



Health Canada
Health Products and Food Branch

OUR MANDATE:

To take an integrated approach to managing the health-related risks and benefits of health products and food by minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food, and promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Health Products and Food Branch Inspectorate

(GUIDE-0031)

Good Manufacturing Practices (GMP) for Medical Gases

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Disclaimer

This document does not constitute part of the Food and Drugs Act (Act) or the Food and Drugs Regulations (Regulations) and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies. This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel

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1. INTRODUCTION

These guidelines state generally applicable principles and practices that are acceptable to the Inspectorate and that should facilitate compliance of fabricators, packagers/labellers, distributors, importers, and home care providers of medical gases with Division 2, Part C of the *Food and Drug Regulations* on Good Manufacturing Practices (GMP). Commercial operations involving sales are subject to GMPs. The Inspectorate does not consider transfilling operations 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.

Interpretations provided in the main GMP Guidelines are replaced by those given in this document for medical gases. During establishment inspections carried out under the authority of section 23 of the *Food and Drugs Act*, 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. Establishments may use this guideline as a basis for the development of specific requirements appropriate to their individual needs.

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 raw material or it may be sold as a bulk drug 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 Health Canada's Compliance and Enforcement website at:

http://hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/index_e.html

2. PURPOSE

The purpose of this guideline is to facilitate compliance with and enhance consistency in the application of Division 2 of the *Food and Drug Regulations* for fabricators, packagers/labellers, testers, distributors, and importers of medical gas establishments.

3. SCOPE

The guidelines apply to medical gases and were developed by Health Canada in consultation with stakeholders.

4. QUALITY MANAGEMENT

4.1 GUIDING PRINCIPLE

The holder of an establishment licence, or any operation to which the requirements of Division 2 Part C of the *Food and Drug Regulations* are applicable, must ensure that the fabrication, packaging, labelling, distribution, testing and wholesaling of drugs comply with these requirements and the marketing authorization, and do not place consumers at risk due to inadequate safety and quality.

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 ensure compliance, there must be a comprehensively designed and correctly implemented quality management system that incorporates GMP and quality control. The system should be fully documented and its effectiveness monitored. All parts of the quality management system should be adequately resourced with qualified personnel, suitable premises, equipment, and facilities.

4.2 RELATIONSHIP AMONG QUALITY ELEMENTS

The basic concepts of quality assurance, Good Manufacturing Practices, and quality control are inter-related. They are described here in order to emphasize their relationships and their fundamental importance to the production and control of drugs.

4.2.1 QUALITY ASSURANCE

Quality assurance is a wide-ranging concept that covers all matters that individually or collectively influence the quality of a drug. It is the total of the organized arrangements made with the objective of ensuring that drugs 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.

A system of quality assurance appropriate for the fabrication, packaging, labelling, testing, distribution, importation, and wholesale of drugs should ensure that:

1. Drugs are designed and developed in a way that takes into account the GMP requirements;
2. Managerial responsibilities are clearly specified;
3. Systems, facilities, and procedures are adequate and qualified;
4. Production and control operations are clearly specified;
 5. Analytical methods and critical processes are validated;
 6. Arrangements are made for the supply and use of the correct raw and packaging materials;

7. All necessary control on intermediates, and any other in-process monitoring is carried out;
8. Outsourced activities are subject to appropriate controls and meet GMP requirements;
9. Fabrication, packaging/labelling, testing, distribution, importation, and wholesaling are performed in accordance with established procedures;
10. Drugs are not sold or supplied before the quality control department has certified that each lot has been produced and controlled in accordance with the marketing authorization, and of any other regulations relevant to the production, control, and release of drugs;
11. Satisfactory arrangements exist for ensuring that the drugs are stored, distributed, and subsequently handled in such a way that quality is maintained throughout their shelf life;
12. The effectiveness, applicability, and continuous improvement of the quality management system is ensured through regular self-inspection and management review;
13. An annual product quality review of all drugs should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both raw materials and finished product to highlight any trends and to identify product and process improvements.

4.2.2 GOOD MANUFACTURING PRACTICES (GMP) FOR DRUGS

Good Manufacturing Practices (GMP) are the part of quality assurance that ensures that drugs are consistently produced and controlled in such a way to meet the quality standards appropriate to their intended use, as required by the marketing authorization.

GMP basic requirements are as follows:

1. Manufacturing processes are clearly defined and controlled to ensure consistency and compliance with approved specifications;
2. Critical steps of manufacturing processes and significant changes to the process are validated;
3. All necessary key elements for GMPs are provided, including the following:
 - qualified and trained personnel;

- adequate premises and space;
 - suitable equipment and services;
 - correct materials, containers, and labels;
 - approved procedures and instructions;
 - suitable storage and transport;
4. Instructions and procedures are written in clear and unambiguous language;
 5. Operators are trained to carry out and document procedures;
 6. Records are made during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented;
 7. Records of fabrication, packaging, labelling, testing, distribution, importation, and wholesaling that enable the complete history of a lot to be traced are retained in a comprehensible and accessible form;
 8. Control of storage, handling, and transportation of the drugs minimizes any risk to their quality;
 9. A system is available for recalling drugs from sale;
 10. Complaints about drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.

4.2.3 QUALITY CONTROL

Quality control is the part of GMP that is concerned with sampling, specifications, testing, documentation, and release procedures. Quality control ensures that the necessary and relevant tests are carried out and that raw materials, packaging materials, and products are released for use or, sale, only if their quality is satisfactory. Quality control is not confined to laboratory operations but must be incorporated into all activities and decisions concerning the quality of the product.

The basic requirements of quality control are as follows:

1. Adequate facilities, trained personnel, and approved procedures are available for sampling, inspecting, and testing of raw materials, packaging materials, intermediate bulk and finished products, and, where appropriate monitoring environmental conditions for GMP purposes;
 - 1.1 Samples of raw materials, packaging materials, and intermediate, bulk, and finished products are taken according to procedures approved by the quality control department;

- 1.2 Test methods are validated;
- 1.3 Records demonstrate that all the required sampling, inspecting, and testing procedures were carried out, and any deviations are recorded and investigated;
- 1.4 Records are made of the results of self-inspection and management reviews;
- 1.5 The procedures for product release include a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
- 1.6 No drug is released for sale or supply prior to approval by the quality control department;
- 1.7 Sufficient samples of raw material and finished product are retained to permit future examination if necessary.

5. REGULATION

C.02.002

In this Division,

- "medical gas" means any gas or mixture of gases manufactured, sold, or represented for use as a drug; (gaz médical)

- "packaging material" includes a label; (matériel d'emballage)

- "specifications" means a detailed description of a drug, the raw material used in a drug, or the packaging material for a drug and includes:

- (a) a statement of all properties and qualities of the drug, raw material or packaging material that are relevant to the manufacture, packaging, and use of the drug, including the identity, potency, and purity of the drug, raw material, or packaging material,
- (b) a detailed description of the methods used for testing and examining the drug, raw material, or packaging material, and
- (c) a statement of tolerances for the properties and qualities of the drug, raw material, or packaging material. (spécifications)

SALE

C.02.003

No distributor referred to in paragraph C.01A.003(b) and no importer shall sell a drug unless it has been fabricated, packaged/labelled, tested, and stored in accordance with the requirements of this Division.

PREMISES

C.02.004

The premises in which a lot or batch of a drug is fabricated, packaged/labelled or stored shall be designed, constructed and maintained 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 drug and the addition of extraneous material to the drug.

