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Medicines Control Authority of Zimbabwe

MCAZ/LED/GL-03

MINIMUM REQUIREMENTS FOR EMERGENCY USE AUTHORISATION OF MEDICAL OXYGEN

EFFECTIVE DATE:

Medicines Control Authority of Zimbabwe

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Authorised for use by: Director-General	pp. Ngambazi ..... Signature	10/08/2023 ..... Date

1.0 APPLICATION

The guideline focuses on the production, control, storage and distribution of medical oxygen gas.

2.0 PURPOSE

The guideline details the application process, conditions and the minimum requirements of issuance of emergency use authorisation of medical oxygen gas.

3.0 BACKGROUND / INTRODUCTION

Arising from an increased demand for medical gases, in particular the use of oxygen in the treatment of patients with Coronavirus disease 2019 (COVID-19), the Authority has seen the need for preparation of a guidance document on the minimum requirements for Emergency Use Authorization (EUA) of medical oxygen. This followed several enquiries from companies with industrial oxygen plants that wish to supply medical oxygen.

4.0 DEFINITIONS

4.1 **Gas -** Any substance that is completely gaseous at 1.013 bar and +20 °C or has a vapour pressure exceeding 3 bar at +500 °C.

4.2 **Medicinal gas -** Any gas or mixture of gases classified as a medical product.

4.3 **Tank -** A static thermally insulated container designed for the storage of liquefied or cryogenic gas (also called a fixed cryogenic vessel).

4.4 **Tanker -** A thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas.

5.0 GUIDELINES

5.1 GENERAL REQUIREMENTS AND APPLICATION PROCESS

5.1.1 The manufacturing facility should be located in Zimbabwe;

5.1.2 The applicant should be willing to be inspected by the Authority and to pay the requisite inspection fees. Requests should be submitted through mcaz@mcaz.co.zw and copy gmp@mcaz.co.zw

5.1.3 The applicant should write a commitment letter to submit full product dossier within six (6) months of receiving Emergency Use Authorization letter.

5.1.4 The Emergency Use Authorization shall be valid for a period not exceeding twelve (12) months

5.1.5 The applicant must comply with all other applicable national laws and by-laws

5.2 TECHNICAL REQUIREMENTS

5.2.1 Product Details

5.2.1.1 Chemical Name: Oxygen (O_2); CAS Reg.No.7782-44-7

5.2.1.2 Description: A colorless, odorless gas

5.2.2 Critical Quality Attributions and Key Tests

5.2.2.1 Identity test

Assay: Not Less Than 99.5% % v/v of O_2

5.2.2.2 Impurities

Carbon Monoxide: Not More Than 10 µl/L.

Caron Dioxide: Not More Than 300 µl/L.

5.2.2.3 Oxidizing substances

Water Content: not more than 60 µg/l.

5.3 QUALITY ASSURANCE

The manufacturer must assume responsibility for the quality of the medical oxygen to ensure that it is fit for its intended purpose, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy.

5.3.1 Good Manufacturing Practices

Good Manufacturing Practice, GMP is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP is concerned with both production and quality control, QC. GMP is aimed primarily at managing and minimizing the risks inherent in manufacturing process to ensure the quality, safety and efficacy of products.

5.3.2 GMP requires that;

5.3.2.1 The company should have a robust system to capture traceable records. Such records should include;

i. Full details of customers (distribution records),
ii. Batch details and identification numbers of cylinders as a minimum
iii. Details of suppliers of starting materials and packaging materials
iv. Batch processing records
v. Batch testing records

5.3.2.2 Adequate labeling of cylinders with the following minimum information:

i. the name of the medical gas;

ii. the concentration of the Oxygen
iii. the batch number assigned by the manufacturer;
iv. the expiry or use before date;
v. any special storage conditions or handling precautions that may be necessary;
vi. the name and address of the manufacturer.

Note: Detachable tags can be used in place of actual fixed labels.

5.3.2.3 The company should document all activities in approved written standard operating procedures, SOPs. Particular attention should be paid to the SOPs for

i. Complaints handling;
ii. Product recall
iii. Cleaning of premises and equipment
iv. Operation of production and analytical equipment
v. Batch numbering
vi. Labelling of containers
vii. Pest control

5.3.2.4 The premises should meet the following minimum conditions

i. The premises, where medical gases are manufactured, should be located, designed, constructed and maintained to suit the operations to be carried out.
ii. The layout and design of the premises should aim to minimize the risk of errors, mix-ups, contamination and cross-contamination. In addition, it should allow for effective cleaning and maintenance without any adverse effect on the quality of the products.
iii. Adequate and demarcated areas for separate storage of empty and filled cylinders, additionally Cylinders should be stored under cover and be protected from adverse weather conditions.

