BELIZE:

STANDARDS (BELIZE STANDARD CODE OF GOOD MANUFACTURING PRACTICES FOR MEDICAL GASES) (DECLARATION AS A COMPULSORY STANDARD) ORDER, 2025

ARRANGEMENT OF PARAGRAPHS

BELIZE:

STATUTORY INSTRUMENT

No. 133 of 2025

ORDER made by the Minister responsible for the Bureau of Standards, on the recommendation of the Belize Bureau of Standards, in exercise of powers conferred upon him by section 9(2) of the Standards Act, Chapter 295 of the Substantive Laws of Belize, Revised Edition 2020, and all other powers thereunto him enabling.

(Gazetted 29th September, 2025).

WHEREAS, section 9(3) of the Standards Act, Chapter 295 of the Laws of Belize, provides that the Minister shall, by publication in the Gazette, give at least thirty days' notice of his intention to make an Order declaring a compulsory standard and shall thereby indicate the date on which it is intended that the compulsory standard shall come into force;

AND WHEREAS, aa notice of intention to declare the BELIZE STANDARD CODE OF GOOD MANUFACTURING PRACTICES FOR MEDICAL GASES (BZ CP 7: 2025) to be a compulsory standard was published in the Belize Gazette dated 21st July 2025;

AND WHEREAS, no objections have been received to the making of the said Order;

NOW, THEREFORE, IT IS ORDERED as follows:–

1. This Order may be cited as the **Citation.**

STANDARDS (BELIZE STANDARD CODE OF GOOD MANUFACTURING PRACTICES FOR MEDICAL GASES) (DECLARATION AS A COMPULSORY STANDARD) ORDER, 2025.

Declaration of Compulsory Standard. Schedule.

2. The BELIZE STANDARD CODE OF GOOD MANUFACTURING PRACTICES FOR MEDICAL GASES (BZ CP 7: 2025), the full text of which appears in the Schedule hereto, is hereby declared to be a compulsory standard.

Purpose of Compulsory Standard.

3. The standard referred to in paragraph 2 is intended primarily to–

(a) protect the consumer or user against danger to health or safety;

(b) ensure quality in goods produced for home use or for export;

(c) prevent fraud or deception arising from misleading advertising or labelling;

(d) require adequate information to be given to the consumer or user; and

(e) ensure quality in any case where there is restriction in choice of source of supply.

Commencement.

4. This Order shall come into effect on the 1st day of October 2025

SCHEDULE
[paragraph 2]

BELIZE STANDARD
CODE OF GOOD MANUFACTURING PRACTICES FOR MEDICAL GASES

0 FOREWORD

0.1 There has been an increasing need to ensure medical gases supply comply with appropriate standards, in order to ensure its quality and adequacy to be classified as drugs.

0.2 Practices during production, storage and distribution of medical gases shall ensure these products remain free from undesired contaminants and are appropriate to be administered to patients. Industrial gases shall not be used in medical applications.

0.3 This standard outlines requirements for manufactures and distributors of medical gases classified as drugs.

0.4 In preparing this draft, assistance was received from the following documents:

a) CGA M-3 Standard for the Manufacturer of Bulk Medical Gases. 2021;

b) WHO Good Manufacturing Practices for medicinal gases (Draft). 2021; and

c) FDA Current Good Manufacturing Practices for Medical Gases. Guidance for Industry.

1 SCOPE

1.1 This code of good manufacturing practices for medical gases provides requirements for the production, storage, and distribution of the following medical gases:

a) Oxygen;
b) Nitrogen;
c) Carbon dioxide;
d) Nitrous Oxide;

e) Air; and
f) Any other gases classified as drugs.

1.2 This standard is not intended to be used in hospitals or at home for personal use.

1.3 Atmospheric air contains a large variety of trace constituents. It is impractical to set individual limits for many of these; however, this specification qualifies certain grades of air by limiting the concentrations of specific trace constituents.

2 NORMATIVE REFERENCES

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

a) BZS 1: Part 8 - Belize Standard Specification for Labelling Part 8: Labelling and Marking of Medical Gas Cylinders

b) Belize Standard Specification for Medical Gases: General Requirements

c) CGA M-3 Standard for the Manufacturer of Bulk Medical Gases, 2021

d) WHO Good Manufacturing Practices for medicinal gases (Draft), 2021

e) FDA Current Good Manufacturing Practices for Medical Gases, Guidance for Industry, 2017

f) US Code of Federal Regulations. 21 CFR Part 211

3 TERMS AND DEFINITIONS

For the purpose of this standard, the following definitions of terms shall apply:

3.1 **Adulterated** means a condition in which a drug product actually or potentially does not meet all required or claimed

standards of purity, strength, identity, or quality, or contains a foreign substance that can be injurious to health.

3.2 **Alternate test method** means an analytical method that is different from those described in the official USP/NF monograph and has been validated to produce results that meet or exceed those achieved using the official USP/NF monograph method.

3.3 **Assay** means an analytical test used to determine the strength of the component of interest (for example, percent oxygen).

3.4 **Automated analysis** means systems in the bulk medical gas filling or testing process that provide for automatic sampling, analysis, recording, and/or storage of required quality control data.

3.5 **Batch** means a specific quantity of a drug or other material that is intended to have uniform character and quality within specified limits and be produced according to a single manufacturing order during the same cycle of manufacture.

3.6 **Bulk medical gas** means a gas produced by various processes (distillation, cooling, purification) that is typically shipped in large quantities in liquid tankers, rail tank cars, or tube trailers.

3.7 **Calibrate** means to check, adjust, or determine by comparison with a certified standard.

3.8 **Calibration** means a process by which an instrument is checked or adjusted to a certified standard.

3.9 **Certificate of analysis (COA)** means a document supplied by the manufacturer that lists the specific analytical results of a shipment of drug product.

3.10 **Commingled** means a condition occurring when two or more noncontinuous batches or lots of bulk medical gas product are blended together.

3.11 **Compendia** means an official compilation of drug monographs, which includes medical gases, containing minimum drug product specifications purity requirements and testing methods.

3.12 **Compendial method** means a specific analytical method contained or referenced in a monograph in an official compendium.

3.13 **Component** means any ingredient intended for use in the manufacture of a drug product, including those that may not be used in thedrug product.

3.14 **Compressed medical gas (CMG)** means medical liquefied or vaporized gas alone or in combination with other gases that is a drug. Gas intended for direct use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in man or animals that achieves its intended purpose through chemical rather than physical means.

3.15 **Container** means a vessel designed and constructed to retain a liquid or gas under positive pressure. For the purpose of this publication, the container is a cryogenic trailer, tank, tanker or rail car.

3.16 **Cylinder** means a cylindrical container suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

3.17 **Contaminant** means any substance that can significantly affect the purity and physical attributes of CMG.

3.18 **Drug** means a **s**ubstance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. Substance (other than food) intended to affect the structure or any function of the body of man or other animals.

3.19 **Medical gas** means any gas intended to be an active substance for a medical product.

3.20 **In-process** means the intermediate stage within the manufacturing operation.

3.21 **Labelling** means labels and other written, printed, or graphic material on a CMG container or wrapper, or the written,printed, or graphic material accompanying a CMG.

