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REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

GUIDELINES FOR INSPECTION OF MANUFACTURERS OF MEDICAL GASES

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HPT/ISE/GMP/GUD/067	GUIDELINES FOR INSPECTION OF MANUFACTURERS OF MEDICAL GASES	Revision No. 0	Effective Date: 14/02/2022 Review Date: 31/01/2027

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1.0 Purpose

1.1 The purpose of this guideline is to facilitate compliance with and enhance consistency in the application of good manufacturing practices and any related Regulations for firms involved in production, packaging/labelling, testers, distribution, import, of medical gases as well as home care providers and commercial operations involving sales of medical gases.

1.2 It is intended to provide interpretations of the main Good Manufacturing Practices (GMP) guidelines and how to comply with Regulations relating to medical gases.

2.0 Scope

2.1 The guidelines apply to medical gases and were developed by the pharmacy and Poisons Board in consultation with internal stakeholders.

2.2 These guidelines apply to medical gases sold by commercial operations. They do not apply to aerosol preparations or to mixtures of solids that are used to generate gases. They also do not apply when fire departments, ambulance services, hospitals or health care facilities package medical gases for their own use or administration to a patient.

2.3 For the purpose of these guidelines, these operations are considered a "produce" activity:

a) producing medical gases through air liquefaction (for example, produced at air separation plants), chemical synthesis, filtration, purification, and/or

b) producing medical gas mixtures

2.4 These operations are considered a “packaging / labelling” activity:

a) transfilling medical gases at a facility

b) curb side filling of medical gases

2.5 The scope of this document does not include establishment licensing.

3.0 Introduction

3.1 These guidelines state generally applicable principles and practices that are acceptable to the Board GMP Inspectorate and that should facilitate compliance of firms involved in production, packaging/ or labelling, distribution, importation, of medical gases as well as home care providers and commercial operations involving sales of medical gases Cap 244 and related regulations and with principles of Good Manufacturing Practices (GMP).

3.2 The inspectorate does not consider packaging of gases (which includes the transfer of gases of a single grade in quality from one grade to another, including curb side or facility), performed within services such as fire departments, ambulance services, hospitals, or health care facilities, to be subject to Establishment Licensing and GMPs when the medical gases are for their own use or administration to a patient.

3.3 During establishment inspections carried out under the Pharmacy and Poisons Board Act (Cap 244) this document will be used as a guide in judging compliance with the GMP Regulations. However, the content of these guidelines should not be regarded as the only interpretation of the GMP Regulations and are not intended to cover every conceivable case. Alternative means of complying with the GMP Regulations will be considered with the appropriate scientific justification. Furthermore, as new technologies emerge, different approaches may be called for.

3.4 Establishments may use this guideline as a basis for the development of specific requirements appropriate to their individual needs. Similarly, Board departments involved in market authorization and quality assurance may find this regulatory guideline beneficial.

3.5 The Board inspects establishments to assess their compliance with the Pharmacy and Poisons Act (the Act) and associated guidelines and regulations. When we conduct an inspection, we will use this document as a guide in assessing your compliance with GMP requirements.

3.6 Due to their unique production and handling characteristics, the application of the GMP Regulations to medical gases may be different from their application to other pharmaceuticals. For example, the synthesis or manufacture of a medical gas constitutes a special situation in that the resulting gas may be used as a starting material or it may be sold as a bulk product or as a finished packaged product. These guidelines do not apply to aerosol preparations or to mixtures of solids that are used to generate gases.

The GMP guidelines are available on Pharmacy and Poisons Board's website at: xxxx

4.0 Pharmaceutical Quality Management

Guiding Principles

4.1 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. This shall cover all aspects of manufacturing of medical gases including production, packaging, labelling, distribution, testing and wholesaling.

4.2 The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of personnel in many different departments and at all levels within the establishment and its suppliers. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System (PQS) incorporating Good Manufacturing Practices (GMP) and Quality Risk Management (QRM).

4.3 The Pharmaceutical Quality System (PQS) should be fully documented and its effectiveness monitored. All parts of the PQS should be adequately resourced with qualified personnel, suitable premises, equipment, and facilities.

4.4 The basic concepts of PQS, Good Manufacturing Practices (GMP) and Quality Risk Management (QRM) are inter-related. They are described here to emphasize their relationships and fundamental importance to the production and control of medical gases.

Developing a Pharmaceutical Quality System

4.5 Quality Management is a wide-ranging concept. It covers all matters that individually or collectively influence the quality of a medical gas. It is the total of the arrangements made to ensure that medical gases are of the quality required for their intended use. Quality assurance therefore incorporates Good Manufacturing Practices, along with other factors that are outside the scope of these guidelines.

4.6 GMP applies to all lifecycle stages: from the manufacture of investigational medical gases, to technology transfer, to commercial manufacturing, through to product discontinuation. The pharmaceutical quality system can even extend to the pharmaceutical development lifecycle stage (as described in ICH Q10 Pharmaceutical Quality System). This should encourage innovation and continual improvement while strengthening the link between pharmaceutical development and manufacturing activities.

4.7 A firm should consider its size and the complexity of activities when developing a new PQS or when modifying and existing one. The system design should incorporate Quality Risk Management (QRM), including the use of appropriate tools. While some aspects of the system can be company-wide and others site-specific, the effectiveness of the system is normally proven at the site level.

4.8 To ensure a firm's pharmaceutical quality system is properly set up for producing, packaging, labelling, testing, distributing, importing and wholesaling medical gases, the firm should:

a) Design, qualify, plan, implement, maintain and continuously improve on your system to allow the consistent delivery of products with proper quality attributes.

b) Manage product and process knowledge throughout all lifecycle stages.

c) Design and develop medical gases in a way that takes into account GMP requirements

d) clearly specify production and control operations in a written form and adopt GMP requirements

e) Clearly outline management responsibilities.

f) Make arrangements for the manufacture, supply and use of the correct starting and packaging materials, selecting and monitoring suppliers and verifying that each delivery is from the approved supply chain.

g) Carry out necessary controls on starting materials, intermediate products and bulk products and other in-process controls, calibrations and validations;

h) Correctly process and check the finished product according to the defined procedures;

i) ensure that pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products;

j) Ensure processes are in place to properly manage outsourced activities.

k) Put in place satisfactory arrangements to ensure, as far as possible, that the medical gases are stored, distributed and subsequently handled so that quality is maintained throughout their shelf-life;

l) Establish a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the PQS;

m) Monitor product and processes and take into account the results in batch release, in the investigation of deviations and, with a view to taking preventive action to avoid potential deviations occurring in the future;

n) Put in place arrangements for the prospective evaluation and approval of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required. Make an evaluation after implementation of any change, to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality

o) Conduct regular reviews of the quality of medical gases with the objective of verifying the consistency of the process and identifying where there is a need for improvement;

p) Establish and maintain a state of control by developing and using effective monitoring and control systems for process performance and product quality;

q) Facilitate continual improvement through the implementation of quality improvements appropriate to the current level of process and product knowledge;

r) Put in place a system for QRM;

s) Report, investigate and record deviations, suspected product defects and other problems. Apply an appropriate level of root cause analysis during such investigations. Identify the most likely root cause(s) and, identify and take an appropriate corrective actions and/or preventive actions (CAPAs). Monitor the effectiveness of CAPAs.

4.9 There should be periodic management reviews, with the involvement of senior management, of the operation of the PQS to identify opportunities for continual improvement of products, processes and the system itself. Unless otherwise justified, such reviews should be conducted at least annually.

4.10 The PQS should be defined and documented. A quality manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.

Good Manufacturing Practices (GMP) for medical gases

4.11 GMP is that part of quality management which ensures that medical gases 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. GMP is aimed primarily at managing and minimizing the risks inherent in medical gases manufacture to ensure the quality, safety and efficacy of products.

4.12 To meet basic GMP requirements, the firm must ensure that:

a) all manufacturing processes are clearly defined, systematically reviewed for associated risks in light of scientific knowledge and experience, and shown to be capable of consistently manufacturing medical gases of the required quality that comply with their specifications;

b) qualification and validation are performed with reference to critical steps of manufacturing processes and significant changes to the process;

c) all necessary resources and key elements of GMP are provided, including:

i. sufficient and appropriately qualified and trained personnel,

ii. adequate premises and space,

iii. suitable equipment and services,

iv. appropriate materials, containers and labels,

v. approved procedures and instructions,

vi. suitable storage and transport,

vii. adequate personnel, laboratories and equipment for in-process controls;

d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;

e) procedures are carried out correctly and personnel are trained to do so (Operators are trained to carry out and document procedures);

f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected. Any significant deviations are fully recorded and investigated with the objective of determining the root cause and appropriate corrective and preventive action is implemented;

g) records covering production, packaging, labelling, testing and distribution, importation and wholesaling which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

h) the proper storage and distribution of the products minimizes any risk to their quality and takes account of good distribution practices (GDP);

i) a system is available to recall any batch of product from sale or supply;

j) complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products to prevent recurrence.

Quality Control

4.13 QC is the part of GMP concerned with:

a) sampling,

b) specifications and

c) testing,

d) organization and documentation

e) release procedures

4.14 This will 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 requirements. QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product.

4.15 The independence of QC from production is considered fundamental. Each manufacturer should have a QC function. The QC function should be independent of other departments and under the authority of a person with appropriate qualifications and experience. Adequate resources must be available to ensure that all the QC arrangements are effectively and reliably carried out.

