

GUI-0031: Good Manufacturing Practices for Medical Gases

March 4, 2026



Date issued: 4 March 2026
Date implemented: 4 March 2026
Replaces: Good manufacturing practices for medical gases (GUI-0031)
(February 28, 2018)

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. Health Canada is committed to improving the lives of all of Canada's people and to making this country's population among the healthiest in the world as measured by longevity, lifestyle and effective use of the public health care system.

Également disponible en français sous le titre: Bonnes pratiques de fabrication des gaz médicaux

To obtain additional information, please contact:

Health Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
Email: hc.publications-publications.sc@canada.ca

© His Majesty the King in Right of Canada, as represented by the Minister of Health, 2026

Publication date: March, 2026

This publication may be reproduced for personal or internal use only without permission provided the source is fully acknowledged.

Cat.: H139-98/2026E-PDF
ISBN: 978-0-660-97740-9
Pub.: 250403

Disclaimer

This document does not constitute legislation. In the event of any inconsistency or conflict between the legislation and this document, the legislation takes precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the legislation and the applicable administrative policies.

Table of contents

1. Purpose.....	4
2. Scope	4
3. Introduction	5
4. About Quality Management	6
4.1 Guiding principles.....	6
4.2 Developing a pharmaceutical quality system	7
4.3 About good manufacturing practices for medical gases	9
4.4 Quality control.....	10
4.5 Quality risk management.....	11
5. The regulations	12
5.1 Division 2: GMP (C.02.002, C.02.002.2)	12
5.2 Sale (C.02.003, C.02.003.1, C.02.003.2).....	13
5.3 Use in fabrication (C.02.003.3)	13
5.4 Premises (C.02.004).....	13
5.5 Equipment (C.02.005).....	15
5.6 Personnel (C.02.006)	18
5.7 Sanitation (C.02.007, C.02.008)	20
5.8 Raw material testing (C.02.009, C.02.010)	22
5.9 Manufacturing control (C.02.011, C.02.012)	25
5.10 Quality Control (C.02.012.1, C.02.013, C.02.014, C.02.015).....	34
5.11 Packaging material testing (C.02.016, C.02.017)	40
5.12 Finished product testing (C.02.018, C.02.019)	44
5.13 Records (C.02.020 – C.02.024.1)	50
5.14 Medical gases (C.02.030).....	58
6. Glossary and Terms	58
6.1 Glossary	58
6.2 Terms.....	59
7. References	65



1. Purpose

This guide is for people who are required to hold an establishment licence under Part C, Division 1A of the Food and Drug Regulations (regulations). This includes people who work with medical gases as:

- fabricators
- packagers
- labellers
- testers
- distributors
- importers
- wholesalers
- home care providers

This guide will help you understand and comply with Part C, Division 2 of the regulations, which is about good manufacturing practices (GMP).

Whether a licence is required or not, any person storing a medical gas (for example, a wholesaler) must comply with GMP.

For more information on establishment licences or to understand how to comply with GMP requirements in order to get an establishment licence, refer to the following guidance:

- [Guidance on drug establishment licences \(GUI-0002\)](#)

2. Scope

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

For the purpose of these guidelines, the following operations are considered a "fabricate" activity:

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



The following operations are a “packaging/labelling” activity:

- trans filling medical gases at a facility
- curbside filling of medical gases

3. Introduction

These guidelines replace the:

- Good Manufacturing Practices (GMP) Guidelines for Drug Products (GUI-0001) and
- Good Manufacturing Practices (GMP) for Active Pharmaceutical Ingredients (API) (GUI-0104) for Medical Gases

Health Canada developed the guidelines in consultation with stakeholders.

Medical gases have unique properties that affect production and handling characteristics. The way the GMP regulations apply to medical gases may be different from other drugs. For example, when manufacturing a medical gas, the resulting gas may be either:

- used as a raw material or
- sold as a bulk drug or a finished packaged product

Note about guidance documents in general

Guidance documents like this one are not legally binding. They are administrative tools to help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff, ensuring that the rules enforced are fair, consistent and effective across Canada. This document is a guide to assess your compliance with the relevant GMP requirements for medical gases.