RATIONALE

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

INTERPRETATION

1. Buildings in which medical gases are fabricated or packaged are located in an environment that, when considered together with measures being taken to protect the manufacturing processes, presents a minimal risk of causing any contamination of materials or medical gases.
2. The premises are adequate for the operation performed therein and are designed to avoid mix-ups and prevent contamination.
 - 2.1 There is sufficient space for receiving and all production activities.
 - 2.2 Working spaces allow the orderly and logical placement of equipment (including parts and tools) and materials.
 - 2.3 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.
 - 2.4 Working areas are well lit.
3. Adequate segregation and area designation should be provided to distinguish:

- 3.1 containers set aside for cleaning, testing or maintenance from containers that have been released for filling;
 - 3.2 different gases;
 - 3.3 medical gases from non-medical gases including their respective empty containers;
 - 3.4 empty from full containers; and
 - 3.5 quarantined finished products from those available for distribution.
4. Outlets are clearly identified as to their content.
 5. Dead legs in which circulation may be restricted should be minimized.
 6. Pipelines carrying medical gases between areas should be identified by colour or by standard markings at suitable intervals and direction of flow shown.
 7. 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. Filters, especially the ones to trap desiccants after driers, are of suitable construction, examined and changed as necessary.
 8. 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.
 9. Fabrication and filling areas are adequately lighted.
 10. Premises are maintained in a good state of repair.
 11. Premises and vehicles used to store medical gases are secured from unauthorized entry.
 12. 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. Filled cylinders/mobile 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 (PIC/S).

EQUIPMENT

C.02.005

The equipment with which a lot or batch of a drug is fabricated, packaged/labelled or tested shall be designed, constructed, maintained, operated and arranged in a manner that:

- a) permits the effective cleaning of its surfaces;
- b) prevents the contamination of the drug and the addition of extraneous materials to the drug;
and

- c) permits it to function in accordance with its intended use.

RATIONALE

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. 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 fabrication of medical gases of consistent quality requires that equipment perform in accordance with its intended use.

INTERPRETATION

1. 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.
2. 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.
3. Tanks and tankers should be dedicated to a single and defined quality of gas. However medicinal gases may be stored or transported in the same tanks, other containers used for intermediate storage, or tankers, as the same non-medicinal gas, provided that the quality of the latter is at least equal to the quality of the medicinal 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 medicinal gas service (after transporting non-medicinal gas or after a maintenance operation). This should include analytical testing. (PIC/S)
4. Filling and storage equipment are 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.
5. Equipment used during the critical steps of fabrication, packaging and testing, including computerized systems, is subject to installation and operational qualification. Equipment qualification is documented. Further guidance is provided in the Health Canada documents entitled “Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)” and “Annex 11 to the Current Edition of the Good Manufacturing Practices Guidelines - Computerised Systems (GUI-0050)”

6. A common system supplying gas to medicinal and non-medicinal gas manifolds is only acceptable if there is a validated method to prevent backflow from the non-medicinal gas line to the medicinal gas line. (PIC/S)
7. Equipment used in the fabrication, 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.

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 National Institute of Standards and Technology or another recognized standard. 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.

8. Repair and maintenance operations (including cleaning and purging) of equipment, should not adversely affect the quality of medicinal gases. In particular, procedures should describe the measures to be taken after repair and maintenance operations involving breaches of the system's integrity. Specifically it should be demonstrated that the equipment is free from any contamination that may adversely affect the quality of the finished product before releasing it for use. Records should be maintained. (PIC/S)
9. Openings for connections on lines supplying medical gases are adequately protected from contamination.
10. Check valves used to prevent contamination are verified on a scheduled frequency to ensure functionality.
11. A hoke bomb is acceptable for sampling gases from a storage tank provided the firm has validated the process. A hoke bomb is a stainless steel cylinder with a valve on each end which allows a gaseous product to flow through. 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.

PERSONNEL

C.02.006

Every lot or batch of a drug shall be fabricated, 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 Director considers satisfactory in the interests of the health of the consumer or purchaser.

RATIONALE

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

It is essential that qualified personnel be employed to supervise the fabrication and packaging of medical gases. The operations involved in the fabrication 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. 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

1. The individual in charge of the quality control department of a fabricator, and the individual in charge of the manufacturing department of a fabricator:
 - 1.1 may be a person registered as a respiratory therapist under applicable provincial legislation governing health professionals; or qualified by pertinent training; and
 - 1.2 has practical experience in their responsibility area.
 - 1.3 directly controls and personally supervises on site, each working shift during which activities under their control are being conducted; and
 - 1.4 may delegate duties and responsibility (e.g., to cover all shifts) to a person who meets the requirements defined under 1.1, while remaining accountable for those duties and responsibility.
2. The individual in charge of the quality control department of a packager/labeller, tester, importer and distributor of medical gases:
 - 2.1 may be a person registered as a respiratory therapist under applicable provincial legislation governing health professionals; or qualified by pertinent training; and
 - 2.2 has practical experience in their responsibility area.
 - 2.3 can delegate their duties and responsibilities to a person who meets the requirements defined under 2.1

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.

3. The individual in charge of the filling/packaging operations, including control over printed packaging materials and withdrawal of bulk gases of a packager/labeller:
 - 3.1 is qualified by training and experience
 - 3.2 can delegate their duties and responsibilities to a person who meets the requirements defined under 3.1
4. An adequate number of personnel with the necessary qualifications and practical experience appropriate to their responsibilities are available on site.
 - 4.1 The responsibilities placed on any one individual are not so extensive as to present any risk to quality.
 - 4.2 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.
 - 4.3 When key personnel are absent, qualified personnel are appointed to carry out their duties and functions.
5. All personnel are aware of the principles of GMP that affect them and receive initial and continuing training relevant to their job responsibilities.
 - 5.1 Training is provided by qualified personnel having regard to the function and in accordance with a written program for all personnel involved in the fabrication of a medical gas, including technical, maintenance and cleaning staff. The training programs should include the tanker drivers. (PIC/S)
 - 5.2 The effectiveness of continuing training is periodically assessed.
 - 5.3 Training is provided prior to implementation of new or revised SOPs.
 - 5.4 Records of training are maintained.
 - 5.5 Personnel working in areas where highly active, toxic, infectious or sensitizing materials are handled, are given specific training.
 - 5.6 Performance of personnel is periodically reviewed.
6. Consultants and contractors have the necessary qualifications, training, and experience to advise on the subjects for which they are retained. Personnel of subcontractors that could influence the quality of medicinal gases (such as personnel in charge of maintenance of cylinders or valves) should be appropriately trained. (PIC/S)

SANITATION

C.02.007

- (1) Every person who fabricates or packages/labels a drug shall have a written sanitation program that shall be implemented under the supervision of qualified personnel.
- (2) The sanitation program referred to in subsection (1) shall include:
 - a) cleaning procedures for the premises where the drug is fabricated or packaged/labelled and for the equipment used in the fabrication or packaging/labelling of the drug; and
 - b) instructions on the sanitary fabrication and packaging/labelling of drugs and the handling of materials used in the fabrication and packaging/labelling of drugs.

RATIONALE

Sanitation in a medical gas fabricating 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 fabricated and packaged free from contamination.

A written sanitation program provides some assurance that levels of cleanliness in the facility are maintained and that the provisions of Sections 8 and 11 of the *Food and Drugs Act* are satisfied.

INTERPRETATION

1. Even though medical gases are handled in closed systems, areas where medical gases are filled are kept clean and tidy.
 - 1.1 Every facility that fabricates or packages/labels a medical gas shall have a written sanitation program available on the premises.
2. The sanitation program contains procedures that describe the following:
 - 2.1 cleaning requirements applicable to the facility;
 - 2.2 cleaning requirements applicable to processing equipment.
3. Cleaning of critical equipment used in fabrication, 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. Special attention is given to the tankers and trailers owned by a contracting firm. Further guidance is provided in the Health Canada document entitled "Cleaning Validation Guidelines (GUI-0028)".