4.16 The basic requirements of quality control are as follows:

a) Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and

where appropriate for monitoring environmental conditions for GMP purposes;

b) Sampling of starting materials, packaging materials, intermediate products, bulk products and finished products must be performed by methods and personnel approved by the QC department;

c) qualification and validation should be undertaken. For example, test methods must be validated;

d) records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;

e) the finished medical gases must contain ingredients complying with the qualitative and quantitative composition as described in the marketing authorization or clinical trial authorization; the ingredients must be of the required purity, in their proper container and correctly labelled;

f) Records of the results of self-inspection and management reviews should be kept;

g) records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished medical gases against specifications;

h) The procedures for product release include a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

i) No medical gas should be released by the Authorized Person for sale or supply prior to approval by the quality assurance department;

Quality risk management

4.17 Quality risk management is a systematic process for assessing, controlling, communicating and reviewing risks to the quality of a medical gas across the product lifecycle. It can be applied both proactively and retroactively.

4.18 The principles of quality risk management are that:

a) The evaluation of the risk to quality is based on scientific knowledge and experience with the process, and ultimately links to the protection of the patient.

b) The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

4.19 Examples of the processes and applications of quality risk management can be found in ICH Q9 Quality Risk Management.

Guidance

5.0 Regulation (requirements)

5.1 For each section below, the exact text of the requirement from WHO TRS 986 Annex 2 is provided first. This is followed by the rationale (explanation why the requirement is important) and The Kenya Pharmacy and Poisons Board's interpretation (what the firm needs to comply with) where needed.

5.2 Operational terms are terms used in this document and are borrowed from internationally recognized GMP guidelines for medical gases. These guidelines are referenced in this document.

Operational terms

5.3 In the regulation of medical gases;

a) "Medical gas" means any gas or mixture of gases produced (manufactured), packaged and labeled sold, or represented for use as a product or medicinal substance.

b) "Packaging material includes a label

c) "specifications" means a detailed description of a medicinal product, the starting material used in a medicinal product, or the packaging material for a medicinal product and includes:

i. a statement of all properties and qualities of the product, starting material or packaging material that are relevant to the manufacture, packaging, and use of the product, including the identity, potency, and purity of the product, starting material, or packaging material,

ii. a detailed description of the methods used for testing and examining the product, starting material, or packaging material, and

iii. a statement of tolerances for the properties and qualities of the product, starting material, or packaging material.

Sale

5.4 No manufacturer, distributor, importer or exporter shall sell a medical gas unless it has been produced, packaged/labelled, tested, and stored in accordance with PPB requirements contained in this document.

5.5 A firm involved in production, packaging and labelling shall ensure that related accessories of medical products shall comply with established standards.

6.0 Premises

Principle 12

6.1 The premises in which a lot or batch of a medicinal product is produced, packaged/labelled or stored shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out and in a manner that:

a) permits the operations therein to be performed under clean, sanitary and orderly conditions;

b) permits the effective cleaning of all surfaces therein; and

c) prevents the contamination of the medicinal gas and the addition of extraneous material to the product.

Rationale

6.2 In a medical gas production or packaging establishment appropriate cleanliness of work areas permit the achievement of sanitary conditions; orderliness helps to prevent mix-up; control of airborne and other contaminants safeguard product integrity.

6.3 Cleanliness, orderliness, and prevention of contamination call for initial good design and continuing maintenance. Regular maintenance is also required to prevent deterioration of premises. The ultimate objective of all endeavors is product quality.

Interpretation

6.4 Buildings in which medical gases are produced or packaged are located in an environment that, when considered together with measures being taken to protect the manufacturing processes, presents a minimum risk of causing any contamination of materials or medical gases.

6.5 The premises are adequate for the operation performed therein and are designed to avoid mix-ups and prevent contamination or cross contamination.

a) There is sufficient space for receiving and all production activities.

b) Working spaces allow the orderly and logical placement of equipment (including parts and tools) and materials.

c) Where physical quarantine areas are used, they are well marked, with access restricted to designated personnel. Where electronic quarantine is used, electronic access is restricted to designated personnel.

d) Working areas are well lit.

6.6 Adequate segregation and area designation should be provided to distinguish:

a) containers set aside for cleaning, testing or maintenance from containers that have been released for filling;

b) different gases;

c) medical gases from non-medical gases including their respective empty containers;

d) empty from full containers; and

e) quarantined finished products from those available for distribution.

6.7 Outlets are clearly identified as to their content.

6.8 Dead-legs in which circulation may be restricted should be minimized.

6.9 Pipelines carrying medical gases between areas should be identified by color or by standard markings at suitable intervals and direction of flow shown.

6.10 Intakes of air to be used in the production of medical gas are located such that contamination with waste gases and other pollutants is avoided.

6.11 Filters, especially the ones to trap desiccants after driers, are of suitable construction, examined and changed as necessary.

6.12 Rest, change, wash-up, and toilet facilities are well separated from production areas and are sufficiently spacious, well ventilated, and of a type that permits good sanitary practices.

6.13 Production and filling areas are adequately lit.

6.14 Premises are maintained in a good state of repair.

6.15 Premises and vehicles used to store medical gases are secured from unauthorized entry.

6.16 Empty cylinders/home cryogenic vessels after sorting or maintenance, and filled cylinders/home cryogenic vessels should be stored under cover, protected from adverse weather conditions.

6.17 Filled cylinders/cryogenic vessels 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.

7.0 Equipment

Principle 13

7.1 The equipment with which a lot or batch of a product is produced, packaged/labelled or tested must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.

7.2 The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

7.3 Equipment must be installed in such a way as to minimize any risk of contamination or the addition of extraneous materials and in such a manner that permits it to function in accordance with its intended use.

Rationale

7.4 The purpose of these requirements is to prevent the contamination of medical gases by other gases, by dust, and by foreign materials such as rust, lubricant, and particles coming from the equipment. Contamination problems may arise from poor maintenance, misuse of equipment, exceeding the capacity of the equipment, and use of worn-out equipment.

7.5 Equipment arranged in an orderly manner permits cleaning of adjacent areas and does not interfere with other processing operations. It also minimizes circulation of personnel and optimizes flow of material. The production of medical gases of consistent quality requires that equipment perform in accordance with its intended use.

Interpretation

7.6 Parts that are in contact with medical gases are designed, constructed, and located so as to permit cleaning and to avoid contamination. Where required, fittings and accessory assemblies are designed for easy dismantling.

7.7 Tankers and trailers and their ancillary equipment (hoses, valves, pumps, etc.) are of suitable construction and maintained in a good state of repair. Special attention is given to the tankers and trailers owned by a contracting firm.

7.8 Bulk 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 bulk tanks, other containers used for intermediate storage, or tankers, as the same non-medical 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. A procedure should describe the measures to be taken when a tanker is back into medical gas service (after transporting non-medical gas or after a maintenance operation). This should include analytical testing.

7.9 Filling and storage equipment should be appropriate to medical gases. Materials used are non-toxic, and non-reactive to medical gases, and are corrosion-resistant. Medical gas filling equipment is designed to prevent wrong connections. It should be impossible to fill a container with the wrong gas. Containers may be connected either to different valves through an adapter or to a manifold that is itself connected to different medical gas outlets, provided the procedure is fully validated and documented to ensure no cross contamination. Either procedure precludes the possibility of connecting a container to the wrong line.

7.10 Equipment used during the critical steps of production, packaging, and testing, including computerized systems, is subject to installation and operational qualification. Equipment qualification is documented. Further guidance is provided in the WHO guidance documents entitled “supplementary guidelines on good manufacturing practices: validation” (WHO TRS 937 Annex 4)

7.11 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. (PIC/S)

7.12 Equipment used in the production, packaging/labelling and testing of medical gases, including computerized equipment, is routinely checked and maintained and measuring devices are calibrated in accordance with a written program. Temporary devices for repairs are avoided. Records of maintenance and calibration are kept.

7.13 Vacuum gauges used during the essential evacuation of residual gas from high pressure cylinders need adequate calibration. At periodic intervals, vacuum gauges should be calibrated to standards established by the Kenya Bureau of Standards (KEBS). The frequency of calibration should be based on manufacturer's recommendations. A firm could also establish its own frequency based on usage and experience. Vacuum gauges should be checked prior to use with no vacuum present to ensure that the needle on the gauge returns to the "zero". Records should be maintained.

7.14 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. Checks for the absence of contaminants should be carried out before the equipment is released for use. Records of the use and maintenance operations should be maintained.

7.15 Openings for connections on lines supplying medical gases are adequately protected from contamination.

7.16 Check valves used to prevent contamination are verified on a scheduled frequency to ensure functionality.

7.17 A stainless-steel cylinder with a valve on each end which allows a gaseous product to flow through is acceptable for sampling gases from a storage bulk tank provided the firm has validated the process. The most significant step in the validation process is the time required to fully purge the cylinder which provides assurance that complete evacuation of the cylinder has been accomplished.

8.0 Personnel

Principle 9

8.1 The establishment and maintenance of a satisfactory system of QA and the correct manufacture and control of medical gases and active ingredients rely upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

8.2 Every lot or batch of medical gas shall be produced, packaged/labelled, tested and stored under the supervision of personnel who, having regard to the duties and responsibilities involved, have had such technical, academic and other training as the Board considers satisfactory in the interests of the health of the consumer or purchaser.

Rationale

8.3 People are the most important element in any medical gas operation, for without the proper staff with the appropriate attitude and sufficient training, it is almost impossible to produce, package/label, test or store good quality medical gases.

8.4 It is essential that qualified personnel be employed to supervise the production and packaging of medical gases. The operations involved in the production of medical gases can be highly technical in nature and require constant vigilance, attention to details, and a high degree of competence on the part of employees.

8.5 Inadequate training of personnel, or the absence of an appreciation of the importance of production control, often accounts for the failure of a product to meet the required standards.

Interpretation

8.6 The individual in charge of the quality control department, and the individual in charge of the production department of a manufacturer should have the professional or technical qualifications, which may include a production Pharmacist, respiratory therapist or qualified by pertinent training; and

a) has practical experience in their responsibility area;

b) directly controls and personally supervises on site, each working shift during which activities under their control are being conducted; and

c) may delegate duties and responsibility (for example to cover all shifts) to a person who meets the requirements (defined under a), while remaining accountable for those duties and responsibility.

