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TANZANIA FOOD AND DRUGS AUTHORITY

GUIDELINES FOR REGULATING MEDICAL GASES

(Made under Section 52(1) of the Tanzania Food, Drugs and Cosmetics Act, 2003)

First Edition

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FOREWORD

Medical gases have been in use for decades in hospital and home settings as key components of life supporting systems in human beings. They are packed as compressed gas under pressure in cylinders or liquefied gas at high or low pressure and administered to patients through designated valves or evaporation and delivery by using hospital delivery systems.

Despite long history of use in Tanzania, quality, safety and effectiveness of medical gases had never been ascertained because of absence of regulatory system. Considering that manufacturers and dealers of medical gases are also dealing in business of other types of gases with different quality requirements (such as industrial gases and food grade gases), absence of regulation jeopardizes health of patients because of potential for inhalation of gases of inadequate quality for medical purposes and/or storage and delivery of the respective gases in facilities that allows contamination with other innocuous substances.

Because of critical use and potential hazards to patients, TFDA has developed these guidelines for comprehensive regulation of medical gases in Tanzania. The guidelines are intended to be read in conjunction with other guidelines related to regulation of human medicinal products and medical devices as most of the requirements also apply to medical gases. The guidelines are aimed at regulating medical gases imported into Tanzania, produced within Tanzania as well as those produced in situ within health facilities. They present the current thinking in regulation of medical gases in the main areas of licensing of dealers, marketing authorization, product labeling and information, handling, transportation, storage and safety of operators of the systems.

Dealers of medical gases are encouraged to familiarize themselves with these guidelines and follow up all aspects of the manufacture, distribution and post marketing surveillance of their products. Adherence to these guidelines will facilitate efficient and effective regulation by TFDA and effective compliance by dealers. This will enable protection of health of the patients and operators within manufacturing facilities and hospital settings.

Agnes S. Kijo
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INTRODUCTION

The guidelines for medical gases provides guidance for manufacturers, suppliers and distributors of medical gases on regulatory requirements for personnel, premises and facilities, handling and control, documentation, complaints and recall. All medical gases dealers shall follow these guidelines developed under the principles of Good Manufacturing Practice (GMP) and Quality Management System (QMS).

The main objective of the Guidelines is provide the dealers with the necessary information to enable them comply with the law and regulations governing the business of medical gases and supply of medical gases which are safe and of good quality.

The requirements have been prepared to assist Medical Gas dealers to carry out their activities according to prescribed standards of quality and safety of medical gases in order to produce and supply safe medical gases. These activities shall also comply with all of other appropriate operational, safety and environmental requirements applicable in Tanzania and any relevant national / international standards and regulations. Approval for establishing manufacturing facility, business premises, import and export will base on fulfillment of the requirements prescribed in these guidelines.

The guidelines has twelve (12) sections including annexes which covers the following areas; general requirements, licensing of premises, importation, registration, labeling, Good Manufacturing Practice, Post Market Surveillance, Handling including transportation, documentation and disposal.

GLOSSARY

"Bulk Gas" means any gas intended for medicinal 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 oxygen because it avoids the risk of adiabatic compression.

"Compressed Gas" means a gas which when packaged under pressure is entirely gaseous at –50°C.

"Container" means a container is a cryogenic vessel, a tank, a tanker, a cylinder, a cylinder bundle or any other package that is in direct contact with the medicinal gas.

"Cryogenic Gas" means Gas, which liquefies at 1.103 bar at a temperature below –150^{o}C.

"Cryogenic Vessel" means a static or mobile thermally insulated container designed to contain liquefied or cryogenic gases. The gas is removed in gaseous or liquid form.

"Cylinder" means a transportable, pressure container with a water capacity not exceeding 150 liters. In this document when using the word cylinder it includes cylinder bundles (or cylinder pack) when appropriate.

"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.

"Filling Ratio" means relationship between the weight of gas introduced into a container and the weight of water at room temperature that will fill the same container ready for use.

"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.

“High Pressure Liquefied Gas” means a gas with a critical temperature between -50 °C and +65 °C.

“Hydrostatic Pressure Test” means Test performed for safety reasons as required by national or international guidelines in order to make sure that cylinders or tanks can withhold high pressures.

“Liquefied Gas” 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.

“Medicinal Gas” means Gases for medicinal use may be classified as medicinal products according to Article 1.2 of Council Directive 65/65/EEC.

“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 contain liquefied or cryogenic gases. The gas is removed in liquid form. It is filled in the filling area of the pharmaceutical establishment, then transported to the site of utilization.

“Mobile Evaporator” means a mobile thermally insulated container designed to contain liquefied or cryogenic gases. The gas is removed in gaseous form, filled in the filling area and then transported to the site of utilization.

“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.

“Permanent Gas” means gas which has a critical temperature below –10°C.

“Posology” means the concentration of gas mixture, which is related to gas administration output.
“Pressure Regulator” means Medical device for pressure reduction.

“Refrigerated Liquefied Gas” means gas, which when packaged for storage or transport, is made partially liquid because of a refrigeration system.

“Tank” means large-sized static thermally insulated container designed to contain liquefied or cryogenic gases, located in the production station or the filling area.

“Tanker” means container fixed on a vehicle for the transport of liquefied or cryogenic gas.