C.02.008

- (1) Every person who fabricates or packages/labels a drug shall have, in writing, minimum requirements for the health, and the hygienic behaviour and clothing of personnel to ensure the clean and sanitary fabrication and packaging/labelling of the drug.
- (2) No person shall have access to any area where a drug is exposed during its fabrication 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

The manufacture of medical gases is carried out in closed equipment. Potential for environmental contamination of the product is minimal. The requirements for hygiene of personnel engaged in the production of medical gases are similar to those that are applicable to personnel involved with other dosage forms, although the extent to which they are applicable will greatly depend on the operation and the procedures used.

INTERPRETATION

1. Minimum health requirements are available in writing:
 - 1.1 assurance as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture and packaging of medical gases;
 - 1.2 assurances that individuals responsible for performing odour tests do not have ailments that can adversely affect test results;
 - 1.3 assurances that employees responsible for performing inspections involving distinguishing colours can distinguish colours appropriately.
2. The written hygiene program clearly defines clothing requirements and hygiene procedures for company personnel and visitors.
 - 2.1 Where a potential for contamination of a medical gas exists, individuals wear clean clothing and protective covering.
 - 2.2 Direct contact is avoided between the operator's hands and any parts of equipment that come in direct contact with the medical gas.
 - 2.3 Unsanitary practices are not permitted in processing areas.

- 2.4 Requirements concerning personal hygiene are outlined when significant to the quality of the product.

RAW MATERIAL TESTING

Note: Sections C.02.009 and C.02.010 are applicable only to batches of gases that are used in the fabrication of medical gas mixtures. For testing of bulk gases that are not used to produce gas mixtures, see sections C.02.011, C.02.018, and C.02.019.

C.02.009

- (1) Each lot or batch of raw material shall be tested against the specification of the raw material prior to its use in the fabrication of a drug.
- (2) No lot or batch of raw material shall be used in the fabrication of a drug unless that lot or batch of raw material complies with the specifications for that raw material.
- (3) Notwithstanding subsection (1), water may, prior to the completion of its tests under that subsection, be used in the fabrication of a drug.
- (4) Where any property of a raw material is subject to change on storage, no lot or batch of that raw material shall be used in the fabrication of a drug after its storage unless the raw material is retested after an appropriate interval and complies with its specifications for that property.
- (5) Where the specifications referred to in subsections (1), (2) and (4) are not prescribed, they shall:
 - a) be in writing;
 - b) acceptable to the Director, who shall take into account the specifications contained in any publication mentioned in Scheduled B to the *Act*; and
 - c) be approved by the person in charge of the quality control department.

RATIONALE

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

INTERPRETATION

1. Raw materials are tested to specification on receipt at the fabricating facility.
2. Specifications are in compliance with the marketing authorization. When a monograph exists in a pharmacopeia listed in Schedule B to the *Food and Drugs Act*, specifications meet the monograph.

3. Test methods are validated, and the results of such validation studies are documented. Full validation is not required for methods included in any standard listed in Schedule B to the *Food and Drugs Act*, but the user of such a method establishes its suitability under actual conditions of use. 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 document entitled “ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology” or in any standard listed in Schedule B to the *Food and Drugs Act*.

4. Deliveries of raw material may be added to a bulk storage tank containing the same gas from previous deliveries. In this case:
 - 4.1 a sample of the delivered raw material is tested and found to be satisfactory; or
 - 4.2 when the raw 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;
 - 4.3 when the raw material is a mixture, the testing verifies each component.

C.02.010

- (1) The testing referred to in section C.02.009 shall be performed on a sample taken
 - a) after receipt of each lot or batch of raw material on the premises of the fabricator; or
 - b) subject to subsection (2), before receipt of each lot or batch of raw material on the premises of the fabricator, if
 - (I) the fabricator:
 - (A) has evidence satisfactory to the Director to demonstrate that raw materials sold to him by the vendor of that lot or batch of raw material are consistently manufactured in accordance with and consistently comply with the specifications for those raw materials; and
 - (B) undertakes periodic complete confirmatory testing with a frequency satisfactory to the Director; and
 - (ii) the raw material has not been transported or stored under conditions that may affect its compliance with the specifications for that raw material.
- (2) After a lot or batch of raw material is received on the premises of the fabricator, the lot or batch of raw material shall be tested for identity.

RATIONALE

Section C.02.010 outlines options as to when the testing prescribed by section C.02.009 is carried out. The purchase of raw materials is an important operation that requires a particular and thorough knowledge of the raw materials and their vendor.

INTERPRETATION

1. The testing is performed on a sample taken after receipt of the raw material on the premises of the facility that fills medical gas into containers. Specific identity testing is conducted on all lots of any raw material in accordance with Regulation C.02.009, interpretation 2.
2. For tests other than identity tests, paragraph C.02.010 (1) (b) outlines conditions to be met, should the person choose to rely on the test results provided by the vendor.
 - 2.1 Evidence satisfactory to the Director should include:
 - 2.1.1 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 raw material fabricator 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.
 - 2.1.2 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;
 - 2.1.3 Complete confirmatory testing is conducted on a minimum of one lot per year of a raw material received from each vendor, with the raw material being selected on a rotational basis.
 - 2.1.3.1 In addition, where multiple raw materials are received from the same vendor, confirmatory testing is carried out for each raw material at least once every five years.
 - 2.2 If any lot is rejected, the vendor must be requalified.
3. Conditions of transportation and storage should be such that they prevent alterations to the potency and purity of the raw material. In order to demonstrate that these conditions have been met, standard operating procedures and records for shipping and receiving are available and contain:
 - 3.1 the type of packaging to be employed;
 - 3.2 labelling requirements;
 - 3.3 mode of transportation;
 - 3.4 seal of package;

- 3.5 verification required to ensure that each package has not been tampered with and that there are no damaged containers;
- 3.6 evidence that special shipping requirements have been met.

MANUFACTURING CONTROL

C.02.011

- (1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003 (b) and importer of a drug shall have written procedures, prepared by qualified personnel, in respect of the drug to ensure that the drug meets the specifications for use of that drug.
- (2) Every person required to have written procedures referred to in subsection (1) shall ensure that each lot or batch of the drug is fabricated, packaged/labelled and tested in compliance with those procedures.

RATIONALE

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

The following operations are considered a "fabricate" activity:

- 1. medical gases produced via air liquefaction (i.e., meaning produced at air separation plants) and/or
- 2. medical gas mixtures made by filling into cylinders

Transfilling of gases either at the facility or curbside is considered a "package" activity pursuant to Section C.01A.001(1) of the Food and Drug Regulations, which defines the term "package" as "to put a drug in its immediate container", and section C.01.001, which defines the term "immediate container" as "the receptacle that is in direct contact with a drug". If the company transfilling holds the drug identification number (DIN), the activity would be classified as both distribution and packaging/labelling, and must meet the requirements of Divisions 1A and 2 of the Food and Drug Regulations.

INTERPRETATION

- 1. All handling of raw materials, products, and packaging materials such as receipt, quarantine, sampling, storage, tracking, labelling, dispensing, processing, packaging and distribution is done in accordance with pre-approved written procedures or instructions and recorded.
- 2. 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.