8.7 The individual in charge of the quality control department of a packager/labeller, tester, importer and distributor of medical gases:

a) have the professional or technical qualifications, which may include a pharmacist, respiratory therapist; or qualified by pertinent training; and

b) has practical experience in their responsibility area;

c) can delegate their duties and responsibilities to a person who meets the requirements

Note: *At medical gas filling stations, personnel performing simple analytical tests and quality control functions in accordance with standard company procedures may be individuals with practical experience only.*

8.8 The individual in charge of the filling/packaging operations, including control over printed packaging materials and withdrawal of bulk gases of a packager/labeller:

a) is qualified by training and experience;

b) can delegate their duties and responsibilities to a person who is equally qualified by training and experience.

8.9 An adequate number of personnel with the necessary qualifications and practical experience appropriate to their responsibilities should be available on site.

a) The responsibilities placed on any one individual are not so extensive as to present any risk to quality.

b) All responsible personnel have their specific duties relating to medical gases recorded in a written description and have adequate authority to carry out their responsibilities.

c) When key personnel are absent, qualified personnel are appointed to carry out their duties and functions.

8.10 All personnel are aware of the principles of GMP that affect them and receive initial and continuing training relevant to their job responsibilities.

a) Training is provided by qualified personnel having regard to the function and in accordance with a written program for all personnel involved in the production, packaging/labelling, testing and importing of a medical gas, including technical, maintenance and cleaning staff.

b) The effectiveness of continuing training is periodically assessed.

c) Training is provided prior to implementation of new or revised SOPs.

d) Records of training are maintained.

e) Personnel working in areas where highly active, toxic, infectious or sensitizing materials are handled, are given specific training.

f) Performance of personnel is periodically reviewed.

8.11 Consultants and contractors have the necessary qualifications, training, and experience to advise on the subjects for which they are retained. Evidence of this should be included in the training records. Personnel of subcontractors that could

influence the quality of medical gases (such as personnel in charge of maintenance of cylinders or valves) should be appropriately trained.

9.0 Sanitation

Principle 3

9.1 A high level of sanitation and hygiene should be practiced in every aspect of the production and labelling of medicines. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product.

9.2 Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene that shall be implemented under the supervision of qualified personnel. The sanitation program shall include:

a) cleaning procedures for the premises where the medicinal product is produced or packaged/labelled and for the equipment used in the production or packaging/labelling of the product; and

b) instructions on the sanitary production and packaging/labelling of products and the handling of materials used in the production and packaging/labelling of products.

Rationale

9.3 Sanitation in a medical gas production and packaging facility, as well as employee attitude, influences the quality of medical gas products. The quality requirement for medical gas demand that it be produced and packaged free from contamination.

9.4 A written sanitation program provides some assurance that levels of cleanliness in the facility are maintained and that the provisions of Principles 11 and 12 of the WHO Expert Committee on Specifications for Pharmaceutical Preparations Forty-eighth report 986 annex 2 are satisfied.

Interpretation

9.5 Even though medical gases are handled in closed systems, areas where medical gases are filled are kept clean and tidy.

9.6 Every facility that produces or packages/labels a medical gas shall have a written sanitation program available on the premises.

9.7 The sanitation program contains procedures that describe the following:

a) cleaning requirements applicable to the facility;

b) cleaning requirements applicable to processing equipment.

9.8 Cleaning of critical equipment used in production, transportation, storage, and filling of medical gases, and cleaning and purging of pipelines that carry medical gases follow written procedures, including checks for the absence of cleaning agents or other contaminants. All of these procedures are validated and documented.

9.9 Special attention is given to the tankers and trailers owned by a contracting firm. Further guidance is provided in the World Health Organization document entitled Supplementary guidelines on good manufacturing practices: validation (WHO Technical Report Series, No. 937 Annex 4)

10.0 Training and Personal Hygiene

Principle 10 and 11

10.1 Every person involved in production or packaging/labelling a medicinal product shall have, in writing, minimum requirements for the health, and the hygienic behaviour and clothing of personnel to ensure the clean and sanitary production and packaging/labelling of the product.

10.2 No person shall have access to any area where a product is exposed during its production or packaging/labelling if the person:

a) is affected with or is a carrier of a disease in a communicable form; or

b) has an open lesion on any exposed surface of the body.

Rationale

10.3 The manufacture of medical gases is carried out in closed equipment. Potential for environmental contamination of the product is minimal.

10.4 The requirements for hygiene of personnel engaged in the production of medical gases are similar to those that are applicable to personnel involved in production of other pharmaceutical dosage forms, although the extent to which they are applicable will greatly depend on the operation and the procedures used.

Interpretation

10.5 Minimum health requirements are available in writing that would provide assurance that:

a) as far as is practicable that no person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should be allowed to handle starting materials, packaging materials, in-process materials or medicines until the condition is no longer judged to be a risk.

b) individuals responsible for performing odour tests do not have ailments that can adversely affect test results;

c) employees responsible for performing inspections involving distinguishing colours can distinguish colours appropriately.

10.6 The written hygiene program clearly defines clothing requirements and hygiene procedures for company personnel and visitors.

a) Where a potential for contamination of a medical gas exists, individuals wear clean clothing and protective covering.

b) Direct contact is avoided between the operator's hands and any parts of equipment that come in direct contact with the medical gas.

c) Unsanitary practices are not permitted in processing areas.

d) Requirements concerning personal hygiene are outlined when significant to the quality of the product.

11.0 Testing of Starting Material

Note: Requirements on raw material testing (Priciples14 WHO TRS 986 Annex 2) are applicable only to batches of gases that are used in the production of medical gas mixtures. For testing of bulk gases that are not used to produce gas mixtures apply requirements on manufacturing controls (Principle 16 WHO TRS 986 Annex 2) and, requirements on finished product testing (Section 17 WHO TRS 986 Annex 2).

11.1 Each lot or batch of starting material shall be tested against the specification of the starting material prior to its use in the production of a product.

11.2 No lot or batch of starting material shall be used in the production of a product unless that lot or batch of starting material complies with the specifications for that starting material.

11.3 Notwithstanding subsection (11.1), water may, prior to the completion of its tests under that subsection, be used in the production of a medicinal product.

11.4 Where any property of a starting material is subject to change on storage, no lot or batch of that starting material shall be used in the production of a medicinal product after its storage unless the starting material is retested after an appropriate interval and complies with its specifications for that property.

11.5 Where the specifications referred to in subsections (11.1), (11.2) and (11.4) are not prescribed, they shall:

a) be in writing;

b) acceptable to the Pharmacy and Poisons Board, who shall take into account the specifications contained in any publication and

c) be approved by the person in charge of the quality Assurance or control department.

Rationale

11.6 The testing of starting materials before their use has three objectives: confirm the identity of the starting materials, provide assurance that the quality of the medical gas in dosage form will not be altered by starting material defects, and obtain assurance that the starting materials have the characteristics that will provide the desired quantity or yield in a given manufacturing process.

Interpretation

11.7 Starting materials are tested against specification on receipt at the production facility.

11.8 Specifications are in compliance with the marketing authorization. When a monograph exists in pharmacopeia list recognized by the Pharmacy and Poisons Board, ensure specifications meet the monograph.

11.9 Test methods are validated, and the results of such validation studies are documented. Full validation is not required for Pharmacopeia methods, but the user of such a method establishes its suitability under actual conditions of use.

Pharmacopoeia methods are considered to be validated for the intended use as prescribed in the monograph(s).

11.10 However, the laboratory should also confirm that, for example, for a particular medical gas examined for the first time, no interference arises from the excipients present, or that for an API, impurities coming from a new route of synthesis are adequately differentiated. If the pharmacopoeia method is adapted for another use then it should be validated for such a use to demonstrate that it is fi t-for-purpose. Method transfer studies are conducted when applicable.

Note : Guidance for the validation of particular types of methods can be obtained in publications such as the International Council on Harmonization (ICH) document entitled "Validation of Analytical Procedures : Text and Methodology Q2(R1)"

11.11 Deliveries of starting material may be added to a bulk storage tank containing the same gas from previous deliveries. In this case:

a) a sample of the delivered starting material is tested and found to be satisfactory; or

b) when the starting material is a single gas accompanied by a Certificate of Analysis, the sample may be taken and tested after allowing for sufficient mixing of the delivery in the bulk storage tank after the sampling line has been adequately purged;

c) when the starting material is a mixture, the testing verifies each component.

11.12 The testing of starting materials shall be performed on a sample taken after receipt of each lot or batch of starting material on the premises of the manufacturer; or

a) subject to subsection (10.1), before receipt of each lot or batch of starting material on the premises of the producer, if

i. the producer:

- has satisfactory evidence to demonstrate that starting materials sold to him by the vendor of that lot or batch of starting material are consistently manufactured in accordance with and consistently comply with the specifications for those starting materials; and
- undertakes periodic complete confirmatory testing with a appropriate frequency; and

ii. the starting material has not been transported or stored under conditions that may affect its compliance with the specifications for that starting material.

b) After a lot or batch of starting material is received on the premises of the producer, the lot or batch of starting material shall be tested for identity.

Rationale

11.13 This Section outlines options as to when the testing of starting materials is carried out. The purchase of starting materials is an important operation that requires a particular and thorough knowledge of the starting materials and their vendor.

Interpretation

11.14 The testing is performed on a sample taken after receipt of the starting material on the premises of the facility that fills medical gas into containers. Specific identity testing is conducted on all lots of any starting material.

11.15 When the starting material is a bulk gas accompanied by a Certificate of Analysis, the sample may be taken after allowing for comingling of the delivery in the bulk storage tank.

