	Stand-alone	Stand-alone	Manifold connection and stand-alone

Annex VII – EXAMPLE OF OXYGEN CYLINDER TECHNICAL SPECIFICATIONS

Oxygen Cylinders Technical Specifications

1. General technical requirements
 - Oxygen and medical air cylinders are refillable containers for such gas, in a compressed form, available in international standard capacity/pressure and dimensions.
 - The cylinders can be made of steel, aluminium/alloy, carbon fibre or other composite material.
 - Nominal pressure should be 13 700 kPa (137 bar, 1987 psi) for standard cylinders and 23 000 or 30 000 kPa (230 or 300 bar, 3336 or 4351 psi) for cylinders fitted with integral valves.
 - Each cylinder is fitted and supplied with a valve.
 - Multiple options for pressure regulators fitting and outlets, and integral valves should be available separately.
 - Specific ISO, American National Standards Institute (ANSI) and other international colour coding for oxygen and medical air should be available.
 - Accessories like holders, racks and trolleys should be available separately.

Oxygen cylinders:

**Oxygen Cylinders Technical Specifications**

- Refillable cylinders for compressed oxygen (oil-free and compliant to ISO standards) or air (compliant to ISO standards) for medical use.
- Fitted with a primary valve, standard (pin index or bullnose) or integral, refillable.
- Nominal pressure 13 700 kPa (137 bar, 1987 psi), for standard valve cylinders, or 23 000–30 000 kPa (230–300 bar, 3336–4351 psi) depending on the cylinder model, for integral valve cylinders.
- Compressed Gas Association (CGA) approved seamless steel/aluminium alloy/composite body, colour coding according to ISO/ANSI/CGA/NFPA, sizes ISO/US standard.
- Cylinders supplied with optional pressure regulators, multiple fitting according to all the international standards.
- Safety over-pressure release valve (if not built-in in the integral valve fitted cylinders).
- Primary valve and pressure regulator assemblies:
- Pin index or bullnose primary valve and compatible pressure regulators, providing pressure regulated supply of oxygen (oil-free and compliant to ISO standards) or medical air (compliant to ISO standards).
- Steel/plated brass/aluminium casing, brass valve.
- Pin index and bullnose primary valve versions, handle/key operated, supplied with tools.
- Nominal inlet pressure 13 700 kPa (137 bar, 1987 psi), maximum 20 000 kPa (200 bar, 2901 psi).
- Outlet pressure 345 kPa (3.5 bar, 50 psi).
- Integrated manometer, 0–20 000 kPa (0–200 bar, 0–2901 psi).
- Safety over-pressure release valve.
- Pressure regulator supplied with flowmeter, if required – see configurations/options for specifications.



Oxygen Cylinders Technical Specifications

Integral valves:

- All-in-one cylinder valve for oxygen (oil-free and compliant to ISO standards) or medical air (compliant to ISO standards), providing direct attachment to the cylinder, pressure regulation and supply of medical gas with adjustable flow rate.
- Steel/plated brass/aluminium casing, brass valve.
- 6 mm barbed and BS 5682 Schrader (if applicable depending on the size of the cylinder) outlets.
- Integrated open/close valve, outlet nominal pressure 400 kPa (4 bar, 58 psi).
- Inlet pressure 23 000–30 000 kPa (230–300 bar, 3336–4351 psi), depending on the cylinder model.
- Integrated refill valve ISO 5145/CGA 540 compliant.
- Integrated manometer, covering the full nominal pressure range of the cylinder, standard 23 000–30 000 kPa (230–300 bar, 3336–4351 psi), for integral valve cylinders, or whatever applicable.
- Integrated flowmeter.
- Safety over-pressure release valve.
- Capable of being stored in ambient temperature of at least 5–50 °C, relative humidity of at least 15–95% non-condensing.
- Suitable for continuous operation in ambient temperature of at least 5–45 °C, relative humidity of at least 15–90% non-condensing.
- Specific requirements for altitude may be required, depending on the installation site.
- Applicable regulations on transport and storage of cylinders may vary if the cylinders are empty or

**Oxygen Cylinders Technical Specifications**

partially/fully filled.

- Compliance with regulations on hazardous goods, flammable, explosive, compressed gas, according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and international standards, is mandatory.