3.22 **Lot or batch** means an amount of a product produced during a period and with the same characteristics, identified by a specific code.

NOTE: For bulk manufacturing, the lot is considered the amount in a single container.

3.23 **Lot number** means any distinctive combination of letters, numbers, or symbols from which the complete history of the manufacture and distribution can be determined.

3.24 **Manufacturer** means a person or firm that produces CMGs; fills CMG containers by liquid-to-liquid, liquid-to-gas, or gas-to-gas; or relabels filled containers of CMGs.

3.25 **Misbranded** means a condition in which the label or labelling of the medical gas does not clearly identify the medical gas; does not bear all required information; bears the required information in an inconspicuous manner; or gives information that is misleading, inaccurate, incomplete, or dangerous.

3.26 **Monograph** means specifications and test methods for CMGs.

3.27 **Prefill** means operations or procedures performed to ensure the suitability of residual medical gas product in a container beforethe introduction of the intended gas.

3.28 **Production record** means quality record that is used to record significant GMP process steps.

3.29 **Quality Control Unit (QCU)** means any person or organizational element designated by the firm as responsible for the duties relating to quality control.

3.30 **Quarantine** means physical isolation, segregation, or identification of medical gases or materials pending a decision on their subsequent disposition.

3.31 **Residual** means medical gas product remaining in a container upon return to the manufacturer.

3.32 **Review / Release** means by the quality control unit (QCU) to evaluate production and quality control records for accuracy, completeness, and compliance and then approve or reject the medical gas for release.

NOTE: The person performing the release and review cannot be the same person that conducts and records the production.

3.33 **Validation** means documented evidence providing a high degree of assurance that a specific process consistently produces aproduct that meets its predetermined specification and quality attributes.

4 HEALTH AND SAFETY CONSIDERATIONS

4.1 All individuals associated with the manufacture of bulk medical gases shall be trained in the applicable current good manufacturing practices for gases:

a) licensing requirements for wholesale prescription drug distributors by state licensing authorities;

b) minimum qualifications for firms being licensed;

c) minimum qualifications for personnel employed by a firm engaged in wholesale distribution; and

d) storage, security, and handling requirements for prescription drugs; and establishing and maintaining prescription drug distribution records.

4.2 Any firm engaged in the manufacture of medical gases shall register each of its manufacturing sites on a biannual basis.

Submission of a biannual registration renewal is subject to verification status of a firm's operation.

5 ORGANIZATION

5.1 Quality Unit

a) The establishment of an effective quality system reflects the principle that quality shall be built into the product; testing alone cannot ensure product quality. This standard provides that the quality control unit or quality unit has the authority needed to create, monitor, and implement a quality system.

b) The quality unit's responsibilities and procedures shall be in writing and its procedures shall be followed.

c) Manufacturers shall have a quality unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labelling, and drug products and the authority to review production records to ensure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality unit is also responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

d) Production personnel and the quality unit typically remain independent. Some medical gas manufacturing sites, however, have limited personnel, and the individuals assigned to the quality unit also perform production functions. These individuals implement all the controls and review the results of manufacture to ensure that product quality standards established by the manufacturer have been met, regardless of their production functions or other roles.

e) This approach is considered to comply with GMP requirements provided that each individual who performs quality unit functions is adequately trained and experienced in all quality unit tasks assigned.

f) Individuals who are part of the quality unit shall be identified by function and title in written.

g) procedures to ensure that the appropriate quality unit responsibilities are fulfilled.

5.2 **Supplier Qualifications**

a) Written procedures shall explain how manufacturers qualify and approve suppliers.

b) Manufacturers shall determine supplier qualifications to ensure that quality standards are met and that purchased gases, including feeder gases, have an accurate and complete certificate of analysis (COA). If using a supplier's COA, manufacturers shall conduct at least one specific identity test and establish the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

c) Such periodic testing may be performed by the manufacturer, a third party, or a contract-testing laboratory.

d) Manufacturers shall periodically verify the qualification of approved suppliers by conducting audits (on-site or remote), analyzing trends in the quality of received goods, testing, and evaluating the timeliness of supplier responses to complaints. The methodology to qualify suppliers shall be established by the manufacturer in a written document or SOP.

6 QUALITY MANAGEMENT

6.1 **General**

a) Companies that are involved in the manufacture, control, storage and distribution of medicinal gases shall document, implement and maintain a comprehensively designed and clearly defined quality management system. This is the responsibility of senior management.

b) Senior management shall also assume responsibility for the quality of the medicinal gases manufactured, controlled, released, stored and distributed.

c) All parts of the quality system shall be adequately resourced and maintained.

d) The quality system shall consider the life cycle of the medical gases. From the receipt of raw materials, manufacturing, filling, testing, release, distribution and containers return after use of the gases.

e) The system for quality risk management shall cover a systematic process for the assessment control, communication and review of risks in the production, filling, control, storage and distribution of medical gases, ultimately, protect the patient from receiving the wrong or contaminated product.

f) The quality management system shall ensure that:

i. Medical gases are manufactured, controlled, stored and distributed in accordance with this standard;

ii. Managerial roles, responsibilities and authorities are clearly specified in job description;

iii. Operations and other activities are clearly described in a written form such as standard operating procedures (SOP) and work instructions;

iv. Arrangements are made for the manufactures, supply and use of the correct containers and labels;

v. All necessary controls are in place;

vi. There is a system for quality risk management;

vii. Calibrations and validations are carried out where necessary;

viii. The finished product is correctly processed and checked according to the defined procedures and specifications;

ix. Deviations, suspected product defects, out of specification test results and any other non-conformances or incidents are reported, investigated and recorded;

x. Appropriate corrective actions and preventive actions are identified and taken where required processes are in place to ensure the management of any outsourced activities that may impact product quality and integrity;

xi. Finished products are not released and supplied before the authorized person has certified that each production batch has been manufactured and controlled in accordance with product specifications, and this standard;

xii. There is a system for handling complaints, returns and recalls from the market; and

xiii. There is a system for self-inspection.

6.2 **Documentation**

a) Documents shall have unambiguous content and be laid out in an orderly fashion. The title, nature and purpose shall be clearly stated.

b) Documents shall be periodically reviewed and kept up to date. Superseded documents shall not be used.

c) Where documents require the entry of data, these entries shall be clear, legible and indelible, in compliance with

good documentation practices and data integrity requirements.

d) Records shall be made or completed when any action is taken and in such a way that all significant activities are traceable. Records shall be retained for a period of time as defined by internal procedures or national legislation, as appropriate.

e) Records shall be maintained for each batch of gas manufactured.

f) Written release and rejection procedures shall be available, in particular for the release of the finished product for sale.

g) Records shall be maintained of the distribution of each batch of medicinal gas.

h) Labels shall be clear, unambiguous and in compliance with national or regional legislation asappropriate.

i) Labels on the cylinders of medicinal gases shall contain at least the information as recommended in the pharmacopoeia, where applicable, as well as the following information:
   i. the name of the medicinal gas;
   ii. the batch number assigned by the manufacturer;
   iii. the expiry or use-before date, if applicable;
   iv. any special storage conditions or handling precautions that may be necessary;
   v. directions for use;
   vi. warnings and precautions;
   vii. the name and address of the manufacturer; and
   viii. test date (month and year).