To better understand how risk ratings are assigned during inspections, please refer to the following guidance:

- [Risk classification guide for drug good manufacturing practices observations \(GUI-0023\)](#)

There is flexibility in how you meet the applicable laws and regulations. If you choose to follow an alternate approach to the principles and practices described in this document, you must provide adequate justification. Alternate approaches should be discussed in



advance with the relevant program area. This helps ensure that your approach still meets all legal and regulatory requirements.

Health Canada may request additional information or material, or define conditions not specifically described in this document. These requests help us adequately assess compliance with the act and regulations. We are committed to making such requests only when necessary and to document our decisions clearly and transparently.

This document should be read along with the relevant sections of the regulations and other applicable guidance documents.

If there is a discrepancy between this guidance document and the regulations, the regulations always take precedence.

4. About Quality Management

4.1 Guiding principles

If you hold an establishment licence or run an operation governed by Part C, Division 2 of the *Food and Drug Regulations* (regulations), you must comply with these requirements as well as your marketing or clinical trial authorization. “Running an operation” means you fabricate, package, label, import, distribute, test and/or wholesale medical gases.

You must not place consumers at risk because of poor safety, quality and efficacy or for not complying with the regulations.

You will also need the help and commitment of your suppliers and staff at all levels of your establishment.

To meet the requirements, you should:

- have a well-designed and correctly implemented pharmaceutical quality system (also known as a quality management system) that incorporates good manufacturing practices (GMP) and quality risk management.
- document the pharmaceutical quality system fully and monitor its effectiveness.
- make sure your entire pharmaceutical quality system is properly resourced with qualified staff and that premises, equipment and facilities are suitable/sufficient.

The basic concepts of quality management, good manufacturing practices and quality risk management are inter-related. They are described here to emphasize their relationships and fundamental importance to producing and controlling medical gases.



4.2 Developing a pharmaceutical quality system

Quality management is a wide-ranging concept. It covers all matters that individually or collectively influence the quality of a medical gas. It is the total of the arrangements made to ensure that medical gases are of the quality required for their intended use. It incorporates GMP.

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

You should consider the size and complexity of your company's activities when developing a new pharmaceutical quality system or modifying an existing one. The system design should incorporate risk management principles, including the use of appropriate tools. While some aspects of the system can be company-wide and others site-specific, the effectiveness of the system is normally proven at the site level.

To ensure your pharmaceutical quality system is properly set up for fabricating, packaging, labelling, testing, distributing, importing and wholesaling medical gases, you should:

- design, plan, implement, maintain and continuously improve on your system to allow the consistent delivery of products with proper quality attributes
- manage product and process knowledge throughout all lifecycle stages
- design and develop medical gases in a way that takes into account GMP requirements
- outline management responsibilities clearly
- make arrangements for:
 - the manufacture, supply and use of the correct starting and packaging materials
 - selecting and monitoring suppliers
 - verifying that each delivery is from the approved supply chain
- ensure processes are in place to properly manage outsourced activities
- develop and use effective monitoring and control systems for process performance and product quality

You should also:



- consider the results of product and process monitoring in batch release and when investigating deviations
 - this will allow you to take preventive action to avoid potential deviations in the future
- carry out all needed controls on intermediate products and any other in-process controls and validations
- make quality improvements appropriate to the current level of process and product knowledge
- evaluate and approve planned changes before implementing them
 - regulatory notification and approval of changes must be done as required
- conduct an evaluation after making a change, to confirm that you achieved your quality objectives and there was no unintended negative impact on product quality
- apply a proper level of root cause analysis when investigating deviations, suspected product defects and other problems by using quality risk management principles
- identify the most likely root cause(s) and address those where the true cause(s) of the issue cannot be determined
 - justify where human error is suspected or identified and ensure that process, procedural or system-based errors or problems have not been overlooked, if present
 - determine the full impact of the deviation and document how you reached your conclusion
 - identify and carry out appropriate corrective actions and/or preventive actions in response to investigations
 - monitor and assess the effectiveness of such actions in line with quality risk management principles
- make sure quality control certifies each production batch of medical gases before you sell or supply them
 - you must produce and control medical gases according to marketing authorization requirements and any other regulations relevant to producing, controlling and releasing medical gases