**2. Configuration
s/options****Oxygen cylinder configurations/versions/options:**

- Standard and MRI-compatible versions.
- Specific ISO/ANSI/CGA/NFPA colour coding for oxygen and medical air.
- Seamless cylinders made of steel, aluminium/alloy, carbon fibre or other composite material (CGA approved and compliant to ISO applicable standards).
- Pin index/bullnose and integral valve options.
- OXYGEN and MEDICAL AIR cylinders with STANDARD VALVE available in all the ISO international standard sizes, including size AZ, C, D, E, F, G, H, J, and also US sizes M2 to M 265 (not all sizes apply to both oxygen and medical air).
- The type of standard valve has to be compliant to international ISO and US standards, i.e. pin index ISO 407/BS 850/CGA 870 valve, CGA 540 valve, 5/8 inch BSP (F) Bullnose BS 341 valve, also according to the size/pressure of the cylinder and to any applicable regulation.
- OXYGEN cylinders should be available also with INTEGRAL VALVE (with manometer and flow regulator, 400 kPa (4 bar) nominal outlet pressure, 6 mm barbed and BS 5682 Schrader outlets), in all the ISO international standard sizes, including size ZA, CD, ZD, HX and ZX, and also US sizes in M coding system.

Regulator/integral valve configurations/versions:

- Standard and MRI-compatible versions.

**Oxygen Cylinders Technical Specifications**

- Oxygen and medical air versions.
- Pressure regulators and integral valves should be available with DISS and 6 mm barbed outlet.
- Pressure regulators should be available in basic open/close model and fitted with integrated flowmeter, Thorpe tube or Bourdon gauge.
- Pressure regulators and integral valves with dial style flowmeter should be available at least in the following flow ranges, for oxygen and medical air:
 - Low flow 0–3 or 4 L/min (only for oxygen), discrete (dial) flow setting (indicative steps 0, 0.03, 0.06, 0.12, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0), accuracy 10%.
 - Standard flow 0–15 L/min, discrete (dial) flow setting (indicative steps 0, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 15.0), accuracy 10%.
 - High flow 0–25 L/min minimum, discrete (dial) flow setting (indicative steps 0, 0.25, 0.50, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 15.0, 25.0), accuracy 10%.
- Pressure regulators and integral valves with Thorpe or Bourdon flowmeter should be available at least in the following flow ranges, for oxygen and medical air:
 - Low flow 0–3 or 4 L/min (only for oxygen), accuracy 10%, indicative graduation (L/min) 0.03, 0.06, 0.12, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0.
 - Standard flow 0–7 or 8 and 0–15 or 16 L/min, accuracy 10%, graduation 0.5 L/min (0.5–3 range) and 1 L/min (3–max range).
 - High flow 0–25 L/min minimum, accuracy 10%, graduation 0.5 L/min first increment and 1 L/min full range.
- Cylinder body, primary valve and pressure regulator or integral valve assembly, outlet connectors, safety pressure release valve, valve/regulator knob, manometer and flowmeter (for integral valve).
- Portable or stationary (depending on the size of the cylinder).

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- Brass valve assemblies. Cylinders made of steel, aluminium/alloy, carbon fibre or compound material. Bronze/brass/synthetic sealings. All materials in contact with air certified for medical use.

3. Displayed parameters
 - Pressure and flow (for integral valve cylinders only).
4. User adjustable settings
 - Open/close control, pressure and flow (for integral valve cylinders only).
5. Accessories
 - Cylinder holdings, carts, trolleys. Supplied with keys and tools to operate valves and regulators. Complete set of tubing and adapters to use the pressure regulator and the integral valve with all common international standard fittings, for medical gas sources, patient circuits and other medical devices.
6. Spare parts
 - Common and frequently used spare parts, sensors/transducers/actuators, reusable probes/cables/patient connection accessories, periodic maintenance and calibration kits/materials, renewables that should be procured together with the equipment and in quantity sufficient for 2 years recommended (1 year at least) of typical use. These items should be supplied to each department where the equipment is installed and also to central and local maintenance department. Sealing set, maintenance kit, regulating unit (knob), adapters and connectors, keys and tools to operate the valves.
 - Items in the above-mentioned categories that are not frequently needed or require specialized skills to be used/replaced. The need and the quantity of these items should be assessed by technical staff before procuring the main medical devices, and procured together. It is recommended to store and use them in central and local maintenance department.
7. Mobility, portability (if relevant)
 - Primary valve assembly, regulator valve assembly, pressure safety valve, inlet/outlet connectors, full set of sealings, integral valve assembly, manometer and flowmeter (for integral valves).
 - Portable or stationary (depending on the size of the cylinder).
8. Documentation requirements
 - Set: user and maintenance manuals, hard and soft copies, in English (mandatory) and other languages (preferable).