3. Changes to production processes, systems, equipment, or materials that may affect product quality and/or process reproducibility are validated prior to implementation
4. Any deviation from instructions or procedures is avoided. If deviations occur, qualified personnel investigate, and write a report that describes the deviation, the investigation, the rationale for disposition, and any follow-up activities required. The report is approved by the quality control department and records maintained.
5. Bulk gases are stored under conditions and handled in distribution systems that preclude product mixup, deterioration or contamination.
6. Measuring devices are regularly checked for accuracy and precision, and records of such checks are maintained.
4. Written procedures are available to ensure that raw materials and bulk gases are:
 - 4.1 identified by lot number, receiving number, or laboratory control number;
 - 4.2 released for production or filling operations according to written procedures approved by the quality control department;
 - 4.3 meet Schedule B standards if applicable and Certificates of Analysis are reviewed and available on-site for each shipment of source gas received, and;
 - 4.4 stored under conditions that will preserve their quality and avoid their inadvertent use.
5. Written procedures approved by the quality control department are available to ensure that containers are not filled until they are checked or tested to ensure that they meet their specifications.
6. Processing operations are covered by master formulae, which are prepared by, and subject to independent checks by persons having the qualifications described under section C.02.006.
7. Master formulae, master production documents, or master filling documents are written to provide 100% of label claim and include:
 - 7.1 the name of the product;
 - 7.2 the name and concentration of components, including acceptable tolerances;
 - 7.3 the filling sequence of components;
 - 7.4 the fill pressure or weight of components (compressed gases);
 - 7.5 in-process and final quality control requirements.

8. 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 raw materials, products, product residues, labels or documents not required for the current operation.
9. Manufacturing and filling records contain all information pertinent to the manufacturing and filling of each batch of medical gas including:
 - 9.1 in-process quality control requirements;
 - 9.2 equipment used (if multiple systems are used for same product);
 - 9.3 a mark that is unique to an individual or the initials of personnel; and
 - 9.4 name and references to the specification for each raw material in a mixture.
10. Completed manufacturing orders include:
 - 10.1 appropriate check to ensure the containers have been filled;
 - 10.2 actual results of the quality checks performed;
 - 10.3 batch or lot number, receiving number, or laboratory control number of each raw material in a mixture; and
 - 10.4 a mark that is unique to an individual or the initials of personnel involved in the preparation of the mixture.
11. Deliveries of bulk gas may be added to the bulk storage tanks containing the same gas from previous deliveries. In this case:
 - 11.1 a sample of the delivered bulk gas is tested before it is added to the storage tank, and found to be satisfactory; or
 - 11.2 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;
 - 11.3 when the bulk gas is a mixture, the testing verifies each component.
12. 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.
13. Written instructions ensure that:
 - 13.1 the initials of quality control personnel or qualified designate are recorded in the filling logs;

- 13.2 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;
- 13.3 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;
- 13.4 during manifold filling sequences a heat of compression check is performed, where necessary, on the exterior surface of each cylinder to demonstrate proper filling;
- 13.5 filled containers are effectively quarantined until released by the quality control department;
- 13.6 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.

- 14. 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.
 - 14.1 Labels withdrawal is documented and reconciled.
 - 14.2 Labelling operations are controlled by 100% verification. Verifications are documented.
 - 14.3 Labelling operations are documented.
- 15. 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 colour 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.
- 16. After filling, cylinders valves should be fitted with covers to protect the outlets from contamination. Cylinders and mobile cryogenic vessels should be fitted with tamper-evident seals (PIC/S).
- 17. Materials and labels used to identify containers are stored in a limited access area and restricted to designated personnel.
- 18. Outdated or obsolete materials and labels are destroyed and their disposal recorded.
- 19. Medical gases are not released without the approval of the quality control department.

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

ANNUAL PRODUCT QUALITY REVIEW

51. Regular periodic or rolling 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 raw materials and medical gas to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:
 - 51.1 A review of critical in-process controls, finished product testing results and specifications.
 - 51.2 A review of all batches that failed to meet established specification(s) and their investigation.
 - 51.3 A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.
 - 51.4 A review of all changes carried out to the processes, analytical methods, raw materials, packaging materials, or critical suppliers.
 - 51.5 A review of the results of the continuing stability program and any adverse trends.
 - 51.6 A review of all quality-related returns, complaints and recalls and the investigations performed at the time.
 - 51.7 A review of adequacy of any other previous product process or equipment corrective actions.
 - 51.8 The qualification status of relevant equipment and systems (e.g., HVAC, water, compressed gases, etc.); and
 - 51.9 A review of agreements to ensure that they are up to date.
52. The quality control department of the 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.
53. Where required, there should be an agreement in place between the various parties involved (e.g., importer and fabricator) that defines their respective responsibilities in producing and assessing the quality review and taking any subsequent corrective and preventative actions.
54. The quality control 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.

C.02.012

- (1) Every fabricator, packager/labeller, distributor referred to in section C.01A.003, importer and wholesaler of a drug shall maintain:
 - a) a system of control that permits complete and rapid recall of any lot or batch of the drug that is on the market; and
 - b) a program of self-inspection;
- (2) Every fabricator and packager/labeller and, subject to subsections (3) and (4), every distributor referred to in section C.01A.003(b) and importer of a drug shall maintain a system designed to ensure that any lot or batch of the drug fabricated and packaged/labelled on premises other than their own is fabricated and packaged/labelled in accordance with the requirements of this Division.
- (3) The distributor referred to in paragraph C.01A.003(b) of a drug that is fabricated, packaged/labelled, and tested in Canada by a person who holds an establishment licence that authorizes those activities is not required to comply with the requirements of subsection (2) in respect of that drug.
- (4) If a drug is fabricated or packaged/labelled in an MRA country at a recognized building, the distributor referred to in paragraph C.01A.003(b) or importer of the drug is not required to comply with the requirements of subsection (2) in respect of that activity for that drug if
 - (a) the address of the building is set out in that person's establishment licence; and
 - (b) that person retains a copy of the batch certificate for each lot or batch of the drug received by that person.

RATIONALE

The purpose of a recall is to remove from the market a medical gas that represents an undue health risk.

Medical gases that have left the premises of a fabricator, 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. Fabricators, 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 Health Canada's document entitled "Product Recall Procedures".

This regulation also requires fabricators, 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. The self-inspection program is designed to detect any shortcomings in the implementation of GMPs and to recommend the necessary corrective actions.

Medical gases offered for sale in Canada, regardless of whether they are domestically produced or imported, must meet the requirement of Part C, Division 2 of the *Food and Drug Regulations*. Contract production and analysis must be correctly defined, agreed, and controlled in order to avoid misunderstanding that could result in a product, work or analysis of unsatisfactory quality. Normally, a written agreement exists between the parties involved which clearly established the duties of each party.

INTERPRETATION

1. A written recall system is in place to ensure compliance with Section C.01.051 of the *Food and Drug Regulations* and requires the following:
 - 1.1 Health Canada is to be notified of the recall.
 - 1.2 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.
 - 1.3 The person(s) responsible for initiating and co-ordinating all recall activities are identified.
 - 1.4 The recall procedure is capable of being put into operation at any time, during and outside normal working hours.
 - 1.5 The recall procedure outlines the means of notifying and implementing a recall and of deciding its extent.
 - 1.6 Distribution records enable tracing of medical gas, and account is taken of any medical gas that are in transit.
 - 1.7 The progress and efficacy of a recall is assessed and recorded at intervals, and a final report is issued (including a final reconciliation).
 - 1.8 Recalled medical gas are identified and are stored separately in a secure area until their disposition is determined.
 - 1.9 All Canadian and foreign establishments involved in the fabrication, distribution, or importation of the recalled medical gas are notified.
2. A self-inspection program appropriate to the type of operations of the establishment, with respect to medical gases, ensures compliance with Division 2, Part C of the *Food and Drug Regulations*.
 - 2.1 A comprehensive written procedure that describes the functions of the self-inspection program is available.
 - 2.2 The self-inspection team includes personnel who are suitably trained and qualified in GMP
 - 2.3 periodic self-inspections are carried out.