11.16 For tests other than identity tests, conditions to be met are outlined should the person choose to rely on the test results provided by the vendor and should include:

a) evidence of ongoing GMP compliance including process control and validation in accordance with these guidelines, or an audit report issued by a qualified authority demonstrating that the starting material producer complies with the ICH document entitled "ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" or with any standard or system of equivalent quality.

b) all lots to be accompanied by an authentic certificate of analysis exhibiting actual numerical results, and making reference to product specification and validated test methods used;

c) Complete confirmatory testing is conducted on a minimum of one lot per year of a starting material received from each vendor, with the starting material being selected on a rotational basis.

d) In addition, where multiple starting materials are received from the same vendor, confirmatory testing is carried out for each starting material at least once every five years.

11.17 If any lot is rejected, the vendor must be requalified.

11.18 Conditions of transportation and storage should be such that they prevent alterations to the potency and purity of the starting material. In order to demonstrate that these conditions have been met, standard operating procedures and records for shipping and receiving are available and contain:

a) the type of packaging to be employed;

b) labelling requirements;

c) mode of transportation;

d) seal of package;

e) verification required to ensure that each package has not been tampered with and that there are no damaged containers;

f) evidence that special shipping requirements have been met.

12.0 Manufacturing Control: Good practices in production

Principle 16

12.1 Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

12.2 Production and control operations are clearly specified in a written form and GMP requirements are adopted; the finished product is correctly processed and checked, according to the defined procedures;

Rationale

12.3 This section requires that measures be taken to maintain the integrity of a medical gas from the moment the various starting materials or bulk gases enter the plant to the time the finished product is released for sale and distributed.

12.4 These measures ensure that all manufacturing processes are clearly defined, systematically reviewed in light of experience, and demonstrated to be capable of consistently manufacturing medical gas products of the required quality that comply with their established specifications.

12.5 The following operations are considered a "production" activity:

a) medical gases produced via air liquefaction (for example, meaning produced at air separation plants), chemical synthesis, filtration, purification, and/or

b) medical gas mixtures.

12.6 The following operations are considered a "packaging / labelling" activity:

c) transfilling gases at a facility,

d) curbside filling.

Note: the scope of this document does not include establishment licensing.

Interpretation

12.7 All handling of starting materials, products, and packaging materials such as receipt, quarantine, sampling, storage, tracking, labelling, processing, packaging and distribution is done in accordance with pre-approved written procedures or and records are kept as required.

12.8 All critical production processes are validated. Validation studies are conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions is prepared, evaluated, approved, and maintained.

12.9 Changes to production processes, systems, or equipment that may affect product quality and/or process reproducibility are approved and where applicable validated prior to implementation.

12.10 Any deviation from instructions or procedures is avoided. If deviations occur, qualified personnel investigate, and a report is written that describes the deviation, the investigation, the rationale for disposition, and any follow-up activities required. The report is approved by the quality assurance department and records maintained.

12.11 Bulk gases are stored under conditions and handled in distribution systems that preclude product mix up, deterioration or contamination.

12.12 Measuring devices are regularly checked for accuracy and precision, and records of such checks are maintained.

12.13 Written procedures are available to ensure that starting materials and bulk gases:

a) are identified by lot number, receiving number, or laboratory control number;

b) are released for production or filling operations according to written procedures approved by the quality assurance department;

c) have their Certificates of Analysis reviewed and available on-site for each shipment of source gas received, and;

d) stored under conditions that will preserve their quality and avoid their inadvertent use.

12.14 Written procedures approved by the quality assurance department are available to ensure that containers are not filled until they are checked or tested to ensure that they meet their specifications.

12.15 Processing operations are covered by master formulae, which are prepared by, and subject to independent checks by persons having the qualifications described under section 9 principle 9.6.

12.16 Master formulae, master production documents, or master filling documents are written to provide 100% of label claim and include:

a) the name of the product;

b) the name and concentration of components, including acceptable tolerances

c) the filling sequence of components;

d) the fill pressure or weight of components (compressed gases);

e) in-process and final quality control requirements.

12.17 Before any processing operation is started, all necessary steps are taken and documented to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

12.18 Manufacturing and filling records contain all information pertinent to the manufacturing and filling of each batch of medical gas including:

a) in-process quality control requirements;

b) equipment used (if multiple systems are used for same product);

c) a mark that is unique to an individual or the initials of personnel; and

d) name and references to the specification for each starting material in a mixture.

12.19 Completed manufacturing orders include:

a) appropriate check to ensure the containers have been filled;

b) actual results of the quality checks performed;

c) batch or lot number, receiving number, or laboratory control number of each starting material in a mixture; and

d) a mark that is unique to an individual or the initials of personnel involved in the preparation of the mixture.

12.20 Deliveries of bulk gas may be added to the bulk storage tanks containing the same gas from previous deliveries. In this case:

a) a sample of the delivered bulk gas is tested before it is added to the storage tank, and found to be satisfactory; or

b) when the bulk gas is a single gas accompanied by a Certificate of Analysis, the sample may be taken after allowing for sufficient mixing of the delivery in the bulk storage tank. The sample may be taken from a sampling line or from the first container filled, provided that the sampling, distribution, and filling lines have been adequately purged prior to sampling;

c) when the bulk gas is a mixture, the testing verifies each component.

12.21 Residual batches or lots in cryogenic containers or trailers may be combined or product from the bulk storage tank may be added to the containers or trailers if purity testing is performed after mixing.

12.22 Written instructions ensure that:

a) the initials of quality control personnel or qualified designate are recorded in the filling logs;

b) the lot number of the medical gas is assigned and appears on each container. The lot number may not appear on each bulk transport container, each storage tank filled, and each container filled at curbside, provided that traceability is documented;

c) filling of high-pressure cylinders is controlled either by monitoring the temperature on the wall of cylinders and the pressure or by mass. Correct fill may be verified by reference to a temperature/pressure chart or a target mass chart, as applicable;

d) during manifold filling sequences a heat of compression check is performed, where necessary, on the exterior surface of each cylinder to demonstrate proper filling;

e) filled containers are effectively quarantined until released by the quality control department;

f) each container undergoes a leak test during filling using an appropriate method such as leak detection solution applied to the valve to detect valve packing leaks, safety plug leaks, and other valve leaks. Each filled container undergoes a second leak test after filling to detect valve outlet leaks. Leak test solutions, such as soap, that can cause corrosion or leave films should not be used.

Note : This does not apply to refrigerated or cryogenic liquids.

12.23 Filling is followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures are applied to ensure that no mix-ups or mislabeling can occur.

12.24 Label withdrawal is documented and reconciled.

12.25 Labelling operations are controlled by 100% verification. Verifications are documented.

12.26 Labelling operations are documented.

12.27 All containers are appropriately labelled and identified in such a way as to be readily distinguishable as to their content. Container identification is performed according to predetermined and well-recorded procedures under the supervision of qualified personnel. Product segregation by cylinder color can be an acceptable method if there is evidence that the personnel involved are adequately trained. Additional measures are necessary to segregate quarantined and released cylinders.

12.28 After filling, cylinder post valves should be fitted with covers to protect the outlets from contamination. Cylinders and cryogenic vessels should be fitted with tamper-evident seals or devices (PIC/S).

12.29 Materials and labels used to identify containers are stored in a limited access area and restricted to designated personnel.

12.30 Outdated or obsolete materials and labels are destroyed and their disposal recorded.

12.31 Medical gases are not released without the approval of the quality assurance department.

12.32 Water used for cooling during compression of air is monitored for microbial quality when in contact with the medical gas.

13.0 Product Quality Review (PQR)

Principle 1.10

13.1 The annual product quality reviews of all medical gases should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and medical gas to highlight any trends and to identify product and process improvements.

13.2 Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

a) A review of critical in-process controls, finished product testing results and specifications.

b) A review of all batches that failed to meet established specification(s) and their investigation.

c) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.

d) A review of all changes carried out to the processes, analytical methods, starting materials, intermediate, packaging materials, or critical suppliers.

e) If applicable, a review of the results of the continuing stability program and any adverse trends.

f) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

g) A review of adequacy of any other previous product process or equipment corrective actions.

h) The qualification status of relevant equipment used for production and packaging of medical gases; and

i) A review of quality agreements to ensure that they are up to date.

13.3 The quality assurance department of the producer, packager/labeller, importer or distributor should ensure that the annual product quality review is performed in a timely manner and is accurate. For medical gas companies where a uniform Quality Assurance system has been implemented across all sites of a company which includes a requirement to conduct periodic on-site self-audits of all sites; the medical gas company can perform one annual product quality review instead of one at each individual site. APQR reports are to be available at each site.

13.4 Where required, there should be an agreement in place between the various parties involved (for example importer and producer) that defines their respective responsibilities in producing and assessing the quality review and taking any subsequent corrective and preventative actions.

13.5 The quality assurance department should evaluate the results of this review and an assessment should be made whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection.

14.0 Product recalls, contract production and analysis and, self-inspection

Principle 6, 7 and 8

14.1 Every producer, packager/labeler, distributor, importer and wholesaler of a product shall maintain a system to recall from the market, promptly and effectively, products known or suspected to be defective.

14.2 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements.

14.3 Contract production, analysis and any other activity covered by GMP must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product, or work or analysis, of unsatisfactory quality.

Rationale

14.4 The purpose of a recall is to remove from the market a medical gas that presents an undue health risk. A recall removes from the market a medical gas that either:

a) Does not conform to the Pharmacy and Poisons Act or regulations

b) Presents a risk to a consumer

14.5 Medical gases that have left the premises of a producer, packager/labeller, distributor, or importer can be found in a variety of locations. Depending on the severity of the health risk, it may be necessary to recall a product to one level or another.

