Ethiopian Food and Drug Authority (EFDA)

Medicine Evaluation and Marketing Authorization Led Executive office

Guideline for Medical gas Evaluation and Marketing Authorization

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Seble Shambel

Contents

Acronyms

EFDA Ethiopian Food and Drugs Authority

API Active Pharmaceutical ingredient

MA Marketing Authorization

WHO World Health organization

GMP Good manufacturing practice

GDP Good distribution practice

ADE Adverse drug event

1. Introduction

Medicinal gases, like other medicinal products, are required to have a Marketing Authorization (product license) in order to be sold. The Marketing Authorization (MA) defines the quality specification, when a gas can be used and how it should be administered to a patient. According to article 20(1) of the Food and Medicine Administration Proclamation No. 1112/2019, any medicines shall not be manufactured and imported for use by the public without registration and marketing authorization except with emergency situation.

In addition, the national medical oxygen roadmap II (2022-2027) clearly stated that EFDA need to develop a system for medical oxygen registration.

Therefore, for any medicine to be distributed in to the territory of Ethiopia, it requires a marketing authorization certificates from the EFDA. To get such approval, dossier assessment and endorsement is one of a prerequisite.

This guideline deals with the specific aspects in relation to medicinal gases and document describes the requirements governing the documentation obligation for the authorization of medicinal gases

The aim of the present guideline is to specify the elements relating to the quality of medicinal gases in the context of compiling the pharmaceutical documentation for Module III (Quality) of the dossier.

The MA covers the gas and its primary packing (container including the valve), but not the equipment attached later to the container at the time of use, which falls into the medical device domain *(e.g., pressure regulator and pipe network).* A valve/built-in pressure regulator assembly that cannot be separated from the cylinder is part of the MA.

Gases produced *in situ* in hospitals i.e., manufacturing processes undertaken in or by the hospitals and home care containers of gases are not in the scope of this guideline.

An application for the marketing authorization (MA) of a medicinal gas or mixture of gases should not differ significantly from that of other medicinal products.

2. Definition

1) Medicinal gas API including bulk liquid and compressed gaseous form in containers/tankers.
2) Medicinal gases are gases or gas mixtures intended for the administration to patients for medicinal purpose such as anesthetic, therapeutic, prophylactic and diagnostic use. Medicinal gases are classified into two categories as below:
    a) Medicinal gases classified as a medicinal product / drug is Gases or gas mixtures which mode of action is achieved primarily based on pharmacological, immunological or metabolic action in/on the body, such as gases for hypoxia (oxygen gas). Gases designated for therapeuticmust undergo rigorous testing and meet standards before use. The U.S. Pharmacopeia (USP) provides the purification specifications manufacturers must abide by to distribute their products for human use. Medicinal gases(therapeutic) gases include Oxygen, Nitrogen, nitrous oxide(N_2O), mixture of nitrous oxide and oxygen, Nitric oxide (NO), Mixture of Nitric oxide with oxygen, Carbon oxide, mixture of carbon dioxide with oxygen, medical air (consisting largely of NMT 23.5% oxygen and NLT 19.5% nitrogen) and Helium, mixture of helium with oxygen.
    b) Medicinal gases classified as medical device is Gases or gas mixtures which mode of action is achieved primarily by physical in nature and not achieved primarily based on pharmacological, immunological or metabolic action in/on the body, such as gases for insufflations of the abdominal cavity for laparoscopy and gases for removal of warts (e.g. liquid nitrogen).
3) Medicinal gas product (classified as a medicinal product/drug) means medicinal gas finished product that has undergone all stages of production and quality control, including packaging in its final container and labeling. Gases falling under the definition of medicinal product and filled in gas cylinders in a manufacturing plant is considered as medicinal gas product.
4) **Air separation:** Separation of atmospheric air into its constituent gases using fractional distillation at cryogenic temperatures.