- 2.4 Reports on the findings of the inspections and on corrective actions are reviewed by appropriate senior company management. Corrective actions are implemented in a timely manner.
3. To ensure compliance of contractors performing fabrication and packaging/labelling:
 - 3.1 There is a written agreement covering the fabrication or packaging/labelling arranged among the parties involved. The agreement specifies their respective responsibilities relating to the fabrication or packaging/labelling and control of the product.
 - 3.1.3 Technical aspects of the agreement are drawn up by qualified personnel suitably knowledgeable in pharmaceutical technology, and GMP.
 - 3.1.4 The agreement permits the distributor or importer to audit the facilities of the contractor.
 - 3.1.5 The agreement clearly describes as a minimum who is responsible for:
 - 3.1.5.1 purchasing, sampling, testing, and releasing materials;
 - 3.1.5.2 undertaking production, quality, and in-process controls; and
 - 3.1.5.3 process validation.
 - 3.1.6 No subcontracting of any work should occur without written authorization.
 - 3.1.7 The agreement specifies 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 fabricated and packaged/labelled in compliance with the requirements of the marketing authorization.
 - 3.1.8 The agreement describes the handling of raw materials, packaging materials, in-process medical gas, bulk medical gas and finished products if they are rejected.
 - 3.2 The contractor's complaint/recall procedures 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.
 - 3.3 The fabricator, packager/labeller, distributor, or importer provides 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. The fabricator, packager/labeller, distributor, or importer ensures 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.
 - 3.4 The fabricator, packager/labeller, distributor or importer is 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.
 - 3.4.1 Distributors of medical gases fabricated, packaged/labelled or tested at Canadian sites are required only to have a copy of the relevant valid Canadian establishment licence held by the Canadian fabricator, packager/labeller or tester.
 - 3.4.2 Importers of bulk gases and finished products fabricated, packaged/labelled, or tested at a foreign site must meet the requirements described in Health Canada's policy document entitled "Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080)". The foreign site must be listed on the establishment licence of the importer.

QUALITY CONTROL DEPARTMENT

C.02.013

- (1) Every fabricator, packager/labeller, wholesaler, distributor referred to in paragraph C.01A.003(b) and importer shall have on their premises in Canada a quality control department that is supervised by personnel described in section C.02.006.
- (2) 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.

RATIONALE

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 raw 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. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

Although manufacturing and quality control personnel share the common goal of assuring the high-quality medical gases are fabricated, their interest may sometimes conflict in the short run as decisions are made that will affect a company's output. 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 fabricating and packaging is considered fundamental. The rationale for the requirement that the quality control department be supervised by qualified personnel is outlined under the section C.02.006.

INTERPRETATION

1. A person responsible for making decisions concerning quality control requirements is 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:
 - 1.1 it is impossible to have distinct organizational units on site;
 - 1.2 chances of error are eliminated;
 - 1.3 reporting relationship is different while the employee performs quality control functions and fabrication or packaging/labelling activities;
 - 1.4 the employee is fully aware of his/her dual role, understands clearly responsibilities and line authority and acts accordingly.
2. The quality control department has true and effective access to equipment and facilities for inspecting and testing, having regard to the nature of the products produced.

C.02.014

- (1) Except in the case of a wholesaler, no lot or batch of drug shall be made available for sale unless the sale of that lot or batch is approved by the person in charge of the quality control department.
- (2) A drug that is returned to the fabricator, packager/labeller, wholesaler, distributor referred to in paragraph C.01A.003(b) or importer shall not be made available for further sale unless the sale of that drug is approved by the person in charge of the quality control department.
- (3) No lot or batch of raw material or of packaging/labelling material shall be used in the fabrication or packaging/labelling of a drug, unless that material is approved for that use by the person in charge of the quality control department.
- (4) No lot or batch of a drug shall be reprocessed without the approval of the person in charge of the quality control department.

RATIONALE

The responsibility for the approval of all raw 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. To maintain this level of quality, it is also important to examine all returned medical gases

INTERPRETATION

1. All decisions made by the quality control department pursuant to section C.02.014 are attested to by the signature of the head of the quality control department, or an authorized alternate, and are dated.
2. The quality control department ensures that raw materials, bulk gases, and packaging materials are effectively quarantined, sampled, tested, and released prior to their use in fabrication or packaging/labelling of a medical gas.
3. Finished products returned from the market are destroyed unless it has been ascertained that their quality is satisfactory. Returned goods may be considered for resale only after they have been assessed in accordance with a written procedure. The reason for the return, the nature of the product, the storage and transportation conditions, the product's condition and history, and the time elapsed since it was originally sold are to be taken into consideration in this assessment. Records of any action taken are maintained.

C.02.015

- (1) All fabrication, packaging/labelling, testing, storage and transportation methods and procedures that may affect the quality of a drug shall be examined and approved by the person in charge of the quality control department before their implementation.
- (2) The person in charge of the quality control department shall cause to be investigated every complaint or information that is received respecting the quality of a drug or its deficiencies or hazards and cause any corrective action to be taken, in the case where the complaint or information relates to an activity over which the department exercises quality control.
 - (2.1) In the case where the complaint or information that is received does not relate to an activity over which the quality control department exercises quality control, the person in charge of the department shall forward the complaint or information to the person in charge of the quality control department that exercises quality control over that activity.
- (3) The person in charge of the quality control department shall cause all tests or examinations required pursuant to this Division to be performed by a competent laboratory.

RATIONALE

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. 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.

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

The quality control department is responsible for the following:

1. All decisions made pursuant to section C.02.015 are signed and dated by the person in charge of the quality control department, or a designated alternate who meets the requirements described under Regulation C.02.006, as applicable to the activity.
2. Ensuring 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 (PIC/S).
3. The tests are performed by a laboratory that meets all relevant GMP requirements.

- 3.1 Laboratory facilities are designed, equipped, and maintained to suit the testing and approval (or rejection) of raw materials, medical gases, and containers;
- 3.2 The individual in charge of the laboratory is qualified in accordance with C.02.006 or functionally reports to a person having these qualifications; and
- 3.3 Laboratory personnel are sufficient in number and are qualified to carry out the work they undertake.
- 3.4 Laboratory control equipment and instruments are suited to the testing procedures undertaken. Equipment and records are maintained as per the interpretations under C.02.005.
- 3.5 Computerized systems are validated, and spreadsheets are qualified.
- 3.6 Out of Specification (OOS) test results are investigated to determine the cause of the OOS.
 - 3.6.1 Procedures are in place to describe the steps to be taken as part of the investigation.
 - 3.6.2 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.
 - 3.6.3 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.
 - 3.6.4 All valid test results, both passing and suspect, should be reported and considered in batch release decisions.
 - 3.6.5 If the original OOS result is found to be valid, a deviation is raised against the batch and a complete investigation is conducted.
3. 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. 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.
4. 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 control department, and are identified with the appropriate effective date. Any significant change may necessitate re-validation.

PACKAGING MATERIAL TESTING

C.02.016

- (1) Each lot or batch of packaging material shall, prior to its use in the packaging of a drug, be examined or tested against the specifications for that packaging material.
- (2) No lot or batch of packaging material shall be used in the packaging of a drug unless the lot or batch of packaging material complies with the specifications for that packaging material.
- (3) The specifications referred to in subsection (1) and (2) shall
 - a) be in writing;
 - b) be acceptable to the Director who shall take into account the specifications contained in any publication mentioned in Schedule B to the *Act*; and
 - c) be approved by the person in charge of the quality control department.