“Valve” means device for opening and closing containers.

“Valve Outlet Connection” means screw connector which makes it possible to connect the rubber gas pipe or pressure regulator to the cylinder. It is standardized and ensures fool proofing.

SECTION ONE: GENERAL REQUIREMENTS

1.1 Dealers of medical gases

1.1.1 The following shall fall under the category of medical gases dealers:

a) Manufacturers including hospitals producing in situ
b) Importers
c) Distributors

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

1.1.3 All manufacturers of medical gas shall institute and implement quality management system which includes:-

a) an appropriate infrastructure or "quality system" encompassing the organizational structure, procedures, processes and the resources; and

b) Systematic actions necessary to ensure adequate confidence that a product and documentation will satisfy given requirements for quality.

1.1.4 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.

1.1.5 There shall be written procedures and records to ensure traceability of the products produced, imported and distributed.

1.1.6 In any case where some duties are delegated or contracted out, the activities shall be documented in contracts and shall be periodically audited and records maintained.

1.1.7 Dealers of medical gases shall establish safety mechanisms to avoid injuries and deaths.

1.1.8 All medical gases intended to be marketed in Tanzania shall be required to be registered before market authorization is granted.

1.1.9 Manufacture of the finished product should also be done according to good manufacturing practices (GMP) as per requirements provided in section 6 of these guidelines.

1.1.10 All premises and vehicles dealing with medical gas business shall be required to display one or more safety symbols as annexed in **Annex 1**.

1.2 Licensing of premises

Medical gases dealers shall be licensed after fulfillment of the following requirements:

1.2.1 Application

a) Applicants shall submit a dully filled application form **(Annex 2**) to the Director General, TFDA and pay the relevant fees as prescribed in the TFDA Fees and Charges Regulations in force.

b) The application form may be obtained from TFDA zone or headquarter offices or through the TFDA Website www.tfda.go.tz

1.2.2 Location

a) 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.

b) The premises shall be required to address among other issues, the fire prevention facilities.

c) The premises should have a postal and physical address to include plot and house number, street/hamlet, district and region where the business is to be carried out, clearly indicated in the application form for easy location and identification.

1.2.3 Building

a) Building must be of permanent construction and address and it should be located at a site approved by relevant authorities.

b) The finishing of walls, ceiling and floors shall be such that, they are easy to clean and non-combustible. The building shall be kept clean and maintained.

c) Sufficient lighting and ventilation shall be provided to enable all operations to be carried out.

d) Buildings should protect products from contamination and deterioration, including protection from excessive heat or undue exposure to direct sunlight.

e) Buildings should have sufficient security to prevent unauthorized access and misappropriation of the products.

f) 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.

g) Receiving and dispatch bays shall protect products from the extreme climate conditions. It shall be designed and equipped to allow containers of incoming products to be cleaned.

h) The surrounding should be maintained so as to minimize dust, soil and other contamination to enter the building.

i) Residential houses shall not be used for business of medical gases.

j) Manufacturing premises shall also be required to comply with premises requirements as prescribed under Section 2 of these guidelines.

1.2.4 Layout

Medical gases premises for manufacturers and wholesalers shall in accordance with the requirements provided in the GMP Guidelines and Guidelines for Premises dealing with Medical Devices respectively.

1.2.5 Sanitation

In order to maintain hygienic working conditions, premises shall have good supply of portable water, proper sink for hand washing and accessible toilet.

1.2.6 Registration certificate and permit

a) Successful applicants shall be issued with registration certificate which is issued once and simultaneously a permit/license shall be issued.

b) The permit validity is only one year and is subjected for renewal every end of the financial year i.e. month of June.

c) Dealers who shall delay to renew their permits shall be required to pay the Authority the prescribed annual permit fee together with a penalty as prescribed by TFDA Fees and Charges Regulations in force.

d) All the prescribed information shall be submitted in English or Kiswahili language and all communication regarding the application shall be made in any of these two languages.

1.2.7 Validity of Premises Registration Certificate and Business Permit

Every premise registration certificate shall be issued once and shall remain valid provided that:-

a) The business starts to operate within six (6) months from the date of approval or registration.

b) Business permit is renewed annually and shall expire on the 30th day of June every year.

c) The premises have been maintained and remained in conditions which led to its initial registration.

d) No change of ownership in case of natural person, business name or location without notice to the Authority.

1.2.8 Notification for Change of Registered Premises

a) Any change of location (shift of premises), trade name of the premises, ownership or any other change of registered premises, shall be by notice, made to the Director General.

b) An intention to change location of registered premises shall be made in writings to the Authority before the change is made and the Authority shall notify the applicant on the procedure to be followed.

c) The Authority shall have final say on the location and name of the proposed premises.

1.2.9 Cessation of Business

a) The Authority may at any time suspend a permit as it may determine, or revoke, or vary any provisions of such permit. Such suspension and/ or revocation shall lead the Authority to revoke the premises registration certificate.

b) Any permit that has been suspended and/ or revoked in accordance with the provision of the Tanzania Food, Drugs and Cosmetics Act, 2003 may not be renewed except with the consent of the Authority if satisfied with the reasons given by the permit holder.

c) The Authority among other reasons may issue or declare a business closed down and deleted from the register, if for any reason such premises will be found operating contrary to the prescribed requirements and standards stipulated in the Act.

d) If the proprietor wishes to close down his business because of any reason(s), he shall officially inform the Authority in advance.

e) A business that has been issued with a closure order shall surrender the premises registration certificate and business permit.