5) **Compressed gas:** Gas which, when packaged under pressure for transport, is entirely gaseous at all temperatures above –50°C.
6) **Container:** A container is a cryogenic vessel (tank, tanker or other type of mobile cryogenic vessel) a cylinder, a cylinder bundle or any other package that is in direct contact with the gas.
7) **Cryogenic gas:** A gas which liquefies at 1.013 bar at temperatures below –150°C.
8) **Cylinder:** 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.
9) **Gas:** Any substance that is completely gaseous at 1.013 bar and +20°C or has a vapour pressure exceeding 3 bar at +50°C.
10) **Hydrostatic pressure test:** 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.
11) **Liquefied gas:** A gas which, when packaged for transport, is partially liquid (or solid) at a temperature above –50OC.
12) **Maximum theoretical residual impurity:** Gaseous impurity from a possible backflow that remains after the cylinder pre-treatment process before filling. The calculation of the maximum theoretical residual impurity is only relevant for compressed gases and assumes that the gases behave as perfect gases.
13) **High Pressure Liquefied Gas:** a gas with a critical temperature between -50 °C and +65°C.
14) **The tolerable deviation rate:** the max allowable difference
15) **Posology:** the posology of a gas is not expressed as a weight but as the concentration of gas mixture, which is related to gas administration output
16) **Cylinder Bundle:** an assembly of cylinders, which are fastened together in a frame and interconnected by a manifold, transported and used as a unit.
17) **Filling Ratio:** 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.

3. Scope

The scope covers medicinal gas classified as a medicinal product and which are manufactured and used for medical purpose filled in containers

This guideline does not apply to other types of gases such as:

i) Gases classified as medical devices

ii) Gases that are manufactured, mixed and handled (including extemporaneous preparation) in hospitals for own patients use.

iii) Gases for animal use (veterinary)

iv) Gases use for cosmetic/aesthetic purpose.

v) Gases use in laboratory (e.g., gas for freezing of tissue samples, calibration gas)

vi) Recreational gases (e.g., oxygen gas for diving, mountain climbing)

vii) Industrial gases

viii) This guideline also does not apply to cylinders on its own (empty cylinders).

4. Registration requirement for generic medicinal gases product

In general, registration procedures and general requirements for medicinal gases are similar to other pharmaceutical products as described in medicine registration guidelines of EFDA.

Risk-based dossier assessment approach is one of the strategic directions of the regulatory authority to expedite marketing authorization process and its implementation requires classification of products in to low and high-risk category so as to proportionate risks during dossier assessment. For low-risk medicines, the evaluation process will be limited to a 'partial review of the product dossier; concentrating on the assessment of administrative requirements, product information, specifications, stability and shelf life, and others as applicable. However, full and rigorous dossier assessment might be conducted for a product designated as low risk if there is satisfactory reason for in-depth evaluation.

Accordingly, medical gases can be considered as low risk medical products Specific requirements for registration for medicinal gases are indicated as below.

MODULE 1: ADMINSTRATIVE AND PRODUCT INFORMATION

The general formal requirements for documents and the requirements for Module 1 are similar and as specified in medicine registration guidelines of EFDA.

The safety rules and special conditions of storage, transport and utilization shall be summarized in the SmPC, packaging slip and labeling plans

An application for new marketing authorization of medicinal gases should be submitted on-line through the (https://www.eris.efda.gov.et/) through low-risk medicine application pathway.

MODULE 3: DRUG SUBSTANCE(S)/Active substance

S- MANUFACTURE OF ACTIVE SUBSTANCE GASES

Active substance gases can be prepared by chemical synthesis or be obtained from natural sources followed by purification steps, if necessary (as for example in an air separation plant).

The requirements regarding starting materials for active substances do not apply to the production of active substance gases by air separation (however, the manufacturer should ensure that the quality of ambient air is suitable for the established process and any changes in the quality of ambient air do not affect the quality of the active substance gas);

Active substance is gases and gas mixtures (particularly of known origin and quality) which are manufactured, stored and distributed under GMP conditions and traded under GDP conditions.

However, an active substance can become a medicinal product by appropriate technical processes and the designation or presentation of the gas or gas mixture as having a medicinal effect.

Manufacturers can issue active substances to authorized recipients accompanied by a corresponding certificate of analysis and GMP certificate. Active substances are not subject to authorization.

For part S – ACTIVE SUBSTANCE international pharmacopeia like EP, USP, JP, BP, IP-WHO, other internationals standards and Ethiopian standards should be also considered and recognized by this guideline. It considers Ethiopian IES (institute of Ethiopian standards) approved medicinal gas standards.