RATIONALE

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. 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

1. Containers are carefully examined against their specifications before filling.
2. For high pressure containers returned for filling, checks and tests are performed on each and every container. These checks and tests should include:
 - 2.1 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;
 - 2.2 check to determine that old batch labels with lot numbers and identification, and other damaged labels have been removed;

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.
 - 2.3 venting or blowing down to atmospheric pressure if any gas is present; or inverted and drained;

- 2.4 an odour or sniff test may be performed during the venting of a cylinder to detect the presence of foreign gas or odor;
- 2.5 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:
 - 2.5.1 Steel cylinders are re-qualified every five (5) years unless a “*” follows the testing date which means the cylinder may be re-qualified every ten (10) years.
 - 2.5.2 Aluminum cylinders are re-qualified every five (5) years.
 - 2.5.3 Water used for hydrostatic testing is at least of drinking water quality.
 - 2.5.4 The interior of cylinders are visually examined at appropriate intervals (usually when re-qualification is performed).
- 2.6 a dead ring test or hammer test is performed to determine the absence of internal corrosion;

Note: This does not apply to aluminum cylinders. Cylinders producing a dull sound are quarantined for possible internal corrosion.
- 2.7 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.
3. 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:
 - 3.1 an external vessel check;
 - 3.2 all inlet and outlet connection check;
 - 3.3 a label check.
4. In addition to examinations as identified above, large cryogenic vessels need to be examined for Transport Canada markings and the packager must ensure that the pressure relief device on the unit is appropriate for its intended use.
5. The specifications prescribe that each container be reserved for a particular type of medical gas and be identified as such (e.g., by means of a specific colour).
6. Gauges on containers indicating volume or quantity are checked to ensure proper operation.
7. Containers failing above examinations and testing are quarantined to prevent their use.
8. 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".

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

C.02.017

- (1) The examination or testing referred to in section C.02.016 shall be performed on a sample taken:
- a) after receipt of each lot or batch of packaging material on the premises of the person who packages a drug; or
 - b) subject to subsection (2), before receipt of each lot or batch of packaging material on the premises of the person who packages a drug:
 - (I) if that person
 - (A) has evidence satisfactory to the Director 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
 - (B) undertakes periodic complete confirmatory examination or testing with a frequency satisfactory to the Director; and
 - (ii) the packaging material has not been transported or stored under conditions that may affect its compliance with the specifications for that packaging material.
- (2) After a lot or batch of packaging material is received on the premises of the person who packages a drug:
- a) the lot or batch of the packaging material shall be examined or tested for identity; and
 - b) the labels shall be examined or tested in order to ensure that they comply with the specifications for those labels.

RATIONALE

Regulation C.02.017 outlines options as to when the testing or examination prescribed by Regulation C.02.016 is carried out. As with raw materials, the purchase of packaging materials is an important operation that involves staff who have thorough knowledge of the packaging materials and vendor.

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

1. This section would apply in the unlikely event that the containers would be tested on premises other than those where the filling takes place.
2. 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:
 - 2.1 the type of packaging to be employed;
 - 2.2 labelling requirements;
 - 2.3 mode of transportation;
 - 2.4 the type and seal of package; and
 - 2.5 verification required to ensure the package has not been tampered with and that there are no damaged containers.

FINISHED PRODUCT TESTING

C.02.018

- (1) Each lot or batch of a drug shall, prior to its availability for sale, be tested against the specification for that drug.
- (2) No lot or batch of a drug shall be available for sale unless it complies with the specifications for that drug.
- (3) The specifications referred to in subsection (1) and (2) shall:
 - a) be in writing;
 - b) be approved by the person in charge of the quality control department; and
 - c) comply with the *Act* and these *Regulations*.

RATIONALE

Finished product tests complement the controls employed during the manufacturing process. It is the responsibility of each fabricator, 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

1. Written specifications are approved by the person in charge of the quality control department or by a designated alternate who meets the requirements described under Regulation C.02.006 as applicable to the activity.
 - 1.1 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.
 - 1.2. Specifications are equal to or exceed a recognized standard as listed in Schedule B to the *Food and Drugs Act* and are in compliance with the marketing authorization.

2. Test methods are validated, and the results of such validation studies are documented. 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 document entitled “ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology” or in any standard listed in Schedule B to the *Food and Drugs Act*.

3. 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. 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). For high pressure containers filled individually manually, 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. For mixtures containing more than two gases, every cylinder should be tested to specification of all but one of the gases, and one cylinder from each manifold filling sequence should be tested for the identity of the remaining gas.

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.

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

6. 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.
7. 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 fabricating and/or packaging operations for this gas mixture. A certificate of analysis is required from the fabricator of the gas mixture.
8. 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.

C.02.019

- (1) Subject to subsections (3) and (4), in the case of a packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer, the testing referred to in section C.02.018 shall be performed on a sample taken
 - (a) after receipt of each lot or batch of the drug on the premises in Canada of the packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer of the drug; or
 - (b) subject to subsection (2), before receipt of each lot or batch of the drug on the premises described in paragraph (a), if;
 - (i) the packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer
 - (A) has evidence satisfactory to the Director to demonstrate that drugs sold to him by the vendor of that lot or batch of the drug are consistently manufactured in accordance with and consistently comply with the specifications for those drugs; and
 - (B) undertakes periodic complete confirmatory testing with a frequency satisfactory to the Director; and
 - (ii) the drug has not been transported or stored under conditions that may affect its compliance with the specifications for that drug.
- (2) Where the packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer of a drug receives a lot or batch of a drug on the premises in Canada, and the useful life of the drug is more than 30 days, the lot or batch of the drug shall be tested for identity, and the packager/labeller shall confirm the identity after the lot or batch is packaged/labelled.
- (3) The distributor referred to in paragraph C.01A.003(b) of a drug that is fabricated, packaged/labelled, and tested in Canada by a person who holds an establishment licence that authorizes those activities is not required to comply with the requirements of subsections (1) and (2) in respect of that drug.

- (4) If a drug is fabricated, packaged/labelled, and tested in an MRA country at a recognized building, the distributor referred to in paragraph C.01A.003(b) or importer of that drug is not required to comply with the requirements of subsections (1) and (2) in respect of that drug if
- (a) the address of the building is set out in that person's establishment licence; and
 - (b) that person retains a copy of the batch certificate for each lot or batch of the drug received by that person.

RATIONALE

C.02.019 outlines conditions and exemptions as to when finished product testing is to be performed. Paragraph C.02.019(1)(b) outlines requirements that must be met if the testing is done before receipt on the premises of the packager/labeller, distributor or importer of the medical gas. Paragraphs C.02.019(3) and C.02.019(4) outline exemptions to finished product testing

INTERPRETATION

1. Testing is performed on a sample taken after receipt on the premises of the distributor (C.01A.003 (b)) or importer of the medical gas unless the distributor or importer chooses to rely on test results provided by the supplier.

SITES HOLDING A CANADIAN ESTABLISHMENT LICENCE

2. To demonstrate compliance with specifications, distributors of finished products that are fabricated, packaged/labelled, and tested at Canadian sites are required only to have a copy of the authentic certificate of analysis from the licensed Canadian establishment. This certificate shows actual numerical results and refers to the product specifications and test methods used. Retesting, including identity testing, is not required.

BUILDINGS RECOGNIZED BY A REGULATORY AUTHORITY IN A MRA COUNTRY

3. To demonstrate compliance with specifications, importers of finished products fabricated, packaged/labelled, and tested at recognized buildings authorized by a Regulatory Authority as listed by virtue of Regulation C.01A.019 and identified on their establishment license are required only to have a batch certificate in the format agreed on by the MRA partners for each lot or batch of the drug received. Re-testing, including identity testing, is not required when the drug is fabricated, packaged/labelled, and tested in an MRA country.