1.2.10 Refusal or Revocation of Registration Certificate and Permit

The Authority may by giving reasons refuse to register any premises, and may at any time suspend, cancel, revoke or amend premises registration certificate, permit or both.

1.2.11 Review and Appeals

a) Any person aggrieved by a decision of the Authority in relation to any application for registration of premises or permit may apply for review of the decision to the Director General.

b) The Authority may review its own decision, reject or vary the condition for approval.

c) After reconsideration of the application, if the applicant is dissatisfied by the decision for review, may appeal to Minister responsible for Health.

1.2.12 Importation of medical gases

All importation shall be in accordance with TFDCA Cap 219 of 2003 and current Regulations and Guidelines for Importation and Exportation of Medical Devices, 2016.

SECTION TWO: MANUFACTURE OF MEDICAL GASES

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.

2.1 Personnel

a) Personnel involved in manufacturing of medical gases shall have the education, training, experience or combination of these elements that will allow them to effectively discharge their responsibility.

b) There shall be an adequate number of competent personnel involved in all stages of the distribution of the products and materials in order to ensure that the quality of the products is maintained.

c) Permit to manufacture medical gases shall not be issued or renewed unless the person applying has a supervisor with bachelor degree in either of the following, Chemical and Process, Mechanical, Electrical and Electromechanical Engineering.

d) The supervisor must be registered by the Engineers Registration Board (ERB).

e) Personnel dealing with manufacture and handling (importers/distributors) of medical gases shall be given specific training.

f) Personnel involved in handling of medical gases shall wear working or protective gears suitable for the activities that they perform.

g) All personnel involved in manufacture and distribution of medicinal gases should receive an appropriate GMP training specifically applying to this type of products. They should be aware of the critically important aspects and potential hazards for patients from these products. The training programs should include the tanker lorries drivers.

h) Personnel of subcontractors that could influence the quality of medicinal gases (such as personnel in charge of maintenance of cylinders or valves) should be appropriately trained. There should be established training program and schedule, and training records should be kept as required.

2.2 Premises

a) 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 exchange of cylinders between these areas. However, it could be accepted to check, prepare, fill and store other gases in the same areas, provided they comply with the specifications of medicinal gases and that the manufacturing operations are performed according to GMP standards.

b) 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:
   i. Separate marked areas for different gases;
   ii. Clear identification and segregation of cylinders at various stages of processing (e.g. “waiting checking” "awaiting filling", "quarantine", "certified", “rejected” “prepared deliveries”).

c) 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.

d) 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.

2.3 Equipment

a) Equipment should be designed to ensure that the correct gas is filled into the correct container. There should normally be no cross connections between pipelines carrying different gases.

b) If cross connections are needed (e.g. filling equipment of mixtures), qualification should ensure that there is no risk of cross contamination between the different gases. In addition, the manifolds should be equipped with specific connections.

c) Tanks and tankers should be dedicated to a single and defined quality of gas. However medical gases may be stored or transported in the same tanks, other containers used for intermediate storage, or tankers, as the same non-medicinal gas, provided that the quality of the latter 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 performed and documented.

d) 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.

e) Attempts should be made to ensure that filling manifolds are dedicated to a single medicinal gas. In exceptional cases, filling gases used for other medical purposes on manifolds dedicated to medical gases 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 medicinal gas and GMP standards should be maintained. Filling should then be carried out by campaigns.

f) 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.

2.4 Transfers and deliveries of gases

a) Transfer lines should be equipped with non-return valves or other suitable alternatives. 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. The use of adaptors allowing the connection of tanks and tankers not dedicated to the same gases should be adequately controlled and method of control should be documented and validated.

b) Deliveries of gas 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.

2.5 Filling and labeling of cylinders

a) Before filling cylinders a batch (batches) of gas (es) should be determined, controlled according to specifications and approved for filling. In the case of

continuous processes, there should be adequate in-process controls to ensure that the gas complies with specifications.

b) Cylinders, vessels and valves should conform to appropriate technical specifications and any relevant requirements. They should be dedicated to a single medical gas or to a given mixture of medical gases. Cylinders should be colour-coded and they should preferably be fitted with minimum pressure retention valves with non-return mechanism in order to provide adequate protection against contamination.

c) Cylinders, vessels and valves should be checked before first use in production, and should be properly maintained. Where CE marked accessories are used, the maintenance should address the manufacturer's instructions.

d) Checks and maintenance operations should not affect the quality and the safety of the medical gas product. The water used for the hydrostatic pressure testing carried out on cylinders should be at least of drinking quality.

e) As part of the checks and maintenance operations, cylinders should be subject to an internal visual inspection before fitting the valve, to make sure they are not contaminated with water or other contaminants. This should be done:

   i. when they are new and initially put into medicinal gas service;
   ii. following any hydrostatic pressure test or equivalent test where the valve is removed;
   iii. whenever the valve is replaced.

f) Maintenance and repair operations of cylinders, vessels and valves are the responsibility of the manufacturer of the medicinal product. 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.

g) There should be a system to ensure the traceability of cylinders and valves. Checks to be performed before filling should include:

   i. Positive residual pressure in each cylinder;
   ii. A check to ensure that all previous batch labels have been removed;
   iii. A check that any damaged product labels have been removed and replaced;

iv. A 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. a 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.

h) 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.

i) 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 labeled.