6.3 **Standard Operating Procedures (SOP)**

a) GMP require that each firm develop, approve, implement, and maintain its own SOP.

b) SOP shall be in writing and approved by the QCU. GMP outline the areas that shall be addressed in SOP and suggest minimum requirements.

c) SOP shall be current, accessible, and followed by the applicable personnel.

d) SOPs and associated records shall be available for at least, but not limited to:
   i. equipment;
   ii. analytical apparatus and instruments;
   iii. maintenance and calibration;
   iv. cleaning and sanitization;
   v. personnel matters such as training, clothing and hygiene;
   vi. qualification and validation;
   vii. self-inspection
   viii. complaints;
   ix. recalls; and
   x. returns.

7 PERSONNEL

7.1 Personnel qualification

a) All personnel, including those working on the manufacturing floor or driving to customer sites to distribute medical gas, shall have the education, training, and experience necessary to perform their assigned functions.

b) Inadequately trained personnel could inadvertently fill the wrong gas into a storage tank or connect the wrong gas to a gas supply system, which can result in serious injury or death.

c) Personnel, including drivers, who connect portable cryogenic containers to gas supply systems shall be trained appropriately in the specifics of those supply systems.

d) Drivers who deliver multiple gases (including multiple medical gases or both medical and industrial gases) shall

be trained to accurately identify each gas and distinguish between them.

e) Personnel shall be trained in GMP requirements on annual basis to provide assurance that they remain familiar with the applicable requirements training. The manufacturers keep training records that include time and attendance entries.

7.2 **Education and Experience**

For bulk medical gas manufacturing operations, the ability to read, write, and understand the language in which the firm's applicable SOPs are written as well as the ability to perform simple arithmetic operations may be required for certain job functions. A firm shall establish its own educational/experience requirements based on the specific job function.

7.3 **Training**

a) The GMP regulations require that personnel be trained in the operations they perform as well as in the portions of the GMP regulations that apply to their job functions. Training content and frequency shall be defined in writing and shall occur at intervals that ensure employees remain familiar with the regulations and procedures applicable to their job functions.

b) Training in specific job functions is usually obtained through on-the-job training (OJT) provided by someone within the firm that is knowledgeable in the specific operation and associated written procedures and that has sufficient experience in performing or supervising the operation. Additional training can be obtained by seminars, instructor-led classroom training, self-study, vendors, etc.

c) Training in applicable portions of the GMP regulations can be obtained through internal or external training sessions and/or OJT. The firm shall maintain records of training received by personnel engaged in the manufacturing of medical gases. GMP training is usually

conducted annually; however, some functions can require more frequent training and other functions can require less frequent training.

d) Individuals that review records for accuracy, completeness, and compliance with procedures shall be trained in GMP, documentation review, and the procedures applicable to the operation.

e) All training shall be documented and may include the following as applicable:
   i. identification of the trainer(s);
   ii. identification of the trainee(s);
   iii. date of the training;
   iv. duration of training; and
   v. specific topic(s) covered.

NOTE: Documentation can include any reference material used in the training, e.g., procedures, publication, videotapes, etc.

7.4 Quality Control Unit

7.4.1 Responsibilities

a) Drug manufacturers shall establish a QCU with authority and responsibility to ensure their medical gases are not adulterated or misbranded. The QCU shall have the responsibility and authority to:

b) Approve or reject procedures and specifications impacting the identity, strength, quality, and purity of the bulk medical gases manufactured;

c) Approve or reject supply gases or raw materials used for manufacturing bulk medical gas;

d) Approve or reject in-process and finished bulk medical gases manufactured;

e) Review production and test records to ensure that no errors have occurred, or if errors have occurred that they have been fully investigated;

f) Ensure that any out of specification (OOS) results have been adequately investigated;

g) Ensure adequate laboratory facilities and equipment are available for the testing and approval/rejection of raw materials, in-process, and finished medical gases; and

h) Personnel assigned to the facility QCU may perform other functions not related to quality. However, when performing quality control functions personnel are under the direction of the QCU.

i) An individual that performs quality control functions shall not review their own work.

7.4.2 **Head of quality control**

An individual shall be designated to head the QCU. Multisite companies may wish to designate an individual to head the QCU for the entire firm. The head of quality control can delegate certain functions of the QCU. However, responsibility for the overall acceptable functioning of the QCU remains with the head of the unit.

7.4.3 **Delegation of responsibilities and authorities**

a) Bulk medical gas manufacturers define the responsibilities and assign the required duties to individuals at a site. These individuals shall be qualified by their education, training and experience, or any combination thereof to perform the specific functions assigned to them. During the performance of QCU functions these individuals report to the head of quality control.

b) Employees of a contracted firm can perform quality control functions including but not limited to, reviewing documentation for accuracy, completeness,

and compliance and approving or rejecting the release of medical products providing:

i. The firm using the contracted employee has a written agreement with the contracted firm allowing the approval to release the medical products; and

ii. The contracted employee has the education, training and experience, or any combination thereof necessary to ensure the steps required are performed in accordance with approved procedures and in compliance withthe regulations.

c) The responsibilities and procedures applicable to the QCU shall be documented in writing and the procedures shall be followed.

7.5 **Personnel health and safety**

a) Personnel shall observe good health, safety, and sanitation practices; however, health and sanitation habits are not critical to protect the product from contamination.

b) An illness that impacts a person's ability to perform a job function shall be reported to a supervisor.

c) Specific clothing and apparel requirements may be necessary to ensure safe operations; however personal protective equipment (PPE) has no impact on the product quality.

7.6 **Consultants**

Consultants advising or providing training on the manufacture, processing, packing, or holding of the product shall have sufficient education, training, experience, or any combination thereof, to advise on the subject for which they are retained. A firm shall maintain records stating the name, address, qualifications, and type of service provided by a consultant.

8 BUILDINGS AND FACILITIES

8.1 General

a) Buildings shall have a sufficient number of adequately sized areas for organized sequential operations, including well-defined areas for incoming medical gases, containers, manufacturing equipment, rejected containers and container closure systems, filling, and quarantine, as well as finished product that is ready for distribution.

b) Outdoor spaces and delivery truck beds may be appropriate areas to conduct certain operations (e.g., storage and handling) for medical gases in pressurized containers. For example, industrial and medical gases could be separated physically in the warehouse or in the delivery truck. To separate these areas from other spaces, manufacturers shall use identifiers such as signage, floor demarcation, or tagging.

8.2 Lightning

Adequate lighting shall be provided in appropriate areas, to allow the person performing assigned functions to read items such as procedures, instructions, gauges, scales, test equipment, and designations of defined areas or product status.

8.3 Building maintenance

a) Buildings shall be maintained in a good state of repair and in a neat and orderly fashion.

b) Bulk medical gases filled and stored in a closed system are not affected by environmental conditions such as dust and dirt. Transfer hoses used to fill bulk liquid containers shall be protected. This is accomplished by usinga dust protector/cap or an alternate method.