14.6 Producers, packagers/labellers, distributors, and importers are expected to be able to recall to the consumer level if necessary. Additional guidance on recalls can be found in PPB's document entitled "Product Recall Procedures".

14.7 This regulation also requires producers, packagers/labellers, distributors, and importers to maintain a program of self-inspection. The purpose of self-inspection is to evaluate the compliance with GMPs in all aspects of production and quality control.

14.8 The self-inspection program should be designed to detect any shortcomings in the implementation of GMPs and to recommend the necessary corrective actions.

14.9 Medical gases offered for sale, regardless of whether they are domestically produced or imported, must comply with regulatory requirements and product specifications.

14.10 Unless a written contract between the contract giver and the contract acceptor clearly establishes the responsibilities of each party, outsourced activities covered, the products or operations to which they are related, communication processes relating to the outsourced activities and any technical arrangements made in connection with it, misunderstanding that could result in a product, work or analysis of unsatisfactory quality may result.

Interpretation

14.11 A written recall system should be in place to ensure compliance with applicable regulatory requirements and requires the following:

a) The Pharmacy and Poisons Board is to be notified of the recall.

b) Action that is taken to recall a medical gas suspected or known to be defective is prompt and in accordance with a pre-determined plan. The procedures to be followed are in writing and known to all concerned.

c) The person(s) responsible for initiating and co-ordinating all recall activities are identified.

d) The recall procedure is capable of being put into operation at any time, during and outside normal working hours.

e) The recall procedure outlines the means of notifying and implementing a recall and of deciding its extent.

f) Distribution records enable tracing of medical gas, and account is taken of any medical gas that are in transit.

g) The progress and success of a recall is assessed and recorded at intervals, and a final report is issued (including a final reconciliation).

h) Recalled medical gas are identified and are stored separately in a secure area until their disposition is determined.

i) All establishments involved in the production, distribution, or importation of the recalled medical gas are notified.

14.12 A self-inspection program appropriate to the type of operations of the establishment, with respect to medical gases, should be established entailing:

a) A comprehensive written procedure that describes the functions of the self-inspection program

b) The self-inspection team entailing personnel who are suitably trained and qualified in GMP

c) periodic self-inspections are carried out.

d) A review of reports on the findings of the inspections and on corrective actions by appropriate senior company management.

e) Implementation of corrective actions in a timely manner.

14.13 To ensure compliance of contractors performing production and packaging/labelling:

a) There should be a written agreement covering the production or packaging/labelling arrangment among the parties involved.

b) The agreement should specify their respective responsibilities relating to the production or packaging/labelling and control of the product.

c) Technical aspects of the agreement should be drawn up by qualified personnel suitably knowledgeable in pharmaceutical technology, and GMP.

d) The agreement should permit the distributor or importer to audit the facilities of the contractor.

14.14 The agreement should clearly describe as a minimum who is responsible for:

a) purchasing, sampling, testing, and releasing materials;

b) undertaking production, quality, and in-process controls; and

c) process validation.

14.15 No subcontracting of any work should occur without written authorization.

14.16 The agreement should specify the way in which the quality control department of the distributor or importer releasing the lot or batch for sale, ensures that each lot or batch has been produced and packaged/labelled in compliance with the requirements of the marketing authorization.

14.17 The agreement should describe the handling of starting materials, packaging materials, in-process medical gas, bulk medical gas and finished products if they are rejected.

14.18 The contractor's complaint/recall procedures should specify that any records relevant to assessing the quality of a medical gas in the event of complaints or a suspected defect are accessible to the distributor or importer.

14.19 The producer, packager/labeller, distributor, or importer should provide the contractor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements.

14.20 The producer, packager/labeller, distributor, or importer should ensure that the contractor is fully aware of any problems associated with the product, work or tests

that might pose a hazard to premises, equipment, personnel, other materials or other products.

14.21 The producer, packager/labeller, distributor or importer should be responsible for assessing the continuing competence of the contractor to successfully carry out the work or tests required in accordance with the principles of GMP described in these guidelines.

14.22 Distributors of medical gases produced, packaged/labelled or tested at Kenyan sites are required only to have a copy of the relevant valid manufacturing licence held by the Kenyan producer, packager/labeller or tester.

14.23 Importers of bulk gases and finished products produced, packaged/labelled, or tested at a foreign site must meet the other applicable regulatory requirements for imported products.

14.24 The foreign site must be listed on the PPB foreign manufacturing sites list.

15.0 Quality Control Department

Principle 17

15.1 Each manufacturer should have a QC function.

15.2 The QC function should be independent of other departments and under the authority of a person with appropriate qualifications and experience. Adequate resources must be available to ensure that all the QC arrangements are effectively and reliably carried out.

Rationale

15.3 Quality control is the part of GMP concerned with sampling, specifications, and testing, and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that starting materials and packaging materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

15.4 Quality control is not confined to laboratory operations. It must be incorporated into all activities and decisions concerning the quality of the product.

15.5 Although manufacturing and quality control personnel share the common goal of assuring the high-quality medical gases are produced, their interest may sometimes conflict in the short run as decisions are made that will affect a company's output.

15.6 In the medical gas industry, quality control is performed by personnel in various departments using a matrix organization. For quality control issues, these personnel are responsible to the individual in charge of quality control. The independence of quality control from production and packaging is considered fundamental.

15.7 The rationale for the requirement that the quality control department be supervised by qualified personnel is outlined under the section 9 of WHO TRS 986 Annex 2

Interpretation

15.8 Every producer, packager/labeller, wholesaler, distributor and importer shall have on their premises within Kenya a quality control department that is supervised by personnel described in Section 9 of WHO TRS 986 Annex 2

15.9 Except in the case of a wholesaler, the quality control department shall be a distinct organizational unit that functions and reports to management independently of any other functional unit, including the manufacturing, processing, packaging or sales unit.

15.10 A person responsible for making decisions concerning quality control requirements should be on-site at the manufacturer and importer. At locations with two or fewer operations staff available, the manufacturing and quality control person may be the same, provided that due consideration is given to situations where:

a) it is impossible to have distinct organizational units on site;

b) chances of error are eliminated;

c) reporting relationship is different while the employee performs quality control functions and production or packaging/labelling activities;

d) the employee is fully aware of his/her dual role, understands clearly responsibilities and line authority and acts accordingly.

15.11 The quality control department should have true and effective access to equipment and facilities for inspecting and testing, having regard to the nature of the products produced.

16.0 Control of starting materials & intermediate, bulk & finished medical gases

Principle 14

15.12 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution. Only starting materials released by the QC department and within their shelf-life should be used.

15.13 No batch of product is to be released for sale or supply prior to certification by the authorized person(s). Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

15.14 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

15.15 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabeling, or alternative action taken only after they have been critically assessed by the QC function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

Rationale

15.16 The responsibility for the approval of all starting materials, packaging, materials and finished products is vested in the quality control department. It is very important that adequate controls be exercised by this department in order to guarantee the quality of the end product.

15.17 To maintain this level of quality, it is also important to examine all returned medical gases

Interpretation

15.18 Except in the case of a wholesaler, no lot or batch of product shall be made available for sale unless the sale of that lot or batch is approved by the person in charge of the quality Unit department.

15.19 A product that is returned to the producer, packager/labeller, wholesaler, distributor referred or importer shall not be made available for further sale unless the sale of that product is approved by the person in charge of the quality control department.

15.20 No lot or batch of starting material or of packaging/labelling material shall be used in the production or packaging/labelling of a product, unless that material is approved for that use by the person in charge of the quality control department.

15.21 No lot or batch of a product shall be reprocessed without the approval of the person in charge of the quality control department.

15.22 All decisions made by the quality control department pursuant to Principle 17 are attested to by the signature of the head of the quality control department, or an authorized alternate, and are dated.

15.23 The quality control department ensures that starting materials, bulk gases, and packaging materials are effectively quarantined, sampled, tested, and released prior to their use in production or packaging/labelling of a medical gas.

17.0 Handling of market related complaints

Principle 5

17.1 Documents should be approved, signed and dated and version numbered by the appropriate responsible persons. No document should be changed without authorization and approval.

17.2 All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken. The person responsible for QC should normally be involved in the review of such investigations.

17.3 Special attention should be given to establishing that the product that gave rise to a complaint was defective.

17.4 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

Rationale

17.5 Medical gas processes are designed and developed in a way that takes into account the requirements of GMP. Production procedures and other control operations are independently examined by the quality control department. Proper storage,

transportation, and distribution of materials and products minimize any risk to their quality.

17.6 Complaints are an indicator of problems related to quality. By tracing their causes one can determine which corrective measures should be taken to prevent recurrence. Having tests carried out by a competent laboratory provides assurance that test results are genuine and accurate.

17.7 Written agreements for consultants and contract laboratories describe the education, training, experience, and the types of services provided and are available for examination and inspection. Records of their activities are maintained.

Interpretation

17.8 All production, packaging/labelling, testing, storage and transportation methods and procedures that may affect the quality of a product shall be examined and approved by the person in charge of the quality Unit before their implementation.

17.9 The quality unit(s) shall be responsible for all decisions made pursuant to Principle 17 are signed and dated by the person in charge of the quality unit, or a designated alternate who meets the requirements described under section 9, as applicable to the activity.

17.10 The quality control department shall ensure that guidelines and procedures are in place and implemented for storage and transportation conditions. Filled gas cylinders and home cryogenic vessels should be protected during transportation, so that, in particular, they are delivered to customers in a clean state compatible with the environment in which they will be used.