S -STABILITY

The stability of the active substance should be demonstrated by stability studies. In particular, degradation products are described. If the finished product is a mixture of gases, the reciprocal chemical reactivity of these gases should be documented. In the case of highly stable gases with a long history of utilization, bibliographic data is sufficient *(e.g., for oxygen).*

The requirements regarding on-going stability studies, which are used to confirm storage conditions and expiry/retest dates, do not apply in case initial stability studies have been replaced by bibliographic data. The quality of liquid gas such as purity efficacy and safety of liquified gases that converted and refilled in gas should be maintained

MODULE 3: DRUG PRODUCT (P)

P1 – DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Medicinal gases consist of active substances or of a mixture of active substances and gaseous excipients.

Mixtures can consist of one or more active substances or one active substance diluted in a gaseous excipient. The percentage formula (v/v) and the deliverable volumes should be provided, together with the tolerated deviations. The density or the compressibility factor for each gas and for the mixture under standard conditions (15^{o}C, 1 atm) is provided as scientific data. These data

make it possible to establish the relationship between concentration values expressed as pressure (15ºC), volume (15ºC, 1 atm) and weight, which nevertheless, are quoted.

For each gas, the MA should include details of the physical state, the pressure of compressed gases (15ºC), the type of container and, in case of mixtures, and the concentration of the active substance. Containers that have different types of valves can be included in the same MA.

The names should comply with the EFDA recognized Pharmacopoeia monograph and are completed with the following information:

i. name of the gas followed by medicinal or invented name
ii. physical form of the product
iii. name of manufacturer,
iv. pressure and/or concentration,
v. gas for inhalation, etc.
vi. in a cylinder, in a cylinder bundle in a mobile evaporator, for a fixed evaporator, in a mobile cryogenic container, for a fixed cryogenic container, and that may correspond to separate MAs.

Cylinder/cylinder bundle are included in the same MA. Mobile evaporator/mobile cryogenic container is included in the same MA. Fixed evaporator/fixed cryogenic containers are included in the same MA.

CONTAINER

The brief description of the containers 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 are stated.

In the case of cylinder bundles, the material and dimensions e.g., internal diameter used for the loop are provided. The outlet valves and the suppliers are provided. The containers color should be as per the Ethiopian medicinal gas standards.

This information can be provided as a table. Table to be inserted.

P2 PHARMACEUTICAL DEVELOPMENT

Physical properties of gases

The physical properties of the gases concerned should be stated, together with the relevant laws that govern them (e.g., law on perfect gases).

On this basis, the principle of the manufacturing method chosen by the manufacturer is explained and justified.

The manufacturer should take into account the physical properties of the gases and the container compatibilities.

Single Gases

Due to the long use of medicinal gases, this part may be presented as bibliographical data. Thus, this heading is limited to a brief overview of the historic development of gas pressure equipment.

In addressing the compatibilities of gas with packaging materials the following issues are to be considered:

- The compatibility of the packaging/container material with gas of recent utilization or limited stability. This information will also serve to formulate recommendations concerning equipment for administration.
- The choice of new packaging components, especially the valves, the most fragile part of the cylinder, especially in terms of air-tightness (e.g. residual pressure valves).
- The use of new materials and their gas compatibility (alloys for container shells, plastic materials for valves, etc.).
- Container filling at a pressure not previously used in the medicinal field for this type of container.
- The suitability of the container capacity or the concentration of active ingredient for the posology for gases of limited stability. It should be remembered that the posology of a gas is not expressed as a weight, but as the concentration of gas mixture inhaled which is related to gas administration output.

- The suitability of large capacity cylinders (> 20 L), given the difficulty in handling them, the risks to the safety of personnel and the patient and the difficulty in eliminating traces of water if the valve remains open during the storage.
- The diversity of cylinders used, if they have very different capacities and dimensions and are of different materials.

Mixtures

In some cases, only one gas may be considered as the active substance and the other as excipient. The choice of the excipient gas is justified particularly if this is a new gas or a new combination.

The compatibility between the gases is documented, taking into account their different physical properties and their chemical reactivities. In the case of liquefied gases, the composition and homogeneity of the different superimposed layers of the mixture are described along with their controls, especially at the level of the outlet of the dispensing system.