2.6 Quality Control

a) Each batch of medical gas (cylinders, mobile cryogenic vessels, hospital tanks) should be tested in accordance with the requirements and certified. The sampling plan and the analysis to be performed should comply, in the case of cylinders with the following requirements.

b) In the case of a single medicinal 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.

c) In the case of a single medicinal 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.

d) 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.

2.7 Transportation of packaged gases

Filled gas cylinders should be protected during transportation, so that they are delivered to customers in a clean state compatible with the environment in which they will be used.

2.8 Documentation

2.8.1 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:

i. name of the product;
ii. batch number;
iii. date and time of the filling operation;
iv. Identification of the person(s) carrying out each significant step (e.g. line clearance, receipt, preparation before filling, filling etc.);
v. batch (es) reference(s) for the gas (es) used for the filling operation as referred to in section including status;
vi. equipment used e.g. filling manifold; quantity of cylinders before filling, including individual identification references and water capacity (ies);
vii. pre-filling operations performed;
viii. key parameters that are needed to ensure correct filling at standard conditions;
ix. results of appropriate checks to ensure the cylinders have been filled;
x. a sample of the batch label;
xi. specification of the finished product and results of quality control tests; quantity of rejected cylinders with individual identification references and reasons for rejections;
xii. details of any problems or unusual events, and signed authorization for any deviation from filling instructions; and
xiii. Certification statement by the qualified person, date and signature.

2.8.2 Records should be maintained for each batch of gas intended to be delivered into hospital tanks. These records should, as appropriate, include the following:

i. name of the product;
ii. batch number;

iii. date and time of the filling operation;
iv. identification of the person(s) carrying out the filling of the tank (tanker);
v. specification of the finished product and results of quality control tests ;
vi. details of any problems or unusual events, and signed authorization for any deviation from filling instructions; and
vii. certification statement by the Qualified Person, date and signature.

SECTION THREE: DOCUMENTATION FOR REGISTRATION OF MEDICAL GASES

3.1 Raw materials

3.1.1 Manufacturing and process control

a) Where applicable, the name and address of the manufacturer of raw material should be provided along with copies of licenses and certificates issued by relevant local and foreign authorities.

b) Details should be provided on the source of starting material used to produce the raw material. Detailed process flow diagram and narrative description of the process should be provided including indication of any critical points, tests and acceptance criteria used to ensure the quality and safety of the final raw material. In addition, information should also be provided on production capacity of the plant.

3.1.2 Control of raw material

a) Applicants should demonstrate that the raw material complies with the requirements of the current monograph of the major pharmacopoeia (United States Pharmacopoeia, British Pharmacopoeia or European Pharmacopoeia), applicable ISO standards or any other relevant Tanzania standards.

b) Description of the method used for testing the raw material and certificates of analysis for at least three consecutive lots of the final raw material should be provided.

3.1.3 Container Closure System

a) Details should be provided on the type, nominal volume and material of construction of the storage tanks of the raw material. Preferably, non-corrosive materials should be considered when choosing the materials of construction of the storage tanks that comes into direct contact with the raw material.

b) Applicant should indicate maximum hold time periods applicable for specific type of raw material, data should be provided to demonstrate that the proposed period has been validated.

3.1.4 Stability

In the case of highly stable gases with a long history of utilization, bibliographic data is sufficient (e.g. for oxygen).

3.2 Finished product

3.2.1 Details should be provided on the following:

i. name of the gas followed by ***medical***
ii. physical form of the product
iii. name of manufacturer,
iv. pressure and/or concentration,
v. Intended use of the gas.

3.2.2 The brief description of the containers should be included and it should specify the capacity, type of material used for the container and the reference code for the manufacturer and the supplier(s) of the containers. In addition, in the case of cylinders, the type of valve and its reference code, the suppliers and the type of valve outlet connection should be stated. In the case of cylinder bundles, the material and dimensions e.g. internal diameter used for the loop should also be provided as well as details of the outlet valves and the suppliers.

3.2.3 Manufacture

a) Name and complete address of finished product manufacturing site should be provided and it should be accompanied with a copy of the latest site master file.

b) The name of the gas, followed by the word ***medical*** must be systematically used from the time that the manufacturer designates that the finished product is for medical purposes. Where feasible, dedicated tanks should be used for the purpose of manufacture of medical gas.

c) A detailed diagram of the manufacturing process should be presented, together with the controls carried out at the different critical stages (filling and sealing) with production station that supplies each filling area clearly indicated. All packaging systems and the specification of the equipment (pumps, balances, etc) should be described and validated.

Note: Critical features:

(i) Filling: Safety features of the filling system, fill volume, control of moisture content of the gas, leakages.