17.11 The tests are to be performed by a laboratory that meets all relevant GMP requirements while ensuring that:

a) Laboratory facilities are designed, equipped, and maintained to suit the testing and approval (or rejection) of starting materials, medical gases, and containers;

b) The individual in charge of the laboratory is qualified in accordance with Principle 9 or functionally reports to a person having these qualifications; and

c) Laboratory personnel are sufficient in number and are qualified to carry out the work they undertake;

d) Laboratory control equipment and instruments are suited to the testing procedures undertaken. Equipment and records are maintained as per the interpretations under section 13;

e) Computerized systems are validated, and spreadsheets are qualified;

f) Out of Specification (OOS) test results are investigated to determine the cause of the OOS.

i. Procedures are in place to describe the steps to be taken as part of the investigation.

ii. In the case of a clearly identified laboratory or statistical error, the original results may be invalidated, and the test repeated.

The original results should be retained and an explanation recorded.

iii. When there is no clearly identified laboratory or statistical error and retesting is performed, the number of retests to be performed on the original sample and/or a new sample, and the statistical treatment of the resultant data, are specified in advance in the procedure.

iv. All valid test results, both passing and suspect, should be reported and considered in batch release decisions.

v. If the original OOS result is found to be valid, a deviation is raised against the batch and a complete investigation is conducted.

17.12 All complaints and other information concerning potentially defective products are reviewed according to written procedures. The complaint is recorded with all the original details and thoroughly investigated.

17.13 Appropriate follow-up action is taken after investigation and evaluation of the complaint. All decisions and measures taken as a result of a complaint are recorded and referenced to the corresponding batch records. Complaint records are regularly reviewed for any indication of specific or recurring problems that require attention.

17.14 Establishing a change control system to provide the mechanisms for ongoing process optimization and for assuring a continuing state of control. All changes are properly documented, evaluated, and approved by the quality assurance department, and are identified with the appropriate effective date. Any significant change may necessitate re-validation.

18.0 Packaging Material Testing

Note: The purchase, handling and control of primary and printed packaging materials should be as for starting materials:

18.1 Only packaging materials released by the QC department and within their shelf-life should be used.

18.2 All incoming packaging materials should be quarantined immediately after receipt, until they are released for use or distribution.

18.3 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

18.4 The procedures and specifications shall be in writing and be approved by the person in charge of the quality unit.

Rationale

18.5 Where a medical gas is presented in an inadequate container, the entire effort put into manufacturing control is wasted. Medical gas quality is directly dependent on the packaging quality.

18.6 Packaging materials are required to be tested or examined prior to their use to ensure that materials of acceptable quality are used in the packaging of medical

gases. Inspection and testing of medical gas containers becomes even more important since they are returned and reused.

Interpretation

18.7 Each lot or batch of packaging material shall, prior to its use in the packaging of a product, be examined or tested against the specifications for that packaging material.

18.8 No lot or batch of packaging material shall be used in the packaging of a product unless the lot or batch of packaging material complies with the specifications for that packaging material.

18.9 Containers are carefully examined against their specifications before filling.

18.10 For high pressure containers returned for filling, checks and tests are performed on each and every container. These checks and tests should include:

a) an external examination of valves and containers for dents, arc burns, dings, oil, grease, and other signs of external damage that might cause a container to be unacceptable or unsafe for use;

b) check to determine that old batch labels with lot numbers and identification, and other damaged labels have been removed;

c) Note: Old labels on shoulder need not be removed if they are identical to the labels currently used, in good condition, and applicable to the product being filled.

d) venting or blowing down to atmospheric pressure if any gas is present; or inverted and drained;

e) an odour or sniff test may be performed to detect the presence of foreign gas or odor;

f) check to determine that the container re-qualification has been conducted as required. Each container is required to be coded (cylinder marking) to show the date of the last hydrostatic test:

i. Steel cylinders are re-qualified every five years unless a "*" follows the testing date which means the cylinder may be re-qualified every ten (10) years.

ii. Aluminum cylinders are re-qualified every five years.

iii. Water used for hydrostatic testing is at least of drinking water quality.

iv. The interior of cylinders are visually examined at appropriate intervals (usually when re-qualification is performed).

g) evacuation of each cylinder (at least to a remaining pressure of 150 millibar) or purging by a suitable method is performed before any medical gas is introduced into the cylinder. As an alternative, full analysis of the remaining gas is carried out for each cylinder. Data should be available demonstrating the suitability of the evacuation or purge.

18.11 Cryogenic vessels undergo certain checks prior to filling. The required pre fill checks are usually contained in the manufacturer's manual supplied with each cryogenic vessel. At a minimum there is:

a) an external vessel check;

b) all inlet and outlet connection check;

c) a label check.

18.12 In addition to examinations as identified above, cryogenic vessels need to be examined for Kenya transport markings (if applicable) and the packager must ensure that the pressure relief device on the unit is appropriate for its intended use.

18.13 The specifications prescribe that each container be reserved for a particular type of medical gas and be identified as such (for example by means of a specific colour).

18.14 Gauges on containers indicating volume or quantity are checked to ensure proper operation.

18.15 Containers failing above examinations and testing are quarantined to prevent their use.

18.16 Examination and testing is documented.

Note : Specific testing information can be found in CAN/CSA B-340, "Selection and Use of Cylinders, Spheres, Tubes and Other Containers for the Transportation of Dangerous Goods, Class 2".

18.17 There should be a system to ensure the traceability of cylinders, cryogenic vessels and valves (PIC/S)

Options for testing of packaging materials

18.18 The examination or testing shall be performed on a sample taken after receipt of each lot or batch of packaging material on the premises of the person who packages a product.

18.19 Alternatively, the examination or testing shall be performed before receipt of each lot or batch of packaging material on the premises of the person who packages a product provided that:

a) The person has satisfactory evidence to demonstrate that packaging materials sold to him by the vendor of that lot or batch of packaging material are consistently manufactured in accordance with and consistently comply with the specifications for those packaging materials; and, the person undertakes periodic complete confirmatory examination or testing with a frequency satisfactory to the Director; and

b) the packaging material has not been transported or stored under conditions that may affect its compliance with the specifications for that packaging material.

18.20 All products and packaging materials to be used should be checked on delivery by the packaging department for quantity, identity and conformity with the packaging instructions.

18.21 After a lot or batch of packaging material is received on the premises of the person who packages a product, the lot or batch of the packaging material shall be examined or tested for identity; and the labels shall be examined or tested in order to ensure that they comply with the specifications for those labels.

Rationale

18.22 There are options as to when the testing or examination of packaging materials are carried out. As with starting materials, the purchase of packaging materials is an important operation that involves staff who have thorough knowledge of the packaging materials and vendor.

18.23 Packaging materials originate only from vendors named in the relevant specification. It is of benefit that all aspects of the production and control of packaging materials are discussed between the manufacturer and vendor. Particular attention is paid to printed packaging materials; labels are examined or tested after receipt on the premises of the person who packages a medical gas.

Interpretation

18.24 This section would apply in the unlikely event that the containers would be tested on premises other than those where the filling takes place.

18.25 Conditions of transportation and storage should be such that they prevent alteration of the characteristics of the packaging material. In order to demonstrate that these conditions have been met, standard operating procedures and records are available and contain the following:

a) the type of packaging to be employed;

b) labelling requirements;

c) mode of transportation;

d) the type and seal of package; and

e) verification required to ensure the package has not been tampered with and that there are no damaged containers.

19.0 Finished Product Testing

Principle 14

19.1 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

19.2 The evaluation of finished products and the documentation necessary for release of a product for sale are described in Principle 17, “Good practices in quality control”.

Rationale

19.3 Finished product tests complement the controls employed during the manufacturing process. It is the responsibility of each producer, packager/labeller, distributor and importer to have adequate specifications and test methods that will help ensure that medical gases sold are safe and meet the standard under which they are represented.

Interpretation

19.4 Each lot or batch of a product shall, prior to its availability for sale, be tested against the specification for that product. No lot or batch of a product shall be available for sale unless it complies with the specifications for that product.

19.5 The specifications shall in writing, approved by the person in charge of quality unit and shall comply with the Act and these regulations

19.6 Written specifications are approved by the person in charge of the quality assurance department or by a designated alternate who meets the requirements described under section 9 as applicable to the activity.

a) The written specifications contain a description of the medical gas, which includes all properties and qualities, including identity, purity, and potency. The specifications also include tolerances and a description of all tests or analyses used to measure compliance with the established tolerances, in sufficient detail to permit performance by qualified personnel. The written specifications also contain the name or identification mark that will be employed for each medical gas throughout the processing operation.

b) Specifications are equal to or exceed a recognized standard and are in compliance with the marketing authorization.

19.7 Test methods are validated, and the results of such validation studies are documented. Full validation is not required for Pharmacopeia methods, but the user of such a method establishes its suitability under actual conditions of use. Pharmacopoeia methods are considered to be validated for the intended use as prescribed in the monograph(s)

Note: Guidance for the validation of particular types of methods can be obtained in publications such as the document entitled "ICH Q2(R1) : Validation of Analytical Procedures : Text and Methodology", WHO TRS 937 Annex 4.

19.8 Each medical gas is tested to ensure that it meets its specifications. The test results are recorded in an appropriate document in a clear and concise manner.

19.9 For a given filling operation of a single gas, a representative number of containers are tested to specification (usually one filled container from each manifold filling sequence).

19.10 For high pressure containers filled individually, one filled container is tested per uninterrupted filling sequence. If the filling sequence is interrupted, then additional testing is required. For mixtures of two gases, every cylinder is tested to specifications of one of the gases, usually the active ingredient. In addition, an identity test for the other gas is performed on one cylinder from the manifold filling sequence.

19.11 For a cylinder containing more than two gases, every cylinder should be tested for specification of all excluding one of the gases, and one cylinder from each manifold filling sequence should be tested for the identity of the remaining gas.

19.12 If a mixture of two or more gases is first filled into a series of storage buffer tanks, and the mixing process of the gases in the buffer tanks can be validated to demonstrate that the mixture remains homogenous within the buffer tanks and during the filling process, then full testing of one cylinder per filling sequence or manifold could be acceptable.