SITES IN NON-MRA COUNTRIES

4. 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:
 - 4.1 Evidence of ongoing GMP compliance is provided according to a system described in interpretation of Regulation C.02.012 as demonstrated by listing on the packager/labeller's or importer's establishment licence.
 - 4.2 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;
 - 4.3 periodic complete confirmatory testing is performed on at least one lot per year per fabricator. Products are selected on a rotational basis.
 - 4.4 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 control department, be released for sale prior to completion of all tests.
6. 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:
 - 6.1 re-evaluation of GMP compliance; and
 - 6.2 additional complete confirmatory testing, based on the risk associated with the non-compliance.
7. 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 tanks of imported medical gas:
 - a. foreign site must be listed on the Drug Establishment Licence,
 - b. only labeled dedicated tanks are to be used, tank has traceability identification, and attestation is available for tank dedication declaration,
 - c. importer ensures that:
 - i. certificate of analysis and certificate of manufacture must be verified prior to customer delivery by Quality Control review for release,
 - ii. foreign supplier is qualified by a vendor certification program including,
 - iii. periodic confirmatory testing is performed,
 - d. not applicable for mixed gases.

RECORDS

C.02.020

- (1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer shall maintain on their premises in Canada for each drug sold:
 - a) master production documents for the drug;
 - b) evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and stored in accordance with the procedures described in the master production documents;
 - c) evidence that the conditions under which the drug was fabricated, packaged/labelled, tested and stored are in compliance with the requirements of this division;
 - d) evidence establishing the period of time during which the drug in the container in which it is sold will meet the specifications for that drug; and
 - e) adequate evidence of the testing referred to in section C.02.018.
- (2) Every distributor referred to in paragraph C.01A.003(b) and importer shall make available on request the results of testing performed on raw materials and packaging/labelling materials for each lot or batch of a drug sold.
- (3) Every fabricator shall maintain on his premises:
 - a) the written specifications for the raw material; and
 - b) adequate evidence of the raw materials testing referred to in section C.02.009.
- (4) Every person who packages a drug shall maintain on his premises:
 - a) the written specifications for the packaging materials; and
 - b) adequate evidence of the packaging material examination or testing referred to in section C.02.016.
- (5) Every fabricator shall maintain on their premises in Canada:
 - a) detailed plans and specifications of each building in Canada at which they fabricate package/label or test; and
 - b) a description of the design and construction of those buildings.
- (6) Every fabricator, packager/labeller, and tester shall maintain on their premises in Canada details of the personnel employed to supervise the fabrication, packaging/labelling, and testing including each person's title, responsibilities, qualifications, experience, and training.

C.02.021

- (1) Subject to subsection (2), all records and evidence on the fabrication, packaging/labelling, testing, and storage of a drug that are required to be maintained under this Division shall be retained for a period of at least one year after the expiration date on the label of the drug, unless otherwise specified in the person's establishment licence.
- (2) All records and evidence on the testing of raw materials, and packaging/labelling materials that are required to be maintained under this Division shall be retained for a period of at least five years after the materials were last used in the fabrication or packaging/labelling of a drug unless otherwise specified in the person's establishment licence.

C.02.022

Every distributor referred to in section C.01A.003, wholesaler and importer of a drug shall retain records of the sale or each lot or batch of the drug, which enable them to recall the lot or batch from the market for a period of at least one year after the expiration date of the lot or batch unless otherwise specified in their establishment licence.

C.02.023

- (1) On receipt of a complaint or any information respecting the quality of a drug or its deficiencies or hazards, every fabricator, packager/labeller, wholesaler, distributor referred to in paragraph C.01A.003(b) or importer of the drug, as the case may be, shall
 - (a) in the case of a complaint or information described in subsection C.02.015(2), make a record of the complaint or information, its investigation and, if applicable, any corrective action taken; and
 - (b) in the case of a complaint or information described in subsection C.02.015(2.1), make a record of the complaint or information, the name and business address of the person in charge of the quality control department to whom it was forwarded and the date on which it was forwarded.
- (2) The fabricator, packager/labeller, wholesaler, distributor referred to in paragraph C.01A.003 (b) or importer of the drug, 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 drug, unless otherwise specified in their establishment licence.

C.02.024

- (1) Every fabricator, packager/labeller, distributor referred to in section C.01A.003 importer and wholesaler shall
 - a) maintain records of the results of the self-inspection programme required by section C.02.012 and of any action taken in connection with that programme; and
 - b) retain those records for a period of at least three years.

- (2) Every person who fabricates or packages/labels a drug shall
- a) maintain records on the operation of the sanitation programme required to be implemented under section C.02.007; and
 - b) retain those records for a period of at least three years.

RATIONALE

Good documentation is an essential part of the quality assurance system and, as such, should be related to all aspects of GMP. Its aims are to define the specifications for all materials and methods of fabrication, packaging/labelling and control, to ensure that authorized persons have all the information necessary to decide whether or not to release a lot of a medical gas for sale, and to provide an audit trail that will permit investigation of the history of any suspected defective lot or batch.

Evidence that medical gases have been fabricated 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 fabricated and packaged/labelled in a like manner to those produced in Canada.

INTERPRETATION

C.02.020 to C.02.024

For all sections 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.

All relevant GMP documents (such as associated records of actions taken or conclusions reached) and SOPs are approved, signed, and dated by the quality control department. Documents are not altered without the approval of the quality control department. 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.

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 fabricator, packager/labeller, wholesaler, distributor, or importer.

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.

Any documentation requested for evaluation by Health Canada is provided in one of the official languages.

1. Records must include a copy of master filling and/or 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.
2. Section C.02.020 applies only to fabricators, packagers/labellers, distributors referred to in paragraph C.01A.003(b) and importers to the extent that they perform operations on the medical gas.
3. 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.
4. The following documents must be maintained by the fabricator, packager/labeller, wholesaler, distributor (C.01A.003), and importer of a medical gas as they relate to operations in Canada:
 - 4.1 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 drug. This does not necessary imply tracking by lot number;
 - 4.2 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.
 - 4.3 Records of the results of the self-inspection program and action taken;
5. The following documents must be maintained by the fabricator of medical gas mixtures:
 - 5.1 the written specifications for the raw materials;
 - 5.2 the results of the raw material testing;
 - 5.3 the sources of the raw materials supplied.
6. The following documents must be maintained by the packager/labeller:
 - 6.1 the written specifications for the packaging materials;
 - 6.2 the results of the packaging material examinations or testing;
 - 6.3 the sources of the packaging materials supplied.

Documentation for cylinders and valves include:

1. Certification issued in accordance with Transport Canada's 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.

2. Valves on cylinders should be checked for functionality and records maintained.
7. Records on the operation of the sanitation program required under section C.02.007 must be maintained by the fabricator and the packager of medical gases.
8. Records required under Regulations C.02.021(1), C.02.022, and C.02.023 are ordinarily retained for a period of at least one year past the expiration date of the drug to which the records apply. However, for medical gases which do not require an expiration date, records required under regulations C.02.021(1), C.02.022, and C.02.023 are retained for a period of at least five years from the date of fabrication 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.
9. Records are maintained detailing the qualifications/experience of any consultant employed for GMP purposes, along with the services that each consultant provides.

MEDICAL GASES

C.02.030

The provisions of sections C.02.025, C.02.027 and C.02.028 do not apply to medical gases.

APPENDIX B

ACRONYMS

- DIN: Drug Identification Number
- GMP: Good Manufacturing Practices
- ICH: International Conference on Harmonization
- HPFB: Health Products and Food Branch
- NOC: Notice of Compliance
- MPD: Master Production Documents
- 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 (lot de fabrication) - A quantity of any medical gas, homogeneous within specified limits, and identified by a distinctive batch number.