8.4 Security

All facilities used for bulk medical gas distribution including manufacturing sites shall have security provisions toprevent

unauthorized entry and to protect against theft or diversion. Security provisions may include one or more of the following:

i. limited access from outside, e.g., fence;
ii. well-lit perimeter;
iii. limited access to storage and bulk tanks and trailers; and
iv. theft detections systems, e.g., alarm system if applicable.

9 EQUIPMENT

9.1 Filling equipment qualification

a) Automatic, mechanical, and electronic equipment, or other types of equipment, shall be checked according to a written program designed to ensure proper performance.

b) Equipment qualification helps ensure proper performance:

i. Equipment shall be qualified at the temperature and pressures used during filling.

ii. Manifold valves shall be qualified for use (e.g., appropriately designed to prevent mixups during medical gas filling operations and shown to prevent contamination of medical gas).

iii. Other valves that are critical to the prevention of drug contamination, such as check valves used in filling systems, shall be qualified for use.

9.2 Equipment cleaning and maintenance

a) Equipment shall be adequately cleaned and maintained.

b) Medical gas manufacturers shall:

i. Ensure that equipment used in the manufacture of medical gases (e.g., manifolds, pigtails, valve assemblies, hoses, gauges) is cleaned before initial use and after exposure to a contaminant (e.g., industrial gas impurities).

ii. Tailor their equipment cleaning and maintenance procedures to match the type and complexity of the particular operation, as appropriate.

c) Closed pressurized systems used for filling medical gases (e.g., manifolds) need not be cleaned between batches, unless exposed to a contaminant. To prevent contamination, manufacturers shall ensure that open ends are appropriately covered (e.g., with physical caps).

d) Components and drug product containers and closures shall be handled and stored in a manner to prevent contamination.

e) Accordingly, high-pressure cylinders exposed to the elements and hoses used to fill cryogenic containers shall have caps or other protective means to prevent contamination.

f) Valves that are critical to the prevention of drug contamination, such as manifold or check valves used in supply systems, shall be properly maintained.

g) Equipment used in the manufacturing of drugs shall be cleaned and maintained to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond established requirements.

h) Bulk gases are manufactured and filled utilizing pressurized closed systems and equipment shall not be cleaned between batches and lots. Significant cleaning is performed when initially assembled and prior to commissioning. Unnecessary cleaning introduces a contaminant (the cleaning solution) which shall be completely removed prior to using the system.

i) Written procedures shall be established and followed for the cleaning and maintenance of equipment. These procedures shall include but are not limited to:
   i. assigning responsibilities for cleaning and maintaining equipment;

ii. purging new containers or containers converted from another service;

iii. establishing maintenance and cleaning schedules;

iv. providing a description of the methods and materials used in the cleaning and maintenance operations as applicable, including the cleaning agents used and the cleaning agent's ability to remove residuals or other potential contaminants;

v. inspecting equipment before use.

j) Records shall be maintained for maintenance and cleaning activities.

9.2.1 **Cleaning procedures**

a) All systems or equipment used in the manufacture/processing of medical gases that come in direct contact witha medical gas shall be cleaned for the specific gas service. Cleaned systems shall be inspected and verified that no detectable residual cleaning agents or discernible odors are present.

b) After a piece of equipment or container is cleaned it shall be handled, stored, and packaged to prevent contamination.

c) Bulk medical gas systems including bulk storage tanks, pumps, and the piping to fill trailers are typically maintained under positive pressure to prevent the introduction of foreign material. External surface conditions of the equipment do not affect the integrity of the medical gas.

9.2.2 **Maintenance**

a) Cleaning following maintenance shall be performed on equipment that comes in contact with a medical gas before placing equipment

back in medical gas service. Replacement parts (for example, valves) shall be cleaned before being placed in medical gas service.

b) If replacement parts are packaged and labeled by the vendor as cleaned for its intended service, no additional cleaning is required.

9.3 **Equipment calibration**

a) Manufacturers shall establish an appropriate schedule or frequency for equipment calibration. This can be done using either the equipment manufacturer's recommended calibration schedule or a schedule based on the medical gas manufacturer's own historical data.

b) Medical gas manufacturers can reference the equipment manufacturer's instruction manual in their written procedures if the manual is available for use on-site. Medical gas manufacturers that use automated, mechanical, or electronic equipment such as computer systems shall ensure these systems are routinely calibrated, inspected, or checked according to a written program designed to ensure proper performance.

i. Check the performance of vacuum gauges daily to ensure that the needle on the gauge returns to zero when there is no vacuum or pressure (above atmospheric pressure).

ii. Calibrate vacuum and pressure gauges annually against an established. Low-pressure gauges and flow meters used in filling cryogenic home containers do not require calibration, but manufacturers shall ensure that they function properly for their intended use.

iii. Calibrate thermometers according to the equipment manufacturer's instructions at least annually.

iv. Calibrate oxygen analyzers based on the equipment manufacturer's instructions or a

schedule based on the gas manufacturer's own historical data.

9.4 **Computerized systems**

Computerized or automated systems shall have sufficient controls to prevent unauthorized access or changes to master production control records or other records and to ensure records or data are accurate. In addition, any change to a computerized or automated system shall be made according to approved procedures, and any changes shall be documented. A risk assessment shall be performed to determine the potential of the computerized system to affect product quality, safety, and record integrity. Manufacturers can use an audit trail as part of these systems to address risk.

9.5 **Manufacturing medical and nonmedical gases**

a) Industrial product and medical product may be manufactured on the same system with no additional purging or cleaning if industrial product is treated in the same manner as the medical product.

b) Industrial and medical gases can sometimes be filled at different times on the same manifold rack. This practice is acceptable as long as processes and procedures are in place and followed to prevent any possible contamination caused by backflow from the industrial cylinders into the medical cylinders or from residual industrial gas in the manifold

10 CONTROL OF COMPONENTS AND CONTAINERS

10.1 **General**

a) Written procedures are required for the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components (raw materials) and drug product containers and closures (tanks, vessels, trailers, and associated valves and other connections).

b) Each drug product container used for the distribution of bulk medical gases shall be placarded following specifications.

10.2 **Containers and Container closure systems**

10.2.1 **General**

a) The quality unit shall examine, reexamine as appropriate, and approve or reject containers and container closure systems. A manufacturer shall reexamine a container or container closure system when, for example, it is stored for an extended period or exposed to adverse environmental conditions. Rejected containers and container closure systems shall be identified and quarantined. After customers use containers and container closure systems and send them back for refilling, manufacturers shall store them under quarantine until they have been tested or examined, as appropriate.

b) Containers and container closure systems shall be clean and shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of a medical gas beyond the official or established requirements. Thus, containers and container closure systems shall be cleaned before initial use and after exposure to a contaminant. In addition, if converting a container's use from industrial grade gas to medical gas, or if there is reason to believe there was previous industrial use, manufacturers shall implement appropriate cleaning and retesting procedures.

c) Portable cryogenic containers that are not manufactured with permanent gas-specific use outlet connections (e.g., those that have been silver-brazed) shall have gas-specific use outlet connections that are attached to the valve body so that they cannot be readily removed or replaced (without making the valve inoperable and preventing the container's use) except by the outlet connection can be readily removed and

replaced, a container holding a gas other than oxygen could be inadvertently connected to an oxygen supply system, causing serious injury or death.