19.13 Vessels filled at curbside do not have to be analyzed provided a certificate of analysis is available for the bulk tank used to make the delivery.

19.14 No additional testing is required for deliveries of liquid nitrogen NF in an unpressurized open-top dewar provided that the source container has been tested, met appropriate specifications, has been released and a certificate of analysis is available for the bulk tank used to make the delivery.

19.15 Identity testing only is required when filling homecare units with liquid oxygen USP on company's premises provided a certificate of analysis is available for the source container.

19.16 Due to the carcinogenic nature of ethylene oxide, an identity test is not required to be performed on any medical gas mixtures of ethylene oxide by the importer as long as the importer sells the gas mixture "as is, in the same container" and does not perform any additional production and/or packaging operations for this gas mixture. A certificate of analysis is required from the producer of the gas mixture.

19.17 Any lot or batch of medical gas that does not comply with specifications is quarantined pending final disposition and is not made available for sale.

19.18 Testing is performed on a sample taken after receipt on the premises of the distributor or importer of the medical gas unless the distributor or importer chooses to rely on test results provided by the supplier.

19.19 To demonstrate compliance with specifications, distributors of finished products that are produced, packaged/labelled, and tested at Kenyan sites are required only to have a copy of the authentic certificate of analysis from the licensed Kenyan establishment.

19.20 This certificate shows actual numerical results and refers to the product specifications and test methods used. Retesting, including identity testing, is not required.

19.21 To demonstrate compliance with specifications, importers of finished products produced, packaged/labelled, and tested at PPB recognized laboratories and identified on their establishment license are required only to have a batch certificate in the format agreed on for each lot or batch of the product received. Re-testing, including identity testing, is not required when the product is produced, packaged/labelled, and tested in an MRA country.

Sites in Non-MRA Countries

19.22 For testing other than identity testing, the following conditions are to be met if the importer chooses to rely on the test results provided by an establishment located in a non-MRA country:

a) Evidence of ongoing GMP compliance is provided

b) each lot is accompanied by an authentic certificate of analysis or by a copy thereof (an electronic copy with an electronic signature is acceptable). The certificate of analysis exhibits actual numerical results and makes reference to the product specifications and test methods used;

c) periodic complete confirmatory testing is performed on at least one lot per year per producer. Products are selected on a rotational basis.

d) provided that a specific identity test is performed, a lot or batch of a finished product selected for periodic confirmatory testing may, with the approval of the quality assurance department, be released for sale prior to completion of all tests.

19.23 Should any failure to conform to finished product testing requirements be identified, an investigation of the extent of the non-compliance is to be conducted. This procedure may include:

a) re-evaluation of GMP compliance; and

b) additional complete confirmatory testing, based on the risk associated with the non-compliance.

19.24 Positive identification of each lot or batch in a shipment of a medical gas is carried out on a sample taken after receipt on the premises of the importer. To be exempted from identity testing using the unique identifier principles of labeled dedicated bulk tanks of imported medical gas:

a) foreign site must be listed on the Product Establishment Licence,

b) only labeled dedicated bulk tanks are to be used, bulk tank has traceability identification, and attestation is available for tank dedication declaration,

c) importer ensures that:

i. certificate of analysis and manufacturing license must be verified prior to customer delivery by Quality assurance approval for release,

ii. foreign supplier is qualified by a vendor certification program

iii. periodic confirmatory testing is performed,

d) not applicable for mixed gases.

20.0 Records

Principle 15

20.1 Every producer, packager/labeller, distributor and importer shall maintain specific product information on their premises

20.2 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of products are traceable.

Records should be retained for at least one year after the expiry date of the finished product.

20.3 A batch processing records should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)

20.4 records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected. Any significant deviations are fully recorded and investigated with the objective of determining the root cause and appropriate corrective and preventive action is implemented;

20.5 QC should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

20.6 Stability should be determined prior to marketing and following any significant changes, for example, in processes, equipment or packaging materials.

20.7 For each batch of medicines, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

20.8 Before releasing a starting or packaging material for use, the QC manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

20.9 There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.

20.10 The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt, and in general, any adverse effect on the quality of products.

20.11 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

20.12 Responsible staff should have its specific duties recorded in written descriptions and adequate authority to carry out its responsibilities. Its duties may be delegated to designated deputies with a satisfactory level of qualifications. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.

Principle 15.8

20.13 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

20.14 All records and evidence on the testing of starting materials, and packaging/labelling materials that are required to be maintained shall be retained for a period of at least five years after the materials were last used in the production or packaging/labelling of a product unless otherwise specified in the person's establishment licence.

Principle 6

20.15 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

Principle 5

20.16 All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.

20.17 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

20.18 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for QC should normally be involved in the review of such investigations.

20.19 The producer, packager/labeller, wholesaler, distributor or importer of the product, as the case may be, shall retain it for a period of at least one year after the expiration date of the lot or batch of that product, unless otherwise specified in their establishment licence.

Principle 8

20.20 A report should be made at the completion of a self-inspection. The report should include: self-inspection results; evaluation and conclusions; recommended corrective actions.

20.21 Every person who produces or packages/labels a product shall maintain records on the operation of the sanitation programme required to be implemented under section and retain those records for a period of at least three years.

Rationale (Principle 15)

20.22 Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure

that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a medicine for sale; to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation.

20.23 Good documentation ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases, some or all of the documents described below may be brought together, but they will usually be separate.

20.24 Evidence that medical gases have been produced and packaged/labelled under prescribed conditions can be maintained only after developing adequate record systems. The information and evidence should provide assurance that imported medical gases are produced and packaged/labelled in a like manner to those produced in Kenya.

Interpretation

20.25 For all Principles of the GMP guidelines, standard operating procedures (SOPs) are retained for reference and inspection. These SOPs are regularly reviewed and kept up to date by qualified personnel. The reasons for any revisions are documented. A system is in place to ensure that only current SOPs are in use. Records of SOPs for all computer and automated systems are retained where appropriate.

20.26 All relevant GMP documents (such as associated records of actions taken or conclusions reached) and SOPs are approved, signed, and dated by the quality unit. Documents are not altered without the approval of the quality unit. Any alteration made to a document is signed and dated; the alteration permits the reading of the original information. Where appropriate, the reason for the change is recorded.

20.27 Records may be maintained in electronic format provided that backup copies are also maintained. Electronic data must be readily retrievable in a printed format. During the retention period, such records must be secured and accessible within 48 hours to the producer, packager/labeller, wholesaler, distributor, or importer.

20.28 An electronic signature is an acceptable alternative to a handwritten signature. When used, such a system must be evaluated and tested for security, validity, and reliability, and records of those evaluations and tests must be maintained. The validation of electronic signature identification systems is documented.

20.29 Any documentation requested for evaluation is provided in one of the official languages in Kenya.

20.30 Records must include a master production documents duly verified, dated and signed. Each step of the process is documented. However, rather than repeating in detail each operation in the manufacturing orders, one may refer to the master filling documents that contain all these details.

20.31 Records kept applies only to producers, packagers/labellers, distributors referred to and importers to the extent that they perform operations on the medical gas.

20.32 Documentation must be available to support the expiry date of the medical gas. 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.

For gas mixtures, the expiry date should be based on validation studies pertaining to the physical aspects such as the rate of stratification.

20.33 The following documents must be maintained by the producer, packager/labeller, wholesaler, distributor, and importer of a medical gas as they relate to operations in Kenya:

a) distribution records of all sales of medical gas including those of professional samples are retained or readily accessible in a manner that will permit a complete and rapid recall of any lot or batch of a product. This does not necessarily imply tracking by lot number;

b) records of complaints or other information that is received relating to quality, deficiencies or hazards of a medical gas. Records of any subsequent investigations, including corrective actions taken.

c) Records of the results of the self-inspection program and action taken;

20.34 The following documents must be maintained by the producer of medical gas mixtures:

a) the written specifications for the starting materials;

b) the results of the starting material testing;

c) the sources of the starting materials supplied.

20.35 The following documents must be maintained by the packager/labeller:

a) the written specifications for the packaging materials;

b) the results of the packaging material examinations or testing;

c) the sources of the packaging materials supplied.

20.36 Every distributor and importer shall make available on request the results of testing performed on starting materials and packaging/labelling materials for each lot or batch of a medical gas sold.

20.37 Every producer shall maintain on their premises:

a) detailed plans and specifications of each building at which they produce package/label or test; and

b) a description of the design and construction of those buildings.

20.38 Every producer, packager/labeller, and tester shall maintain on their premises details of the personnel employed to supervise the production, packaging/labelling, and testing including each person's title, responsibilities, qualifications, experience, and training.

20.39 Documentation for cylinders and valves include:

a) Certification issued in accordance with Kenya Bureau of standards requirements may be acceptable as a means of compliance for new cylinders. It is expected that written specifications are available which outline the checks which are to be performed on empty cylinders prior to filling and that a record of those checks is maintained.

b) Valves on cylinders should be checked for functionality and records maintained.

c) Records on the operation of the sanitation program required under Principle 3 must be maintained by the producer and the packager of medical gases.

d) Records of testing performed on raw materials and packaging/labelling materials for each lot or batch of a product sold, records of the sale or each lot or batch of the product, and relevant records for receipt and handling of complaints are ordinarily retained for a period of at least one year past the expiration date of the product to which the records apply. However, for medical gases which do not require an expiration date, these records are retained for a period of at least five years from the date of production or packaging/labelling. Gas chromatograms charts are considered to be records/evidence of testing and must be maintained for 5 years from the date of filling.

e) Records are maintained detailing the qualifications/experience of any consultant employed for GMP purposes, along with the services that each consultant provides.