5.3.2.5 The Equipment should meet the following minimum requirements:

i. Where a common system supplying gas to medical and non-medical gas manifolds exists, there should be a validated method to prevent backflow from the non-medical gas line to the medical gas line.
ii. The layout, design, installation and use of equipment and utilities should aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of the medical oxygen.

iii. Calibration of key instruments must be conducted and be traceable to national or international standard applicable.

5.3.2.6 The medical oxygen separation and purification unit should be clearly defined including the material of construct used. The production process of the medicinal oxygen should be properly and adequately documented including process flows detailing the separation and purification stages and this should include the validated critical process parameters.

5.3.2.7 Tanks and tankers should be dedicated to a single and defined quality of gas. There should be documented evidence of preventative maintenance and calibration of the tanks and tankers.

5.4 QUALITY CONTROL

QC is the part of GMP concerned with sampling, specifications and testing, and with the organization and documentation which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be compliant with the specification and marketing authorisation. QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product.

5.4.1 **Good practice in quality control, QC requires that;**

5.4.1.1 There should be documented critical process parameters that ensure critical quality attributes are met and that the correct fill conditions are achieved

5.4.1.2 There should be a system for continuous monitoring and recording of the critical process parameters

5.4.1.3 There should be a written and approved specification of the starting materials including the containers.

5.4.1.4 There should be a detailed written and approved specification of the finished product.

5.4.1.5 There should be a procedure for routine inspection of cylinders as well as for performance of hydrostatic statutory pressure test or equivalent test

5.4.1.6 There should be a qualified and experienced person responsible for release of the batches to the market, following an approved SOP.

5.4.1.7 There should be a procedure for line clearance that details the checks performed before filling operations are started.

5.4.1.8 Each batch of medical oxygen should be tested in accordance with the requirements of the authorized specification and or

pharmacopoeia and the records of such tests retained for future reference.

5.4.1.9 There should be an authorized sampling procedure with a sampling plan for testing medical oxygen.

5.4.1.10 Valves or taps should not be lubricated with oil or grease unless they are oxygen compatible

6.0 KEY RELEVANT DOCUMENTS

6.1 WHO Good Manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2 http://www.who.int/medicines/publications/pharmprep/en/index.html

6.2 WHO Working Document QAS: 21.875, Good Manufacturing Practices for Medical Gases, Circulated December 2020 https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/qas21_875_gmp_for_medical_gases

6.3 WHO Draft Proposal for Revision in The International Pharmacopoeia, Oxygen Monograph, Circulated December 2020. https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/qas20_867_oxygen

6.4 WHO good manufacturing practices for medicinal gases. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 5.

6.5 The monograph on Medicinal Oxygen adopted at the 56th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations for publication in the 11th Edition of The International Pharmacopoeia.

7.0 HISTORY

DOCUMENT HISTORY		
Revision Number	Date Approved	System Improvement Section 3.0
0	March 2021	**Added** Whilst the urgent supply of medical oxygen is necessary, appropriate standards should be followed for the production, control, storage and distribution of medical oxygen to guarantee that oxygen for medical use is of assured quality when it reaches the patients.

		Section 4.0 **Added** 4.1 **Gas -** Any substance that is completely gaseous at 1.013 bar and +20 °C or has a vapour pressure exceeding 3 bar at +500 °C. 4.2 **Medicinal gas** - Any gas or mixture of gases classified as a medical product. 4.3 **Tank** - A static thermally insulated container designed for the storage of liquefied or cryogenic gas (also called a fixed cryogenic vessel). 4.4 **Tanker** - A thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas Merged section 5.2.2.1 and 5.2.2.2 to 5.2.2.1 Identity test Assay: Not Less Than 99.5% % v/v of O_2 Merged section 5.2.2.4 and 5.2.2.5 to 5.2.2.3 Oxidising substances Water Content: not more than 60 µg/l Section 6.0 Added 6.4 WHO good manufacturing practices for medicinal gases. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 5. 6.5 The monograph on Medicinal Oxygen adopted at the 56th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations for publication in the 11th Edition of The International Pharmacopoeia.