10.2.2 **Prefill inspections**

a) Manufacturers shall conduct prefill inspections to provide assurance that containers and container closure systems are acceptable for use before filling begins. This section addresses prefill inspections that evaluate containers and container closure systems used to hold incoming medical gases and store medical gases and finished product containers and container closure systems.

b) A written procedure describing the prefill inspection shall be developed and implemented.

c) Containers and container closure systems that fail prefill inspections shall be quarantined until the container, container closure system, or valve has been repaired, cleaned, or replaced, as appropriate, and determined to pass reinspection.

d) Performance of the prefill inspection shall be recorded. A check mark on a fill log indicating the step has been performed is acceptable documentation for the prefill analysis provided prefill steps including acceptance criteria are clearly outlined in the firm's SOP.

10.2.2.1 **Containers**

Manufacturers shall carefully examine each container for dents, burns, dings, oil, grease, and other signs of damage or contamination that can cause a container to be unsafe for use. Any container found to have any of these conditions shall

be quarantined until its suitability has been determined.

10.2.2.2 **Valves, inlets, outlets, and connectors**

Manufacturers shall carefully inspect each container's valve assembly, connectors, and fittings to ensure that they are appropriate for the medical gas. The valves, inlets, outlets, gauges, and connectors shall be examined carefully for signs of damage (including fire damage), unusual wear, corrosion, or the presence of debris, oil, or grease. This inspection shall cover any connections that are brazed, welded, or equipped with a locking device.

10.2.2.3 **Label inspection**

a) Manufacturers shall examine the labelling on each container for legibility and accuracy and shall remove and replace damaged labels. Product labels on medical gas containers can be reused. Labels that are obsolete or outdated shall be removed.

b) Each portable cryogenic container shall be conspicuously marked with a 360° wraparound label identifying its contents. The name of the gas shall be printed continuously around, according to Labelling Standard.

10.2.2.4 **Colour code inspection**

Medical Gas	**Color**
Medical Air	White
Carbon Dioxide	Gray
Helium	Shallard yellow and brown or only Brown
Nitrogen	Black
Nitrous Oxide	Navy Blue
Oxygen	Silver and green
Mixture or Blend*	Colors corresponding to each component gas cited in Belize Standard Specification for Medical Gases

NOTE 1: Unlike high-pressure cylinders, portable cryogenic medical gas containers are not required to be colored in whole or in part.

NOTE 2: Manufacturers shall not rely solely or primarily on color coding to identify medical gases; the label shall be used as the primary means of identifying the product. Color coding provides an additional safeguard to facilitate accurate identification and detection of potential errors.

10.2.2.5 **Prefill inspection of high-pressure cylinders**

When inspecting high-pressure cylinders, manufacturers shall conduct the following:

a) Inspection of high-pressure cylinders for the DOT requalification

b) Hammer test on steel cylinders

c) Odor inspection (carbon dioxide, nitrous oxide, or toxic or corrosive gases for safety reasons). A prefill odor test on a cylinder with a qualified residual pressure valve is not necessary if the cylinder has residual pressure.

d) Venting or blow down of cylinders (Not necessary on cylinders with residual pressure valve if the cylinder has residual pressure).

10.2.3 **Stock rotation**

a) Medical gas containers and container closure systems are typically reused over a period of years and undergo prefill testing.

b) Manufacturers shall address the continued suitability of containers and container closure systems after extended storage by having procedures in place to ensure that they are not exposed to conditions that may render them unfit for use.

10.3 **Certificate of Analysis (COA)**

a) The COA is a document agreed to by the manufacturer and the customer, and the manufacturer is not required to furnish it. This document does not require a review before it is issued unless the manufacturer's procedure requires its review and approval.

b) A COA for bulk medical gases can be supplied upon request. The information on a COA shall contain at a minimum:

i. the supplier's name;
ii. the name of the product;
iii. the lot number or other unique identification number;
iv. an actual analytical result obtained for identity, strength, and all other tests performed; and a test method(s) used for analysis.

10.4 **Retesting approved components, drug product containers and closures**

Retesting of bulk medical gas containers is not required due to the length of storage or storage conditions. Bulk medical gases are maintained in closed pressurized systems and are not affected by environmental conditions. Retesting may be necessary if a container has been compromised. An example of this could be if a rupture disk on a trailer failed, retesting may be necessary.

10.5 **Rejected components, drug product containers and closures**

Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable. The firm will follow their internal procedures for disposition of quarantined materials.

11 PRODUCTION AND PROCESS CONTROLS

11.1 **Sampling and testing**

a) Control procedures shall be established to monitor output and to validate the performance of manufacturing processes that may cause variability in the quality of the medical gas.

b) Written procedures shall be established and followed that describe the in-process controls and tests that are conducted at appropriate intervals.

c) Procedures shall be developed stating the control of the critical parameters and the calibration requirements of each.

11.2 **Vacuum Evacuation of High-Pressure Cylinders**

a) For those cylinders that are not equipped with a residual pressure valve with backflow prevention, vacuum evacuation is used to remove residual gases when cylinders are being reused. Manufacturers use 25 or more inches of mercury vacuum for high-pressure cylinders to vacuum evacuate the residual gases. If using less than 25 inches of vacuum, manufacturers shall have data on file demonstrating that the amount of vacuum evacuation sufficiently removes all residual gases from high-pressure cylinders.

b) Manufacturers shall maintain records of any problems that occur with container evacuation, such as the inability to adequately empty the cylinder of residual gases.

11.3 **Filling Procedures Checks**

Components shall be weighed or measured as appropriate. When filling high-pressure cylinders, manufacturers shall include the following checks to demonstrate the presence of gas in the container and to ensure net content is delivered.

11.3.1 **Temperature and Pressure Readings**

a) A medical gas in a high-pressure cylinder increases in pressure as the temperature of the gas rises. Overfilled cylinders can reach dangerously high pressures if exposed to elevated temperatures, even if the pressure at room temperature is safe. To ensure that high-pressure cylinders are filled correctly (i.e., contents as indicated on the label), the manufacturer can attach a thermometer to one cylinder per manifold-filling sequence, or to each cylinder if filling one at a time, and adjust

the final filling pressure according to a temperature/pressure chart.

b) Manufacturers shall use temperature/pressure charts or temperature/pressure calculations to adjust filling pressure, thereby achieving proper content. This is usually stated as the pressure at 70°F with appropriate tolerances.

c) The manufacturer shall record the actual temperature and/or pressure readings on the batch production record.

11.3.2 **Valve assembly leak testing**

a) During filling operations, manufacturers shall test each valve assembly for leaks by spraying or brushing an appropriate leak detection solution (oxygen compatible) on and around the entire assembly, while the cylinder is under pressure in the manifold.

b) Once the cylinders are filled and disconnected, manufacturers shall perform a second valve assembly leak test. If any leaks are detected, the cylinder shall be removed from service and quarantined until repaired.

c) Performing these tests helps ensure that the contents of high-pressure cylinders will not leak during storage or shipment.