(ii) Sealing: Seal integrity

3.2.4 Process Validation and/or verification

a) Validation of the cylinder filling process should be performed by a weighing (or double weighing), including the calculation of the mean, standard deviation and coefficients of variation, or by pressure if justified.

b) This validation should be conducted for all types of cylinders, critical types of containers must be included in the validation protocol. A bracketing approach may be used as a function of the capacity, material used for construction and whether fitted with a built-in pressure regulator or a residual pressure valve.

c) Validation can be performed by determining the amount of gas contained in a cylinder compared with a reference cylinder filled with the charge of gas to avoid the problems of fluctuations in pressure as a function of temperature.

d) The reproducibility of filling should also be verified whatever the composition of the finished product batch (homogenous or heterogeneous).

e) The integrity of the filling system to indicate leak tightness to prevent possible contamination of the system under vacuum.

3.2.5 Control of finished product

3.2.5.1 Specifications

i. For finished products containing a single gas, the specifications of the finished product are at least the same as those of the raw material.

ii. The control of the finished product should be according to the monograph in force or using validated methods if shown to be equivalent. Specifications should at least include tests for identity, assay and purity, the appearance of the cylinders, the labeling and the pressure (for cylinders and cylinder bundles).

iii. The control of the filling charge can be performed during packaging and the control of air- tightness after filling.

3.2.5.2 Analytical Procedures

i. Analytical procedures for control of the finished product should be described in sufficient details to enable the repeat of analysis in another laboratory. Where the product is subject to major international pharmacopoeia or ISO standard, reference to the relevant standard will suffice.

ii. In the case of impurities that are preferentially present in the gaseous phase and eliminated to a large extent during the first drawing off (e.g. nitric oxide in medical nitrous oxide), the order of analyses should be clearly specified. The interval elapsed between manufacture and the control of the finished product should be indicated.

3.2.5.3 Batch Analyses

In the case of cylinders, the batch analysis certificate shall state:-

i. the batch number,
ii. the batch composition and size (the batches are often heterogeneous),
iii. the source of the starting materials,
iv. the number of the cylinder controlled,
v. the capacity of the cylinder controlled,
vi. the value for the charge of the cylinder controlled compared to its theoretical charge to indicate if the analysis was performed at the start, middle or end of cylinder utilization, expressed as pressure (compressed gas)),
vii. the phase analyzed,
viii. the specifications,
ix. the date of analysis,
x. the date of manufacture,
xi. the signature of the relevant person,
xii. place of manufacture.

3.2.5.4 Container Closure System

a) A variety of reference codes exist, dependant on the supplier, capacity and material, particularly in the case of cylinders. For each reference and each capacity, the water capacity of the container (in L), the amount of gaseous product released at 1atm and $15^{o}C$ (in m^{3}), and the weight of product stored (in g for compressed gases or in kg for liquefied gases) should be provided, together with the accepted deviations.

b) The type of safety device (valves or rupture disks) relating to excess pressure should be specified and located (valves or containers with pressure calibration). In the case of valves and outlets, a diagram summarizing the nature of the different constituents should be provided. The method of opening the tap (quarter turn, half-turn, progressive wheel, etc.) the type of standardized outlet connection and the type of gasket and valve used should be specified.

c) In the case of cylinders with a built-in pressure regulator, the number and the valve positions of the flow-meter and the corresponding accuracies should be documented. The specific tests for these cylinders should consist in gas compatibility, adiabatic compression, internal and external air-tightness, endurance test, cap shock resistance, fire-resistance, valve safety, shock vibration, output precision, etc.

d) The containers should comply with the specifications of existing national, European (CEN) or international (ISO) standards concerning equipment intended to contain and deliver gases. The certificate of compliance with the standards in force should also be provided.

e) Information should be provided to demonstrate that cylinders are tested by the suppliers before delivery to finished product manufacturer, and the later has mechanism in place to ensure conformance of the cylinders at delivery, refilling and at indicated re-test period of the cylinder. Test results should be submitted at registration and it should also be availed during inspections and post marketing surveillance.

f) The labeling should be made to allow clear distinction between cylinders for medical use and other cylinders (laboratory gas, welding gas, etc.). The labeling should state ***reserved for medical use***.

3.2.5.5 Stability of the finished product

a) Specific storage conditions should be proposed by the applicant based on properties of the constituent gas. Where necessary as it may be the case of gas mixtures specific shelf life should be specified by the manufacturer.

b) The influence of temperature can only be studied on small cylinders placed in special ovens and under accelerated aging conditions, on condition that they are of the same composition and fitted with the same valves and gaskets. The influence on stability of opening/closing cycles and the decrease in pressure with utilization should also be studied. In the case of very stable gases that have been used for a long time and packaged in containers that have also been used for a long time, bibliographic data is sufficient.

SECTION FOUR: LABELLING REQUIREMENTS

4.1 Particulars in the label shall be easily legible clearly comprehensible and indelible. The labeling must be presented in English and/or Kiswahili. Appropriate placement of the label should ensure access and visibility to all users.

4.2 Labeling information should be provided to all medical gas containers including

a) Cylinders
b) Cylinder bundles or pallets
c) Road tankers
d) Liquid storage tanks

4.3 Product identification labels for other containers such as bulk liquid tankers should be placed in a prominent position, either on the bodies of the containers or on metal panels affixed to the containers.