Thus, the following points should be addressed:

- stability of the gases during the different stages of the manufacturing process as a function of their conditions of storage, transport and handling,
- chemical and physical compatibility between the gases,
- Physical stability and homogeneity of the gas mixture under different conditions of storage and utilization (pressure and output). In the case of gas mixtures that are not very stable, especially mixtures of liquefied gas and permanent gas that can separate at low temperatures, the measures proposed are described and validated *(conditions of storage and transport,* rehomogenisation procedure),
- homogeneity of the gas mixture delivered by the dispensing system, taking into account the varied conditions and duration of storage,
- compatibility and suitability of the packaging,
- justification of the choice of manufacturing procedure, taking the preceding factors into account,
- Highlighting of the critical points of the manufacturing procedure that should be taken into account for its validation.

P3 MANUFACTURE

The name of the gas, followed by medicinal must be systematically used from the time that reference is made to the product being the responsibility of the pharmaceutical establishment so as to clearly delimit the gas to the medicinal field.

Manufacture consists of the operations of division or distribution and filling into dedicated pharmaceutical and medicinal packaging. Packaging is often automated and may include prior modification of the physical state of the gas (vaporization by heating of liquefied gas and compression). It may also include one or several successive mixing operations (by weight or nanometrically, with or without homogenization).

A detailed diagram of the manufacturing process is presented, together with the controls carried out at the different stages.

The production station that supplies each filling area is indicated.

The automated packaging system or mixing systems and the specification of the equipment (pumps, balances, etc) should be described and validated.

P 3.5 PROCESS VALIDATION AND/OR EVALUATION

General case: containers of single gases

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

This validation should ideally be presented for all types of cylinders, but at least for critical types of containers. 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. If needs be, for each type of alloy used, a single validation can be performed on one cylinder of this alloy, on the condition that this is justified.

Validation can be also 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.

The reproducibility of filling is also verified whatever the composition of the finished product batch *(homogenous or heterogeneous).*

For compressed gases, the temperature and pressure stabilization time after filling which depends upon various capacities, nature of material, thermal exchange, ambient temperature (and any variation in it during the stabilization time), rate of filling of the cylinder, airflow over the cylinder and its proximity to any adjacent filled cylinders is specified, unless otherwise justified.

Cylinders, which have been returned for filling, are prepared in accordance with the GMP guideline for medical gases (EFDA or WHO).

The integrity of the filling system to indicate leak tightness to prevent possible contamination of the system under vacuum or an estimate of the yield accounted for losses as an annual average is provided.

The tolerated limits of temperature and pressure are provided *(specifying especially the hydrostatic pressure test and the bursting pressure of the cylinder).* On the safety level, any problems of possible overload of compressed or liquefied gas are addressed.

Other containers for single gases

In the case of cylinder bundles and mobile evaporators, validation of the filling procedure is also performed by weighing or by pressure if justified.

In the case of fixed evaporators, validation can consist of the absence of impurity enrichment due to the formation of degradation products with time, to trapping because of the temperature and to transfers from one container to another during the manufacturing process or during sampling. It is specified whether the impurities remain at the same proportions between the gaseous and liquid phases as the container is emptied. The minimal threshold for filling the fixed evaporator is specified to avoid any risk of impurity enrichment.

Thus, scientific data are provided for:

- a theoretical evaluation of the level of impurity enrichment during blowing down/filling cycles for a cryogenic container,
- an analysis of liquid phase samples (performed on the dedicated tank in the filling area or on the dedicated tank in the production station annex) and of gaseous and liquid phase samples (performed on fixed hospital evaporators), supported by a comprehensive list of potential impurities.

Gas Mixtures

In the case of mixtures, validation is concerned with the manufacturing operation for the mixture considered. It should take into account all the critical parameters of the manufacturing process and especially discuss reproducibility in the case of manual cylinder-by-cylinder filling, the role of the nature of the phase and of the temperature of each gas when introduced into the cylinder and the homogenization conditions. The successive physical states of each gas and of the gas mixture during filling are indicated. A phase diagram is provided.

Validation can also be concerned with other types of mixtures.

In the case of the manufacture of an intermediate product, its validation is carried out under the same conditions and using the same methodology.

P5 CONTROL OF DRUG PRODUCT

P5.1. SPECIFICATION

In the case of a single gas, the specifications of the finished product are at least the same as those of the starting material.