11.3.3 **Heat-of-compression check**

During or immediately after filling high-pressure cylinders, manufacturers shall perform a heat-of-compression check by lightly touching the exterior of each cylinder or by following an alternative method that verifies temperature change. A warm cylinder indicates that the cylinder is filling properly; a cool or cold cylinder indicates that the cylinder may not be filling properly. Manufacturers shall investigate cool or cold cylinders.

11.4 **Calculation of Yield**

a) Medical gas loss is expected during manufacturing and can be variable even under normal operating conditions. Filling to a predetermined and acceptable temperature or pressure limit, along with finished product testing, is sufficient to determine that the medical gas or medical gas mixture in the container is the amount and type indicated by the label and required by the final product specifications.

b) Nevertheless, the calculation of yield is not required for designated medical gases or combinations thereof.

11.5 **Written procedures and deviations**

a) Written procedures describing production and process controls shall be established to ensure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. These written procedures, including any changes, shall be drafted, reviewed, and approved by the responsible organizational units. Procedures that impact the identity, strength, quality, and purity of medical products shall be reviewed and approved by the QCU.

b) The written procedures shall be reviewed at appropriate intervals and updated whenever necessary. Outdated procedures shall be withdrawn from circulation and archived.

c) Any deviations from the written procedures shall be recorded and justified. Production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented.

11.6 **Charge in components**

Written production and control procedures designed to ensure that the drug products produced have the identity,

strength, quality, and purity as in shall include the following as applicable:

a) The batch shall be formulated with the intent to provide not less than 100% of the labeled or established amount of active ingredient; or

b) The component shall be weighed, as applicable.

11.7 **Equipment identification**

a) A firm's SOP shall describe the methods used to identify the major equipment used during the production of the medical gas.

b) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of drug product shall be properly identified to indicate their contents. Major equipment shall be identified by a distinct identification or the equipment name as applicable.

c) The equipment and piping can be identified per company procedures. The equipment need not be referenced in the batch or lot number except where multiple storage tanks are used.

11.8 **Reprocessing**

a) If reprocessing occurs, gas manufacturers shall have written procedures that prescribe a system for reprocessing batches that do not conform to standards or specifications. These procedures shall include the steps to be taken to ensure that the reprocessed batches conform with all established standards, specifications, and characteristics.

b) The QCU shall review and approve any reprocessing.

12 PACKAGING AND LABEL CONTROLS

Medical gases are not over the counter human drug products and do not use conventional labels. Bulk manufacturers shall

have a written procedure describing the requirements for packaging and labelling control.

12.1 **Expiration date**

Medical gases have unique stability characteristics. They do not deteriorate over time, are maintained in a closed, pressurized system and are not affected by environmental conditions. Expiration dating does not apply to bulk medical gases. If a manufacturer uses an expiration date it will be considered as an internal control.

12.2 **Material examination and usage**

a) Manufacturers shall:

i. Representatively sample new labels and other labelling materials and compare them for accuracy to the master label before use in labelling of a medical gas.

ii. Secure labelling by limiting access to authorized personnel.

iii. Destroy obsolete and outdated labelling.

b) Different medical gas labels shall be stored separately. They can be stored in the same cabinet provided they are adequately separated to prevent mix-ups. Industrial gas labels shall be stored in a separate area.

c) Only labelling that meets appropriate written specifications may be approved and released for use. Previous lot numbers on any labelling shall be removed or obliterated.

12.3 **Labelling control**

a) Manufacturers shall strictly control labelling issued for use in medical gas operations. To prevent mix-ups, manufacturers shall compare the number of labels issued the number of labels applied.

b) For cut labelling that does not use a dedicated product labelling and packaging operation,

c) manufacturers shall use appropriate electronic or electromechanical equipment or visual inspection to conduct a 100-percent examination for correct labelling or any automated technique that physically prevents incorrect labelling from being processed by labelling and packaging equipment.

d) Label reconciliation is waived for 360° wraparound labels on portable cryogenic medical gas containers.

12.4 **Packaging and Labelling Operations**

a) Manufacturers shall consider as a batch each:
   i. manifold filling sequence,
   ii. uninterrupted filling sequence, and
   iii. filled rail tank car, trailer, and cryogenic container.

b) Each batch shall be assigned a lot or control number from which the history of the manufacture and control of the batch may be determined.

c) Transfillers receiving shipments of medical gas into a storage tank shall assign a new lot number to the contents of the storage tank each time it is refilled, regardless of whether it contains previously received medical gas.

d) Manufacturers shall ensure that for each container, the labelling accurately identifies the contents of the container and that any other required or included information in labelling is accurate. This is particularly important given that medical gas containers and labels are typically reused many times. Labels shall be affixed to the container in a manner that does not interfere with other labelling and will not be susceptible to wear or inadvertent detachment during normal use.

e) A separate sticker or decal may be used to identify the lot number for a batch of medical gas, as long as the sticker remains adhered to the container and is legible.

The sticker shall be readily visible and shall not obscure required drug information. A separate sticker can also be used for the container's net content information.

13 HOLDING AND DISTRIBUTION

13.1 **Warehousing procedures**

a) Written procedures describing the warehousing of medical gas products are required to be established and followed. These procedures are applicable to bulk storage containers and bulk shipping containers.

b) The manufacturers of bulk medical products fill, test, and release the container in one process. The containers typically leave the facility. A quarantine of medical gas is only necessary if the testing or the release cannot be completed while the container is in the loading area. A written procedure describing how the quarantine is handled in the event of an out-of-specification occurrence or nonconformance shall be established.

c) The storage of bulk medical gases as cryogenic liquids requires insulation or vacuum conditions, which are necessary to maintain cryogenic temperatures. The bulk product is stored in specifically designed containers in which the product is protected from excessive temperatures, humidity, and light.

13.2 **Distribution procedures**

a) Bulk medical gases are prescription drugs and can only be distributed to licensed practitioners, medical gas distributors, hospitals, drug manufacturers, health care institutions, and other businesses that have a proven need for a bulk medical gas.

b) Written procedures describing the distribution of medical gas products shall be established and followed.

c) These procedures shall include a system by which the distribution of each lot of medical gas product can be readily determined to facilitate a recall if necessary. The procedures shall explain:

i. who would evaluate distribution information,
ii. how a recall would be initiated,
iii. who would be informed about the recall, and
iv. what would be done with the recalled product.

d) Manufacturers of bulk medical product typically ship product when it is loaded into the containers; therefore, distribution of stock is not applicable.

e) Contract drivers are service suppliers that fill, transport, and offload product on behalf of a company. They do not provide the container used to transport the product.

f) Third-party consignees are service suppliers that fill, transport, and offload product on behalf of a company. They provide the container used to transport the product and follow the distribution procedures of the company for which they are contracted.

g) Because of the nature of medical gas manufacturing and the stability characteristics of the gases, is not necessary to establish and follow written procedures to distribute their oldest stock first provided that manufacturers establish a system to manage and handle medical gas stock in an orderly manner and have procedures in place. These procedures shall ensure that the components, containers, and container closure systems:
i. are used in a timely manner,
ii. are not exposed to conditions that may render them unfit for use, and
iii. have undergone prefill and other testing as required before distribution.