4.4 Depending on the type of the medical gas containers, the following minimum information should be provided on the label:-

i. Name and physical address of manufacturer
ii. Batch and Serial number
iii. Production / fill date
iv. Expiry date (where applicable)
v. In case of hospital production, the contact details of person in charge of the product should be indicated
vi. Brand and common name of the product
vii. Hazard identification or pictogram
viii. Hazard statement
ix. Precautionary statement
x. Color code of the gas type
xi. Storage condition based on the properties of the gas

Note:

Below information should be stated under:

(a) Hazard statement:

i. May cause or intensify fire
ii. Contains gas under pressure; may explode if heated

(b) Precautionary statement:

i. Keep away from clothing or other combustible materials
ii. Keep reduction valves free from grease or oil
iii. In case of fire, stop leak if safe to do so
iv. Protect from sunlight; store in well ventilated place

Requirements that have been prescribed in the ISO Standard of the medical gas labeling should be followed.

SECTION FIVE: OTHER REQUIREMENTS

5.1 Handling of medical gases

a) 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.

b) Medical gases shall be received and examined for correctness against an order (where applicable).

c) 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).

d) Products shall be stored in accordance with manufacturer's instructions and relevant guidelines and shall be arranged in a logical manner.

5.2 Storage area

a) Precautions must be taken to prevent unauthorized persons from entering storage area.

b) Where controlled environmental storage conditions are required, these conditions should be continuously monitored and documented. 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.

c) Storage area shall be clean, dry and free from accumulated wastes, 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.

d) Products shall be stored off the floor and suitably spaced to permit cleaning and inspection. Pallets shall be kept in a good state of cleanliness and repair.

e) Gases shall be stored in a dedicated area that is subject to appropriate additional safety and security measures.

5.3 Transportation and deliveries to customers

5.3.1 Products shall be transported in such a way that:

a) Their identification is not lost e.g. Label
b) They do not contaminate and are not contaminated by other products or materials.
c) Adequate precautions are taken against spillage, breakage, or theft.
d) They are secured and not subjected to unacceptable degree of heat, cold, light, moisture or other adverse influence, or attacked by microorganisms or pests.

5.3.2 All cylinders shall be transported vertically.

5.3.3 All vehicles for carriage or transportation of medical gases shall be approved by TFDA. Application for permit shall be made in prescribed form (Annex ….).

5.3.4 Medical gases requiring controlled temperature storage should be transported by appropriate or specialized means e.g. liquid oxygen. The use of temperature monitoring devices during delivery is recommended and such records should be maintained.

5.4 Handling of returned product(s)

5.4.1 All returned products should be kept apart to prevent redistribution until a decision has been reached regarding their disposal.

5.4.2 Medical gases should only be returned to saleable stock if:-

a) They are in their original cylinders and in good condition;
b) It is known that gases have been stored and handled under proper conditions and the remaining shelf life period is acceptable.
c) The products have been examined and assessed by appropriate personnel.
d) The returned products should be formally released to saleable stock by a nominated, responsible person following a satisfactory quality re-evaluation.

5.4.3 Reconditioning, re-packaging or re-labeling of the products shall not be carried out by any distributor unless they hold a license for such activity issued by the authority.

5.5 Substandard and falsified products

5.5.1 If there is a suspected substandard or falsified product Market authorization holder and TFDA should be informed immediately and the distribution chain shall be kept halted and the product should be clearly labeled “Not for Sale”.

5.5.2 Upon confirmation of the products to be substandard / falsified, recall procedures should be instituted and followed by destruction.

5.6 Recalls and withdrawal

5.6.1 Products known or suspected to be defective shall be recalled from the market. A progress report on the recall level shall be submitted to TFDA weekly following the directive from the Authority.

5.6.2 In case of recall of product initiated by the dealer himself, the Authority shall be notified on the reason for recall.

5.6.3 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. quantity, common name, manufacturer, manufacture and expiry dates and batch/lot/serial number.

5.6.4 All actions taken in connection with the recall must be approved by the company and the Authority and recorded.

5.6.5 Upon completion of the recalls, a final report must be provided to the Authority. Reconciliation should be made between delivered and recovered quantities of the products.

5.7 Handling of product complaints

5.7.1 There should be a system of receiving, evaluating and classifying complaints. Complaints relating to the wholesaler's own activity shall be evaluated and measures taken, where appropriate to prevent their recurrence.

a) 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.

b) 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.).

c) 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.

d) Complaint should be reported to the Authority using telephone, email or letter by describing its type, nature and adverse event.

e) Adverse events regarding the products can also be reported through TFDA electronic system for reporting ADRs at www.tfda.go.tz/adr.

5.8 Documentation

5.8.1 There shall be written procedures for production, receiving, storage, dispatch, transportation, recalled, returned, expired, complaints, substandard, falsified products and ADR /AE or AI.

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

a) TFDA inspection reports file;
b) complaints handling book;
c) unfit products register;
d) controlled gases register;
e) recall register;
f) final invoices with corresponding import permits;
g) copies of delivery notes;
h) Sales invoices with batch/lot numbers.

5.8.3 The records referred above shall be kept and maintained within the premises for a period of not less than five (5) years.

5.8.4 All documents shall be completed, approved, signed (as required) and dated by an appropriate authorized person(s) and shall not be changed without the necessary authorization.

5.9 Electronic data

5.9.1 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.

5.9.2 Only authorized personnel should be allowed to enter or modify data in the computer. 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.