Medical Gases

20.40 The following are not applicable to medical gases

a) The retention of a sample of each lot or batch of the packaged/labelled product for one year after the expiration date of the product by distributor and importer of a product in dosage form

b) The requirement for a distributor and an importer or a manufacturer of a product in dosage form to monitor, by means of a continuing program, the stability of the product in the package in which it is sold.

c) The retention of sample of each lot/batch of the packaged/labelled medicine for one year after the expiration date of the medicine in an amount that is sufficient to determine whether the product or raw material complies with the specifications for that product or raw material.

d) the requirements for a product that is intended to be sterile being produced and packaged/labelled in separate and enclosed areas, under the supervision of personnel trained in microbiology; and by a method scientifically proven to ensure sterility

Appendices

Appendix A: Acronyms and Glossary of Terms

Acronyms

DIN : Product Identification Number

GMP : Good Manufacturing Practices

ICH : International Conference on Harmonization

MRA : Mutual Recognition Agreement

PIC/S : Pharmaceutical Inspection Cooperation/Scheme

SOP : Standard Operating Procedure

Glossary of Terms

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

Batch or Lot: A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. (ICH Q7)

Batch Certificate: A certificate issued by the fabricator of a lot or batch of a product that is exported within the framework of a mutual recognition agreement and in which the fabricator:

a) identifies the master production document for the product and certifies that the lot or batch has been fabricated, packaged/labelled and tested in accordance with the procedures described in that document;

b) provides a detailed description of the product, including

   i. a statement of all properties and qualities of the product, including the identity, potency and purity of the product, and

   ii. statement of tolerances for the properties and qualities of the product;

c) identifies the analytical methods used in testing the lot or batch and provides details of the analytical results obtained;

d) sets out the addresses of the buildings at which the lot or batch was fabricated, packaged/labelled and tested; and

e) certifies that the lot or batch was fabricated, packaged/labelled and tested in accordance with the good manufacturing practices of the regulatory authority that has recognized those buildings as meeting its good manufacturing practices standards.

Bulk gas:	A static container that is used to store liquefied or cryogenic gas and is thermally insulated (to keep temperatures stable). Also called "stationary cryogenic vessels."
Certificate of manufacture:	A document issued by a vendor to a distributor or importer that attests that a specific lot or batch of product has been produced in accordance with its master production documents. Such certificates include a detailed summary of current batch documentation, with reference to respective dates of revision, manufacture, and packaging, and are signed and dated by the vendor's quality control department. For products that are fabricated, packaged/labelled and tested in MRA countries, the batch certificate is considered to be equivalent.
Change control:	A written procedure that describes the action to be taken if a change is proposed (a) to facilities, materials, equipment and/or processes used in the fabrication, packaging and testing of products, or (b) that may affect the operation of the quality or support system.
Critical process:	A process that, if not properly controlled, may cause significant variation in the quality of the finished product.
Cryogenic vessel:	A stationary or portable vacuum insulated container designed to contain liquefied gas at extremely low temperatures. Mobile vessels are also called "Dewars."
Curbside delivery:	The filling of cryogenic vessels with cryogenic liquefied gas at the point of use.
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. (PIC/S)
Distributor or manufacturer:	A person, including an association or partnership, who under their own name (or under a trade, design or word mark, trade name or other name, word, or mark controlled by them) sells a food or product. (A.01.010)
Produce:	To prepare and preserve a product for the purposes of sale." Also referred to as "fabricate" or "manufacture."
Finished product:	A product that has undergone all stages of production, including packaging in its final container and labelling.
Gas:	Products in gaseous phase and products in liquid phase at cryogenic temperatures or liquefied compressed gases at 15 °C and 1 atmosphere.
Home cryogenic vessel:	Mobile tanks designed to hold liquid oxygen (at very low temperatures) and dispense gaseous oxygen at patients' homes.
Hydrostatic pressure test:	A test performed as required by national or international regulations, to ensure that containers are able to withstand pressures up to the container's design pressure. (PIC/S)
Immediate container:	The receptacle/vessel that is in direct contact with a product.
Liquefied gas:	A gas that has a critical temperature above 200C, which remains as a liquid in the container when under pressure.
Manifold:	Equipment or apparatus designed to allow one or more medical gas containers to be filled at a time.
Manifold	filling sequence of many containers at one time, using a multiple

filling sequence:	outlet manifold or rack.
Marketing authorization:	A legal document issued by the Pharmacy and Poisons Board, authorizing the sale of a product or a device based on the health and safety requirements of the *Food and Products Act* and its Regulations. The marketing authorization may be in the form of a Notice of Compliance (NOC), Product Identification Number (DIN), a device licence for classes II, III and IV medical devices, a natural product number (NPN), or a homeopathic DIN (DIN-HM).
Master filling documents:	A set of instructions for the filling of containers with a medical gas in dosage form. They contain a description of the filling operation, controls, procedures, specifications and methods of quality control of the medical gas.
Master formula:	A document or set of documents specifying the raw materials with their quantities and the packaging materials, a detailed description of the procedures and precautions required to produce a specified quantity of a finished product, and the processing instructions (including in-process controls).
Master production documents (MPD):	Documents that include specifications for raw material, for packaging material and for packaged dosage form; master formula (including composition and instructions as described in the definition above), sampling procedures, and critical processing related standard operating procedures (SOPs), whether or not these SOPs are specifically referenced in the master formula.
Medical gas:	Any gas or mixture of gases manufactured, sold or represented for use as a product.
MRA country:	A country that is a participant in a mutual recognition agreement (MRA) with Kenya.
Mutual recognition agreement (MRA):	An international agreement that provides for the mutual recognition of compliance certification for good manufacturing practices for products.
Package/label:	To put a product in its immediate container or to affix the inner or outer label to the product. This includes the repackaging and relabeling of previously packaged and labelled products.
Packaging material:	includes a label. Note: For the purpose of these guidelines, this definition also includes: Labels, printed packaging materials, any material intended to protect the intermediate or API or product during storage and transport and those components in direct contact with the final API or product.
Qualified authority:	A member of the Pharmaceutical Inspection Cooperation/Scheme (PIC/S).
Quality control department:	A unit in an establishment that monitors the quality of production operations, and exercises control over the quality of materials required for and resulting from those operations.
Quality Manual:	Document specifying the quality management system of an organization.
Quarantine:	The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection. (ICH Q7)

Raw material:	The individual gases that are used in the production of medical gas mixtures.
Regulatory authority:	A government agency or other entity in an MRA country that has a legal right to control the use or sale of products within that country, and that may take enforcement action to ensure that products marketed within its jurisdiction comply with legal requirements.
Specifications:	Means a detailed description of a product, the raw material used in a product, or the packaging material for a product and includes: a) a statement of all properties and qualities of the product, raw material or packaging material *(a)*that are relevant to the manufacture, packaging, and use of the product, including the identity, potency, and purity of the product, raw material, or packaging material, b) a detailed description of the methods used for testing and examining the product, raw *(b)*material, or packaging material, and c) a statement of tolerances for the properties and qualities of the product, raw material, or *(c)*packaging material.
Standard operating procedure (SOP):	A written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (for example: equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documents.
Tanker:	A thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas. (PIC/S)
Uninterrupted filling sequence:	A single, continuous filling sequence with no breaks or shutdowns during filling and no change of personnel, equipment, or lots of raw materials. This procedure applies to the individual filling of high-pressure cylinders (one cylinder at time).
Validation:	A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criterion. (ICH Q7).
Vendor:	Any person or company that sells or supplies goods or services to another company. Also called “supplier.”
Wholesaler:	A person who is not a distributor and who sells any of the following products other than at retail sale: (a) a product in dosage form or (b) an active ingredient

Appendix B- Questions and answers

Finished product testing –

1. ***When produced synthetically from oxygen and nitrogen raw materials (that respectively meet United States Pharmacopeia (USP) and National Formulary (NF) specifications), should medical air USP be exempt from analysis for water/oil, carbon dioxide, nitric oxide/nitrogen dioxide, and sulphur dioxide?***

   If compendial specifications require impurity tests, then they must be performed.

2. ***When is oxygen exempt from being tested for carbon dioxide?***

   The USP exempts oxygen with purity of no less than 99% from the requirements of the tests for carbon dioxide and carbon monoxide when the oxygen has been produced by the air liquefaction method. Other Schedule B (compendial) monographs may have similar exemptions.
   You should have documentation available showing that the specific lot of oxygen has been produced by the air liquefaction process.

3. ***Can mixtures of medical gases be labelled only as being a USP mixture?***

   Only mixtures of medical gases which meet USP monographs as mixtures may be labelled as USP.

4. ***A firm receives liquid nitrogen from a supplier with a valid certificate of analysis for each delivery. The firm's operation involves the filling of high-pressure cylinders via a heat exchanger or a vaporizer. Should a test for identity and assay be performed on one filled container from each manifold filling sequence, or can we rely on the test results provided by the supplier with no further testing?***

   Liquid nitrogen received from a supplier should be tested according to the GMP requirements under Manufacturing control. Also, one filled cylinder from each manifold filling sequence should be tested according to the GMP requirements under Finished product testing.

5. ***Is a company required to notify the Board of a change in key personnel, such as the person in charge of quality control or manufacturing?***

   No. But it is your responsibility to make sure the new person meets the requirements of interpretations 8.6 and 8.7 under section Principle 9 “Personnel” (depending on the activities performed).

Appendix C-References

1. *Pharmacy and Poisons Act Cap 244 of the Laws of Kenya* https://www.kpacentral.or.ke/documents/2018%20CAP%20244.pdf

2. 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/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. *Good manufacturing practices (GMP) guidelines for product products (GUI-0001)* https://www.canada.ca/en/health-canada/services/products-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001.html

4. *ICH Q2 Validation of Analytical Procedures: Text and Methodology* https://www.canada.ca/en/health-canada/services/products-health-products/product-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/validation-analytical-procedures-text-methodology.html

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