In the case of mixtures, the specifications chosen for the starting materials, any intermediate products and the finished product are consistent *(taking into account, for example, dilution factors for the active substances).*

The control of the finished product consists of the control according to international pharmacopeia like EP, USP, JP, BP, IP-WHO, other internationals standards and Ethiopian standards. The monograph in force or using validated methods if it is shown to be equivalent (identity, assay, and purity), the appearance of the cylinders, the labelling and the pressure (for

cylinders and cylinder bundles). All the constituents of the mixture are identified including excipients. The different constituents of the mixture are assayed, unless otherwise justified.

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

P5.2. ANALYTICAL PROCEDURES

Analytical procedures are fundamental in ensuring that the medicinal gases produced meet the required specifications of identity, purity, assay and others unspecified test parameters

The analytical methods should be validated/verified to ensure the methods suitable for their intended purpose and provide accurate and reliable results.

In the case of liquefied gases, the nature of the phase *(liquid or gaseous)* is indicated, as is the method of sampling for the control. 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 is specified.

The interval elapsed between manufacture and the control of the finished product is indicated according to the recognized pharmacopeia by EFDA like European Pharmacopoeia and others. In the case of gases of limited stability, it is specified whether a second control, performed sometime after the first to detect the appearance of impurities, is necessary.

P5.4. BATCH ANALYSES

In the case of cylinders, the batch analysis certificate will state**:**

- the batch number,
- the batch composition and size *(the batches are often heterogeneous)*,
- the source of the starting materials,
- the number of the container controlled,
- the capacity of the container controlled,

- the value for the charge of the container controlled compared to its theoretical charge so as to indicate if the analysis was performed at the start, middle or end of cylinder utilization, expressed as pressure *(compressed gas)* or weight *(liquefied gas),*
- the phase analyzed,
- the specifications,
- the date of analysis,
- the date of manufacture,
- the signature of the relevant person,
- place of manufacture
- shelf-life as applicable

P7 – CONTAINER CLOSURE SYSTEM

Medicinal gases are often packaged in a wide range of containers:

- compressed gas cylinders,
- liquefied gas cylinders, with or without a dip tube,
- cylinder bundle,
- mobile evaporator,
- fixed evaporator,
- mobile cryogenic container,
- fixed cryogenic container.

A variety of reference codes exist, dependent 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 15oC *(in m3)*, and the weight of product stored *(in g for compressed gases or in kg for liquefied gases)* are provided, together with the accepted deviations.

This information is necessary for compressed gas cylinders, given the variable operating pressures *(200 bar, 150 bar, etc at 15°C).* For liquefied gas cylinders, the pressure remains constant then falls suddenly at the end of use. Therefore, only the weight monitors the state of filling.

The filling pressure *(at 15°C)* is justified in comparison with the weight formula.

In the case of liquefied gases, the filling ratio in accordance to national and international standards (ISO standards) is provided so as not to exceed a maximal pressure with the risk of explosion, which can occur in the event of a change from the liquid to the gaseous or supercritical state after a temperature increase above the critical temperature.

The type of safety device *(valves or rupture disks)* relating to excess pressure is 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 is 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 are specified

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 are documented. The specific tests for these cylinders consist in particular of gas compatibility, adiabatic compression if needs be *(oxygen)* internal and external air-tightness, endurance test, cap shock resistance, fire-resistance, valve safety, shock vibration, output precision, hydrostatic pressure test etc.

The containers comply with the specifications of existing national, international *(ISO)* standards concerning equipment intended to contain and deliver gases. The certificate of compliance with the standards in force is provided and the important points of these standards are quoted.

In particular, the standards provide for the existence of connections **(**cylinder valve outlet connection) and for the painting of the cylinder shoulder.

The labeling, marking, engraving and painting that results from these different prescriptive and regulatory sources *(including drug regulations)* are described in a detailed manner, together with a diagram of the container *(packaging plan)*.

In particular, the labeling makes it possible, to clearly distinguish between cylinders for medicinal use and other cylinders *(laboratory gas, welding gas, etc.)*, as both types of cylinders are found together in a hospital environment

P 8 STABILITY OF THE MEDICINAL GAS PRODUCT

This is documented particularly as a function of the interval before the batch is used.

STABILITY OF THE FINISHED PRODUCT

ICH guidelines on stability are not relevant for this kind of product. Specific storage conditions are proposed by the applicant.

The stability of the finished product is documented by stability studies that are concerned with the container/content's interactions (as a function of capacity, material and supplier). There are screening tests for degradation products. A sufficient number of cylinders from the same batch is used for the study to avoid performing too many intermediate analyses on the same cylinder, since the decrease in pressure and, in the case of liquefied gases, the de-gasification, can alter the content of impurities, preferentially present in the gaseous phase.