5.9.3 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")

5.9.4 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.

5.10 Disposal of products

Expired, damaged, substandard, falsified products shall be disposed off at the manufacturing site under supervision of the Authority.

SECTION SIX: ANNEXES

ANNEX 1: SAFETY SYMBOLS OF MEDICAL GASES

Smoking
Never let anybody smoke in a vehicle when carrying gas cylinders. This includes everybody - not just the driver. Ignition of a flammable gas following a leak could be catastrophic. Oxidizing gases 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 healthy 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. Transport in an open vehicle.

Fire
It is mandatory to carry a fire extinguisher if at work. The driver is to be trained in its use. A 2 kg dry powder extinguisher is the minimum requirement. Strongly recommended for personal use.

Keep your cylinders secure
Cylinder storage
Cylinders are to be securely stowed, preferably in the luggage area.If involved

All valves are to be closed
Ensure the valves are closed on all cylinders. Check there are no leaks. Disconnect and remove any ancillary equipment.

Legal requirements
It is the driver's responsibility to ensure their vehicle is safe. The driver should have appropriate training and knowledge about the gases being carried and understand the basic actions required in the event of an emergency.

Documents
The driver does not need to carry any special documents to transport small quantities of gas cylinders. However, it is useful to have the right information to assist the emergency services in the event of an incident. See 'Helping the emergency services'.

Signs on your vehicle
You are not required to display any hazard warning labels or signs on your vehicles if you are only carrying small quantities of gas cylinders.

Insurance for the vehicle
Make sure you have informed your insurance company that you are carrying gas cylinders on the vehicle.

ANNEX II: APPLICATION FORM

TANZANIA FOOD AND DRUGS AUTHORITY

APPLICATION FORM FOR REGISTRATION OF PREMISES AND BUSINESS PERMIT

(Made under Regulation 5(1) of the Tanzania Food, Drugs and Cosmetics (Registration of Premises, Importation and Exportation of Medicine Products and Raw materials) Regulations. 2015)

Director General
Tanzania Food and Drugs Authority
P.O. Box 77150
Dar es Salaam

SECTION A: APPLICANT INFORMATION

I / We hereby apply for registration of my/our existing/ new premises and business permit in accordance with the Tanzania Food, Drugs and Cosmetics Act, Cap 219

1. Name of applicant.....
2. Postal address.....Tel, No.....Fax.....Email.....
3. In case of

(a) *Corporate body; name of Directors.....

(b) *Partnership; name of Partners.....

(c) Joint venture; name of Consortium.....

4. Situated at/lying between Plot /Vessel/ Truck No .....
.....Street/Village/Ward.....District/Municipality/City
5. Premises to be registered for the business of
.....

6. The importation business will be under the Superintendent, Mr /Ms /Mrs. /Dr. /Prof (Full name).....who is a Pharmacist and his/her registration number is .....of .....(Year). (Please attach a copy of registration certificate and contract agreement)

7. The proposed name of the premises is .....

SECTION B: DECLARATION BY APPLICANT

8. I/we.....have not been convicted for any offence relating to any provision of the Tanzania Food, Drugs and Cosmetics Act, Cap 219 and Regulations made there under or any other written law related to the business being

applied for within 12 months immediately preceding this application neither disqualified nor suspended.

N.B. False declaration constitutes an offence.

Date…… Signed……

Applicant
* Attach Certificate of Incorporation

ANNEX III: VIGILANCE FORMS

TFDA Tanzania Food & Drugs Authority	**MEDICAL DEVICES ADVERSE EVENT/INCIDENT REPORTING FORM FOR CONSUMERS AND HEALTH FACILITIES**	**TFDA/DMC/MDR/F/009 Rev #:1**

Identities of reporter, patient and institution will remain confidential

TFDA Internal Use Only	
Report Number:	Date received:

1. Device details	
Full name (Brand and Common):	Type of device:
Manufacturing date:	Serial number:
Expiry date:	Batch number/lot number:
Manufacturer name :	Address:
Source of device (1)Hospital (2)Store (3)Other, please give details	Name/Area
Current location of the device:	

2. Event/Incident details	Date of event/incident:	
Type of incident(patient related):☐Death ☐Life threatening ☐ Caused persistent disability or incapacity☐ Required or prolonged hospitalization ☐Other, please give details:		
Type of incident(device related): ☐ Inadequate design ☐Inaccurate labeling/instruction for use☐Malfunction ☐Deterioration ☐Other, please give details:		
Event/Incident description narrative (explain what went wrong with the product):		
Number of medical devices involved:		
Number of patients involved:		
Operator at the time of event/incident Please (√) where required	☐ Medical practitioner	☐Other, Please give details:

TFDA Tanzania Food & Drugs Authority	**MEDICAL DEVICES ADVERSE EVENT/INCIDENT REPORTING FORM FOR CONSUMERS AND HEALTH FACILITIES**	**TFDA/DMC/MDR/F/009 Rev #:1**

Measures taken by the user:		
Have you informed the supplier/ manufacturer?	☐Yes ☐No	Date:

3.Reporter details	
Name of Reporter:	
Address:	Street:
City:	District/Region:
Telephone/Mobile phone:	
Email of contact person:	
Date of report:	

Send to:

The Director General,
Tanzania Food and Drugs Authority (TFDA),
P.O.Box 77150,Nelson Mandela Road, Mabibo External,
Dar Es Salaam, Tanzania
Tel: +255 22 2450512 / 24507551
+255685701735/743110375
Email: info@tfda.go.tz
Website: www.tfda.go.tz

TFDA Tanzania Food & Drugs Authority	**MEDICAL DEVICES ADVERSE EVENT/INCIDENT REPORTING FORM FOR IMPORTER/MANUFACTURER**	**TFDA/DMC/MDR/F/010 Rev #:1**

Identities of reporter, patient and institution shall remain confidential.