14 LABORATORY CONTROLS

14.1 General requirements

a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms including changes to such specifications shall be drafted by the appropriate organizational unit and reviewed and approved by the QCU. Laboratory control procedures shall be followed

and shall be documented at the time of performance. Deviation from written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

b) Laboratory controls shall include the establishment of appropriate specifications, standards, sampling plans, and test procedures that ensure components, drug product containers, closures, in-process materials, labelling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

c) Laboratory controls shall include:

i. Procedures to determine conformance to appropriate written specifications for the acceptance of each lot of drug products. The specifications shall include a description of the sampling and testing procedures used;

ii. Program developed for applicable equipment as defined by the equipment manufacturer for the calibration of analyzers, instruments, apparatus, gauges, and recording devices at suitable intervals and in accordance with the equipment manufacturer's recommendation. The established written program contains specific directions, schedules, and provisions for remedial action if equipment doesn't meet specifications.

iii. Analysers, instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used. If the equipment manufacturer's manual does not specify a calibration interval, then approved scientifically sound studies shall be developed and documented to establish calibration frequency.

14.2 **Specifications**

a) Each firm shall establish medical gas specifications that meet or exceed the applicable requirements in monographs. Monographs establish identity, strength,

quality, and purity requirements for medical gases and outline specific tests for these characteristics.

b) Each firm shall establish specifications for containers and closures.

14.3 **Sampling plans**

Written sampling plans shall be established that describe the containers to be sampled and the sampling methodology.

14.4 **Testing**

a) Each firm shall establish written procedures for testing finished medical gas for conformance to that firm's finished product specifications.

b) Returned cryogenic bulk medical gas containers can contain residual product. It is common practice to refill these containers without removal of the residual product. All appropriate prefill, fill, and post fill operations including commingled lot testing of each unit shall be performed.

c) Upon the completion of loading, delivery vehicles shall be tested to ensure they meet all applicable criteria.

d) Generally, products failing to meet prefill and post fill specifications shall be vented. Repeated testing to pass a drug product is not allowed unless a thorough investigation is performed, completed, documented, and reviewed/approved by the QCU.

14.5 **Calibration of testing equipment**

a) Analytical equipment, e.g., paramagnetic analyzer, fuel cell, gas chromatograph, etc., used to test medical gas shall be calibrated or a calibration check performed in accordance with the manufacturer's recommendations or a firm's SOP. Calibration shall occur with sufficient frequency to ensure the accuracy of the measurement and that proper operation is maintained.

b) Written procedures for calibration shall include the standards used and acceptable performance criteria, Standards used in calibration shall be traceable to national or international standards.

c) Records of calibration shall be maintained and have traceability to the equipment's unique identification number.

d) Calibration is not required for certain analytical methods, e.g., gas detector tubes or certified burettes.

e) Records for all calibrations performed on analytical equipment and traceability documentation on the calibration standards shall be maintained.

f) Manufacturers shall verify that the calibration gas is traceable to a standard. The COA for the calibration gas shall be specific to the cylinder of calibration gas received and shall contain the following:

i. Name and address of the supplier.
ii. Name of the calibration gas.
iii. Lot number or unique identification number.
iv. Description of the analytical method used to assay the calibration gas.
v. Analytical results expressed quantitatively (e.g., 99.9 percent nitrogen).
vi. Statement that the calibration gas is traceable to a nationally recognized standard.
vii. Responsible person's signature and the date signed.

14.6 **Calibration gas standards**

a) Manufacturers of bulk medical gases typically use certified gas standards to calibrate analyzers used in the process and final product testing. These standards shall be ordered per the equipment manufacturer's recommendation and/or shall be in the range in which the analyzer is operated.

b) A COA certifying the actual test results for the gas standard shall be provided. For gas mixtures, this

certification shall demonstrate traceability back to a national or international standards organization.

c) Due to the level of scientific sophistication needed to properly produce a gas calibration standard for medical gas use, these products generally can only be manufactured by specialty gas companies. Bulk medical gas production facilities shall not use their on-site manufactured products as calibration standards unless that product is certified by a different analyzer (not the same analyzer that was used to certify the bulk medical products). The calibration gas for independent analytical equipment shall be certified from a facility that is separate from the facility that manufactures the bulk medical product.

d) In addition, firms that receive gas calibration standards shall record the date when the calibration gas is put into service and when it is taken out of service. This can be documented on the COA.

e) Calibration standards that have an expiration date shall not be used beyond that date.

14.7 **Certificate of calibration - Gas calibration standards**

Each COA for a gas calibration standard is specific for that individual cylinder and shall provide the following information:

a) supplier's name and complete address;

b) name of the product and the standard it is traceable to;

c) lot number or unique identification number;

d) actual analytical results obtained for the gas standard requested, i.e., 99.9% nitrogen;

NOTE: Other gases present in the standard can be expressed on the certificate either quantitatively or by the term "balance" providing the firm making the standard can

clearly demonstrate to the receiving firm the accuracy, through traceability methods, by which the term balance was determined.

e) analytical test methodology used to assay the standard; and

f) signature and date from the supplier's representative certifying the information and test results.

14.8 **Testing and release for distribution**

a) Before release, each batch of drug product shall have an appropriate laboratory determination of its satisfactory conformance to final specifications for the drug product including identity and strength.

b) Each company shall establish its own internal release criteria based on GMP requirements, internal requirements, customer requirements, intended use, analytical methods, and meeting or exceeding the monograph requirements.

c) Sampling and testing plans shall be described in written procedures that shall include the method of sampling and the sample(s) to be tested per batch: such written procedures shall be followed. Acceptance criteria for the sampling and testing conducted by the QCU shall ensure that each batch of drug product meets each appropriate specification before approval and release. The bulk manufacturer shall perform tests to ensure the lot or container has the identity, strength, quality, and purity it purports to have.

d) For medical oxygen, carbon monoxide and carbon dioxide tests are only required if the oxygen is not produced by the air liquefaction process.

e) For medical nitrogen, the identification of nitrogen gas at an air separation facility is distinct through process validation, dedicated piping, and unique CGA fittings. Additional identification is not required.

f) For medical nitrous oxide, the compendial identity test for nitrous oxide is not performed. A suitable alternative method shall be used (for example, a paramagnetic oxygen analyzer, etc).

g) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected.

h) If a failing test result is obtained, the product is out-of-specification and the manufacturer shall investigate. A written procedure describing investigating and reporting out-of-specification incidents shall be developed and followed. The investigation shall be documented and the quality control manager shall approve or reject the results of the out-of-specification investigation.

14.9 **Stability testing**

Bulk designated medical gases do not deteriorate over time, therefore no stability testing is required.

14.10 **Reserved samples**

Because of the inherent properties of the gases, it is not necessary to reserve samples of each batch of production of medical gases.

15 RECORDS AND REPORTS

15.1 **General requirements**

a) A firm shall establish and maintain a record system that documents the medical gas manufacturing history and its compliance with GMPs. Required records may include but are not limited to:
   i. receiving records;
   ii. training records;
   iii. certificates of analysis;
   iv. equipment cleaning and maintenance records;
   v. calibration logs;
   vi. batch production records;
   vii. testing records;
   viii. complaints files; and

ix. distribution records.

b) Records can be maintained as originals or as true copies. True copies include photocopies or other accurate reproductions of the originals.

c) Records may be in electronic format as scanned files as pdf format or any image format.

d) Corrections shall be made so the original data is visible, i.e., a single line through the error, the correct data recorded and initialed by the person making the correction, and the date of the correction.

e) Corrections shall not include the use of corrective media, e.g., liquids or tapes.