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 can also be studied.

In order to evaluate the interface between the container and the patient, stability during use is considered, i.e., when administered according to the total system intended by the applicant.

In the case of liquefied gases, the different distribution of impurities between the liquid and gaseous phases as a function of their boiling point and the stage of container utilization are also taken into consideration.

In the case of mixtures, the stability studies include:

i) the stability of the mixture over the declared shelf life. The ingredients and appropriate impurities are assayed.

ii) if necessary, in particular in the case of mixtures of liquefied gas and permanent gas:

iii) the stability of the mixture at extreme temperatures within the safe working temperatures for cylinders,

iv) the stability during cycles of cooling or heating and returning to ambient temperature. The precise separating temperature is determined. A study of the re-homogenization of the mixture can be presented *(e.g. by placing the cylinder horizontal, with or without rolling).*

v) the homogeneity of the mixture during cylinder utilization.

vi) the homogeneity of the mixture in the event of abrupt opening *(study of the internal temperature of the cylinder).*

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.

In the case of evaporators of oxygen, there is, in the strict sense, no expiry date. They gradually empty during use. The length of storage can be set as the time needed for the evaporator to empty itself completely *(e.g. 3 months for a mobile evaporator and 6 months for a fixed evaporator).*

MODULE 4 Non-clinical Safety Requirements for Well Established Medicinal Gases

The aim of this module is to specify the elements relating to the safety of well-established medicinal gases in the context of compiling the non-clinical documentation for Module IV (Safety) of the dossier. An application for the marketing authorization of a medicinal gas or mixture of gases should not differ significantly from that of other medicinal products.

NON-CLINICAL REQUIREMENTS

Pharmacodynamics:

The potential for effects on lung function and gas exchange should be addressed.

Pharmacokinetics:

The possibility of metabolism, including metabolism within the lungs should be addressed.

Toxicology Studies:

Non-clinical investigations may be needed if safety aspects or concerns are not addressed by available non-clinical data or cannot be justified based on available literature and/or clinical data, especially when these effects are very difficult to detect clinically.

Any non-clinical toxicology studies performed should use the intended clinical route of administration, *i.e.,* inhalation and should be conducted in compliance with the principles of Good Laboratory Practices (GLP) and also include toxicokinetic evaluations. Particular attention should be given to the potential for histopathological changes in the airways and lungs.

Container:

The potential for extraction and leaching of materials from valves and gaskets, *etc*, should be addressed.

In addition, any degradation of the non-metallic components, in the wetted area of the container in contact with the gas, should be addressed.

5. Post approval Changes and Renewal Applications

5.1. Variation

For post approval variations, the applicants are advised to refer to and provide all relevant documents required by the guideline for submission of post approval variation medicine application. Whenever a product has been withdrawn from the market and/or its marketing authorization has been rejected, deferred, or withdrawn from market for any reason (such as deficiencies in GMP, product quality defect or ADE reports) in other countries, the local agent or the manufacturer should notify EFDA as per the article 67(17) of proclamation No 1112/2019.

5.2. Renewal

Applications for Renewal of these category of medicines shall follow requirements specified in Appendix (Requirements for Re-registration) of the Authority`s guideline for registration of medicines, 4th Edition, 2020.

7. Reference

i) *Guideline On Medicinal Gases: Pharmaceutical Documentation (Including Recommendation on Non-Clinical Safety Requirements for Well Established Medicinal Gases), London, 9 July 2008, Doc. Ref. CPMP/QWP/1719/00 Rev 1, European Medicines Agency*

ii) *Guideline on registration Of Medicinal Gases, February 2021, National Pharmaceutical Regulatory Agency, Ministry of Health Malaysia*

iii) *Guidance document authorization of medicinal gases, Identification number ZL000_00_016, Version 1.2, 22/05/2023*

iv) *Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Brussels, 03 February 2010, ENTR/F/2/AM/an D(2010) 3374*

v) *The U.S. Pharmacopeia (USP) http://www.pharmacopeia.cn/v29240/usp29nf24s0_m1000.html*

vi) *Ethiopian Standard, Medical oxygen and medical air specification, ISC:11.040.10, institute of Ethiopian standards, ES7010:2023*