TFDA Internal Use Only	
Report Number:	Date received:
1. Contact details of the reporting company	
Name of company:	Importer/Manufacturer (Please specify):
Postal address:	Street Name:
City:	District/Region:
Tel: Mob:	Fax:
Name and position of contact person:	
Email of contact person:	
2. Device details	
Full name (common and brand name):	
Model number (where applicable):	Serial /batch /lot number:
Manufacturing date:	Expiry date (where applicable):
Name of associated devices/accessories:	
Name of shop where the device was purchased:	
Manufacturer name and address:	
3. Event/Incident details	
Event/Incident description narrative (explain what went wrong with the device and the observed or likely/probable consequences):	
Date :	Place of the event/incident:
Number of users involved:	
Number of devices involved:	

TFDA Tanzania Food & Drugs Authority	**MEDICAL DEVICES ADVERSE EVENT/INCIDENT REPORTING FORM FOR IMPORTER/MANUFACTURER**	**TFDA/DMC/MDR/F/010 Rev #:1**

Place where event/incident occurred:		
For IVDs Please specify type of specimen used		
Have you informed the manufacturer/Importer?	☐Yes ☐No	Date:
Measures taken by the Importer/supplier:		
Date of report:		

The Director General,
Tanzania Food and Drugs Authority (TFDA),
P.O.Box 77150,Nelson Mandela Road, Mabibo External,
Dar Es Salaam, Tanzania
Tel: +255 22 2450512 / 24507551
+255685701735/743110375
Email: info@tfda.go.tz
Website: www.tfda.go.tz

TFDA Tanzania Food & Drugs Authority	**FOMU YA KUTOLEA TAARIFA YA MADHARA/TUKIO LILILOTOKANA NA MATUMIZI YA KIFAA TIBA KWA MTUMIAJI (BINAFSI/KITUO CHA KUTOLEA HUDUMA)**	**TFDA/DMC/MDR/F/011 Rev #:01**

Jina la mtoataarifa/ mgonjwa/ taasisilitabakikuwasiri

Kwa matumizi ya TFDA tu	
Namba ya taarifa:	Tarehe ya kupokelewa:

1. Taarifa za kifaa tiba	
Jina kamili:	Aina ya kifaa:
Tarehe ya kutengenezwa:	Namba ya kifaa:
Tarehe y a mwisho wa matumizi:	Namba ya toleo:
Jina la mtengenezaji :	Anuani:
Kifaa hik i kimepatik ana Hospitali ☐ Dukani ☐ Nyingine (taja) ☐	Jina/Eneo:
Sehemu ambapo kifaa kipo kwa sasa:	

2. Taarifa za madhara/tukio	Tarehe ya madhara/tukio:
Aina ya madhara/tukio (kwa mtumiaji): ☐ Kifo ☐ Mtumiaji angeweza kupote za maisha ☐ Mtumiaji alipata ulemavu ☐ Mtumiaji alilazwa hospitali ☐ Mengine (Eleza):	
Aina ya Madhara/tukio (katika kifaa): ☐ Upungufu kwenye utengenezaji ☐ Uchache/kukosekana kwa taarifa za kifaa ☐ Kuharibika ☐ Kupungua ubora ☐ Mengine (Eleza):	
Ufafanuzi wa madhara/tukio:	
Idad iya watumiaji wa liohusika:	
Idadi ya vifaa tiba vilivyohusika:	

TFDA Tanzania Food & Drugs Authority	**FOMU YA KUTOLEA TAARIFA YA MADHARA/TUKIO LILILOTOKANA NA MATUMIZI YA KIFAA TIBA KWA MTUMIAJI (BINAFSI/KITUO CHA KUTOLEA HUDUMA)**	**TFDA/DMC/MDR/F/011 Rev #:01**

Mtumiaji wakati madhara/tukio linatokea. (Wekaalama (√)panapohusika)	☐ Mtaalam wa afya ☐ Mwingine (Eleza):	
Hatua zilizochukuliwa na mtumiaji:		
Je umemjulisha Msambazaji/Mtengenezaji?	☐ Ndiyo ☐ Hapana	Tarehe:

3.Taarifa za mtoa taarifa (sio lazima)	
Jina la mtoa taarifa:	
Anuani:	Mtaa:
Mji:	Wilaya/Mkoa:
Nambayasimu:	
Baruapepe:	
Tareheyataarifa:	

Tuma kwa:

Mkurugenzi Mkuu,
Mamlaka ya Chakula na Dawa (TFDA),
S.L.P 77150 Mabibo External, Barabara ya Nelson Mandela,
Dar Es Salaam
Simu: +255 22 2450512 / 24507551
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