15.2 **Record retention**

Medical gas firms shall develop a procedure for retaining records required Although expiration dating is not applicable to bulk gases due to physical properties, records shall be retained for at least 1 year after the distribution of the lot. This is the minimum requirement for bulk medical gas manufacturers. If an expiration date is assigned, records shall be retained for at least 1 year after the expiration date of the lot.

15.3 **Record availability**

All required records shall be available for inspection by regulatory agencies. Records not located at the manufacturing site are typically provided within 24 hours of request.

15.4 **Annual drug product review**

A firm shall have written procedures for conducting an annual internal evaluation of production and process control records and shall document any resulting investigations. The evaluation shall include a review of at least ten batches (whether approved or rejected) and where applicable the records associated with the batch and a review of complaints, product recalls, and returned or salvaged drug products.

15.5 **Container and closure records**

a) Bulk medical gases are stored and distributed in bulk storage tanks, cryogenic transports, refrigerated transports and tube trailers. Bulk medical gas manufacturers shall have written procedures defining the identification, sampling, testing, approval or rejection and quarantine of bulk storage tanks and various transport containers.

b) Bulk storage tanks are tested at a defined frequency. The testing corresponds to what iscommonly referred to as a batch. The batch records include, at a minimum, the following information:
   i. date of the batch;
   ii. tank identification number;
   iii. unique batch number; and
   iv. analytical test results.

c) Cryogenic transports, refrigerated transports and tube trailers are sampled prior to filling with product to ensure the container is within a predefined specification. Once filled with product, the container is tested to demonstrate the product meets the medical gas product specification. The contents of the container corresponds to what is commonly referred to as a lot. The lot records include, at a minimum, the following information:
   i. date of the lot;
   ii. container identification number;
   iii. unique lot number; and
   iv. analytical test results.

15.6 **Labelling records**

Bulk medical gases do not use conventional labels and therefore labelling records are not required.

15.7 **Batch production and control records**

a) Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production control of each batch.

b) Medical gases produced by batch processes shall include:
   i. dates of significant events including in-process and laboratory control results as applicable;
   ii. final product testing results as applicable;
   iii. identification of drug product container (bulk storage tank);
   iv. accurate and current analytical equipment calibration logs;
   v. specific identification of each component or in process material used as applicable;
   vi. analytical results within the specified limits;
   vii. review of the critical control points as defined from their risk assessment;
   viii. signature or initials and date of the individuals completing the operation log as applicable;
   ix. signature and date of the individual performing the tests.

15.8 **Out of Specification Results (OOS)**

a) An Out of Specification procedure shall be developed and followed.

b) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected.

c) If OOS results are obtained, a firm shall investigate the cause. The Quality Control Unit shall have the responsibility to ensure an appropriate and adequate documented investigation of the OOS occurs before any retesting is performed. Repeat testing to pass a drug product without investigation is not acceptable. The Quality Control Unit shall have the authorityto accept or reject the results obtained through the investigation and any retest if performed.

15.9 **Documentation of third-party product receipts**

a) Customers can request a COA or other documentation from their suppliers.

b) If product is picked up at the manufacturer by a firm that has an agreement to receive a COA, the information on the manufacturer's COA or on the production record can be transcribed onto a COA of the firm distributing the products, if this is allowed by the distributing firm's SOP.

c) The completed production record/fill log shall be retained by the manufacturer for a period consistent with that firm's record retention guidelines.

d) Traceability from initial manufacture to the final customer shall be maintained for all bulk medical gases.

e) Bulk medical gas manufacturers receiving medical gases into a storage container for the purpose of distribution shall perform full testing of the commingled product before release from the storage vessel.

15.10 **Laboratory records**

a) Laboratory records shall include complete data derived from all tests necessary to ensure compliance with established specifications and standards.

b) COAs that accompany calibration gas standards are considered laboratory records.

c) Certain common analytical equipment only provides a visual indication of the analysis.

15.11 **Distribution records**

Distribution records shall contain, at a minimum:

i. the name and address of the consignee,
ii. the product name,
iii. date, and
iv. quantity shipped.
v. Lot numbers or sufficient information shall be included to permit traceability.

16 COMPLAINT FILES AND PROCEDURES

a) Written procedures describing a firm's complaint management system are required. The handling of written andoral complaints regarding a drug product shall be established and followed.

b) These procedures shall include provisions for the Quality Control Unit's review of any complaint involving the possible failure of a drug product to meet any of its specifications.

c) These procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience.

d) The written report shall include the following information where known:
name (identity) and (strength) purity of the product;

i. lot number;
ii. name of complainant and contact information;
iii. description of complaint;
iv. date the complaint was received;
v. Action initially taken, including dates and identity of the person taking the action;
vi. findings of investigation and evaluation to determine if the complaint is also an adverse event;
vii. follow-up of findings of investigation; and
viii. reply to complainant;
ix. Final outcome regarding the issues raised by the complaint

e) An open file shall be maintained even if there have been no bulk medical gas complaints. All complaints (verbal or written) shall be investigated, and the results documented. The QCU shall ensure that the investigation of eachcomplaint is complete and, if required, appropriate follow-up action taken.

17 RETURNED AND SALVAGED DRUG PRODUCTS

17.1 **Returned drug products**

Cryogenic medical gas containers typically contain residual product upon their return to the manufacturer. These containers do not leave control of the firm; therefore, any product remaining in the container is considered residual and

is not considered returned drug product and can be refilled per a firm's procedure.

17.2 **Drug product salvaging**

a) Designated medical gases or combinations thereof may be salvaged unless their containers have been subjected to adverse conditions that impact the identity, strength, quality, and purity of the product.

b) Medical gases that have been improperly stored shall not be salvaged and returned to themarketplace.

c) Procedures for the holding, testing, and reprocessing of salvaged designated medical gases or combinations thereof shall be in writing and shall be followed.

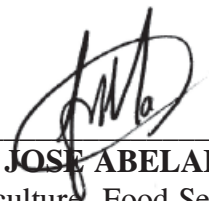
18 ADAPTERS

a) For safety reasons, it is recommended to avoid the use of adapters of any kind to circumvent the specific medical gas valves and connections associated with a specific medical gas.

b) On rare occasions and only under strict control, adapters can be used to fill mixtures of medical gases. However, manufacturers shall have written procedures detailing system checks and controls to prevent mix-ups or contamination, and to promptly identify and quarantine compromised gases if a mix-up or contamination shall occur.

END OF DOCUMENT

MADE by the Minister responsible for the Bureau of Standards this 29th day of September, 2025.



(**HON. JOSE ABELARDO MAI)**
Minister of Agriculture, Food Security and Enterprise
(Minister responsible for the Bureau of Standards)

Printed in Belize by the Government Printer
#1 Power Lane, Belmopan