BATCH CERTIFICATE (certificat de lot) – “A certificate issued by the fabricator of a lot or batch of a drug that is exported within the framework of a mutual recognition agreement and in which the fabricator

- (a) identifies the master production document for the drug 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 drug, including
 - (i) a statement of all properties and qualities of the drug, including the identity, potency and purity of the drug, and
 - (ii) a statement of tolerances for the properties and qualities of the drug;

- (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 standard.” (C.01A.001)

(The certificate’s content is also described in Appendix A).

BULK GAS (gaz en vrac) - A medical gas (either a single gas or a mixture of gases) that requires no further processing in order to be administered, but is not in its final package (e.g., liquefied oxygen).

CHANGE CONTROL (contrôle des changements) - 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 drugs, or (b) that may affect the operation of the quality or support system.

CONTAINER (contenant) - see PACKAGING MATERIAL.

CRITICAL PROCESS (procédé critique) - A process that if not properly controlled may cause significant variation in the quality of the finished product.

CRYOGENIC VESSEL (récipient cryogénique) - A static or mobile vacuum insulated container designed to contain liquefied gas at extremely low temperatures. Mobile vessels could also be known as “Dewars”.

CURBSIDE DELIVERY (livraison au point de remplissage) - 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)

DEAD RING TEST (HAMMER TEST) (essai de martelage) - A test used to determine the sound of a cylinder by striking its side. If a clear bell-like sound results, the cylinder is considered to be satisfactory. If a dull sound results, the cylinder is not considered to be suitable for filling with a medical gas (not applicable to aluminum cylinders).

DISTRIBUTOR (distributeur) - “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 drug.” (A.01.010)

Divisions 1A and 2 to 4 apply to the following distributors (C.01A.003):

- (a) a distributor of a drug listed in Schedule C or D to the *Act* or in Schedule F to these *Regulations*, a controlled drug as defined in subsection G.01.001 (1) or a narcotic as defined in the *Narcotic Control Regulations* who does not hold the drug identification number for the drug or narcotic; and
- (b) a distributor of a drug for which that distributor holds the drug identification number.

DOSAGE FORM (forme posologique) - A drug product that has been processed to the point where it is now in the form in which it may be administered in individual doses.

FABRICATE (manufacturer) - "To prepare and preserve a drug for the purposes of sale."
(C.01A.001)

FINISHED PRODUCT (produit fini) - A product that has undergone all stages of production, including packaging in its final container and labelling.

GAS (gaz) - Products in gaseous phase and products in liquid phase at cryogenic temperatures.

HOME CRYOGENIC VESSEL – Mobile cryogenic vessel designed to hold liquid oxygen and dispense gaseous oxygen at patients' home. (PIC/S)

HYDROSTATIC PRESSURE TEST – Test performed as required by national or international regulations, in order to ensure that pressure containers are able to withstand pressures up to the container's design pressure. (PIC/S)

IMMEDIATE CONTAINER (récipient immédiat) - The receptacle that is in direct contact with a drug.

IMPORTER (importateur) - A person that imports into Canada a drug for the purpose of sale.

LIQUEFIED GAS (gaz liquéfié) - A gas which has a critical temperature above 20⁰C, which remains as a liquid in the container when under pressure.

LOT (lot) - A quantity of any drug, raw material, or packaging material, homogenous within specified limits, constituting all or part of a single batch and identified by a distinctive lot number which appears on the label of the finished product.

MANIFOLD (rampe) - Equipment or apparatus designed to enable one or more medical gas containers to be filled at a time.

MANIFOLD FILLING SEQUENCE (cycle de remplissage sur rampe) - A filling sequence of many containers at one time using multiple outlet manifold or rack.

MARKETING AUTHORIZATION (autorisation de mise en marché) - A legal document issued by Health Canada, authorizing the sale of a drug or a device based on the health and safety requirements of the *Food and Drug Act* and its associated *Regulations*. The marketing authorization may be in the form of a Drug Identification Number (DIN), a device licence for classes II, III and IV medical devices, or a natural health product licence (NPN or DIN-HM).

MASTER FILLING DOCUMENTS (documents-types de remplissage) - A set of instructions for the filling of containers with a medical gas in dosage form containing a description of the filling operation, controls, procedures, specifications, and methods of quality control of the medical gas.

MASTER FORMULA (formule-type) - A document or set of documents specifying the raw materials with their quantities and the packaging materials, together with a detailed description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

MASTER PRODUCTION DOCUMENTS (MPD) (document-type de production) - Documents that include specifications for raw material, for packaging material, for bulk gases, and for packaged dosage form; master formula (including composition and instructions as described in the definition above), sampling procedures, and critical processing related SOPs, whether or not these SOPs are specifically referenced in the master formula.

MEDICAL GAS (gaz médical) - “Any gas or mixture of gases manufactured, sold or represented for use as a drug” (C.02.002)

MEDICAL TAG (étiquette médicale) - Refers also to the term “label” and includes any legend, word or mark attached to, belonging to or accompanying any medical gas for compliance to the *Food and Drug Regulations*.

MRA COUNTRY (pays participant à un ARM) - “A country that is a participant in a mutual recognition agreement (MRA) with Canada.” (C.01A.001)

MUTUAL RECOGNITION AGREEMENT (MRA) (accord de reconnaissance mutuelle (ARM)) – An international agreement that provides for the mutual recognition of compliance certification for Good Manufacturing Practices for drugs. (C.01A.001)

PACKAGE (emballer-étiqueter) - As described in package/label, the action of packaging refers to putting a drug in its immediate container. (C.01A.001)

PACKAGING MATERIAL (matériel d’emballage) - Labels, printed packaging materials and those components in direct contact with the dosage form. (refer to C.02.002)

QUALIFIED AUTHORITY (autorité qualifiée) - A member of the Pharmaceutical Inspection Cooperation/Scheme (PIC/S) or the United States Food and Drug Administration (USFDA).

QUALITY CONTROL DEPARTMENT (service du contrôle de la qualité) - A function maintained by a fabricator, packager/labeller, distributor, or importer, that is responsible only to management, and that monitors the quality of production operations and exercises control over the quality of materials required for and resulting from those operations.

QUARANTINE (quarantaine) - Effective restriction of the availability of material or product for use (physically or by system), until released by a designated authority.

RAW MATERIAL (matière première) - The individual gases that are used in the production of medical gas mixtures.

RECONCILIATION (bilan comparatif) - A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

REGULATORY AUTHORITY (autorité réglementaire) - A government agency or other entity in an MRA country that has a legal right to control the use or sale of drugs within that country and that may take enforcement action to ensure that drugs marketed within its jurisdiction comply with legal requirements.

STANDARD OPERATING PROCEDURE (SOP) (procédure opératoire normalisée (PON)) - A written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., 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.

TANK - Static thermally insulated container designed for the storage of liquefied or cryogenic gas. They are also called “Fixed cryogenic vessels”. (PIC/S)

TANKER - In the context of this guide, thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas. (PIC/S)

UNINTERRUPTED FILLING SEQUENCE (cycle de remplissage ininterrompu) - Single, continuous filling sequence with no breaks or shutdowns occurring during the filling and no change of personnel, equipment, or lots of raw materials. This procedure applies to the individual filling of high pressure cylinders (i.e, one cylinder at time).

VALIDATION (validation) - The documented act of demonstrating that any procedure, process, or activity will consistently lead to the expected results. Includes the qualification of systems and equipment.

VENDOR (vendeur) - For the purpose of these guidelines, vendor means the fabricator of the item.

WHOLESALE (vendre en gros) - “To sell any of the following drugs, other than at retail sale, where the seller's name does not appear on the label of the drugs:

- (a) a drug listed in Schedule C or D to the *Act* or in Schedule F to these *Regulations* or a controlled drug as defined in subsection G.01.001 (1); or
- (b) a narcotic as defined in the *Narcotic Control Regulations*.” (C.01A.001)