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(English language mandatory)

- Certificate of calibration and inspection.
- Troubleshooting, calibration and routine maintenance.
- List of all spare parts and accessories, with part numbers and contact details for parts supply.
- Document with contact details of manufacturer, supplier and local service agent.
- Applicable regulations on transport and storage of cylinders may vary if the cylinders are empty or partially/fully filled.
- Compliant with regulations on hazardous goods, flammable, explosive, compressed gas, according with GHS and international standards is mandatory.
- Sealed container.
- Capable of being transported and stored in ambient temperature of at least 5–50 °C, relative humidity of at least 15–95% non-condensing. Specific requirements for altitude may be required, depending on the installation site.
- Hazardous goods, flammable, explosive, compressed gas labelling according with GHS and international standards and regulations.

Primary packaging:

- Unit of use: one (1) cylinder or valve/regulator in a box or case with manufacturer's instruction for use, spare parts and accessories (when applicable). Cylinder type and content in litres, tare weight (weight when empty), maximum cylinder pressure, cylinder size code.

Labelling on the primary packaging:

- Name and/or trademark of the manufacturer; manufacturer's product reference; type of product and main characteristics; lot number prefixed by the word "LOT" (or equivalent harmonized symbol) (if applicable); information for particular storage conditions (temperature, pressure, light, humidity, etc.), as appropriate (or

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equivalent harmonized symbol); information for handling, if applicable (or equivalent harmonized symbol).

Over packaging:

- Packaging unit.

Labelling on the packaging unit:

- Labelling to be the same as primary packaging. Extra information required: number of units.
- Certified quality management system for medical devices (e.g. ISO 13485). General quality management (e.g. ISO 9001). Application of risk management to medical devices (e.g. ISO 14971).
- Free sales certificate (FSC) or certificate for exportation of medical device provided by the authority in manufacturing country.
- Proof of regulatory compliance, as appropriate, per the product's risk classification (e.g. Food and Drug Administration [FDA] and/or Conformité Européenne [CE]).

10. Standards, for the manufacturer

11. Regulatory approval/certification

12. Standards, for product performance

Compliance to the following international standards or to regional or national equivalent (including the technical tests for safety and performance from accredited laboratory or third party) for:

- Colour coding ISO or ANSI for medical gases.
- Conforms to ISO, NFPA and/or CGA standards, and/or UL or CSA approved.
- ISO 11114 Gas cylinders – Compatibility of cylinder and valve materials with gas contents.
- ISO 10524 Pressure regulators for use with medical gases.
- ISO 15002 Flow-metering devices for connection to terminal units of medical gas pipeline systems.
- ISO 15245 Gas cylinders – Parallel threads for connection of valves to gas cylinders.
- ISO 10297 Gas cylinders – Cylinder valves – Specification and type testing.

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- ISO 17871 Gas cylinders – Quick-release cylinder valves – Specification and type testing.
- ISO 17879 Gas cylinders – Self-closing cylinder valves – Specification and type testing.
- ISO 407 Small medical gas cylinders – Pin-index yoke-type valve connections.
- ISO 5145 Cylinder valve outlets for gases and gas mixtures – Selection and dimensioning.
- ISO 11117 Gas cylinders – Valve protection caps and valve guards – Design, construction and tests.
- ISO 11363 Gas cylinders – 17E and 25E taper threads for connection of valves to gas cylinders.
- ISO 12209 Gas cylinders – Outlet connections for gas cylinder valves for compressed breathable air.
- ISO 14246 Gas cylinders – Cylinder valves – Manufacturing tests and examinations.
- ISO 22435 Gas cylinders – Cylinder valves with integrated pressure regulators.
- ISO 7866 Gas cylinders – Refillable seamless aluminium alloy gas cylinders – Design, construction and testing.
- ISO 20701 Gas cylinders – Refillable welded aluminium-alloy cylinders – Design, construction and testing.
- ISO 9809 Gas cylinders – Refillable seamless steel gas cylinders – Design, construction and testing.
- ISO 11119 Gas cylinders – Refillable composite gas cylinders and tubes – Design, construction and testing.
- ISO 13341 Gas cylinders – Fitting of valves to gas cylinders.
- ISO 32 Gas cylinders for medical use – Marking for identification of content.
- ISO 7225 Gas cylinders – Precautionary labels.
- ISO 10461 Gas cylinders – Seamless aluminium-alloy gas cylinders – Periodic inspection and testing.
- ISO 11623 Gas cylinders – Composite construction – Periodic inspection and testing.

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- ISO 15223-1 Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements.
 - ISO 15996 Gas cylinders -- Residual pressure valves -- Specification and type testing of cylinder valves incorporating residual pressure devices.
 - ISO 15001 Anaesthetic and respiratory equipment -- Compatibility with oxygen.
13. Warranty 5 years recommended for the cylinders, 3 years recommended for the pressure regulators and valves (2 years at least).