Also:

- ensure that medical gases are stored, distributed and handled so that quality is maintained throughout their shelf life
- implement a process for self-inspection and/or quality audit, to regularly appraise the effectiveness and applicability of your pharmaceutical quality system



Your senior management is ultimately responsible for your pharmaceutical quality system. This means making sure the system is properly resourced and that roles, responsibilities and authorities are defined, communicated and implemented throughout the organization. Senior management should also ensure that all staff support and are committed to your pharmaceutical quality system.

Senior management's specific role and responsibilities include the following:

- conduct a management review periodically of your pharmaceutical quality system operation to identify opportunities for continual improvement of products, processes and the system itself
- define and document your pharmaceutical quality system
 - should have a manual or similar documentation that describes the system and outlines management responsibilities

4.3 About good manufacturing practices for medical gases

Good manufacturing practices (GMP) are part of quality assurance. They ensure that medical gases are consistently produced and controlled. Medical gases must meet the quality standards for their intended use. These are outlined in your marketing authorization, clinical trial authorization or product specification.

GMP touches on both production and quality control. To meet basic GMP requirements, you must:

- define all manufacturing processes clearly
 - review them systematically in the light of experience
 - show that they are capable of consistently manufacturing medical gases of the required quality that comply with their specifications
- validate critical steps of manufacturing processes and key changes to the process
- provide all key elements for GMP, including:
 - qualified and trained staff
 - adequate premises and space
 - suitable equipment and services
 - correct materials, containers and labels
 - approved procedures and instructions
 - suitable storage and transport
- write instructions and procedures in an instructional form in clear and direct language, specifically applicable to the facilities provided



- train operators to properly carry out procedures so they understand the importance of meeting GMP requirements as part of their role in assuring patient safety
- create records (manually and/or by recording instruments) during manufacture
 - show that all the steps required by the defined procedures and instructions were followed and met relevant parameters and/or quality attributes
 - show that the quantity and quality of the medical gas was as expected
- document significant deviations and investigate them to determine the root cause and impact
 - ensure proper corrective and preventive action is taken

After manufacture, you must:

- keep records of fabrication, packaging, labelling, testing, distribution, importation and wholesaling in an easy-to-understand and accessible form
 - this allows the complete history of a lot to be traced
- distribute medical gases in a way that minimizes any risk to their quality and takes account of Canadian GMP which incorporate good distribution practice
- control storage, handling and transportation of medical gases to minimize any risk to their quality
- have a system in place for recalling medical gases from sale
- examine complaints about medical gases, investigate the causes of quality defects and take appropriate measures to prevent problems from happening again

4.4 Quality control

Quality control is the part of GMP that is concerned with:

- sampling
- specifications
- testing
- documentation
- release procedures

You must only release raw materials, packaging materials and medical gases for use or sale if their quality is satisfactory. Quality control ensures that you carry out the necessary and relevant tests to guarantee quality.

Note: Quality control measures are not only done in labs. You must incorporate these measures into all activities and any decisions related to the quality of your medical gases.



To meet basic quality control requirements, you must:

- ensure you have adequate facilities, trained staff and approved procedures for:
 - sampling and testing raw materials
 - packaging materials
 - intermediate bulk and finished medical gases
 - monitoring environmental conditions for GMP purposes, where appropriate
- take samples of raw materials, packaging materials and intermediate, bulk and finished medical gases using authorized staff and approved methods
- validate test methods and qualify equipment, instruments and computer systems for their intended use
- keep records (manually and/or by recording instruments) to show that you carried out all required sampling, inspecting and testing procedures
 - record and investigate any deviations
- ensure finished medical gases contain active ingredients that comply with the qualitative and quantitative composition of your marketing or clinical trial authorization
 - that they are of the purity required, in proper containers and correctly labelled
- document the results of your inspection and testing of intermediate, bulk and finished medical gases and materials against specification
- include in your product release procedures a review and evaluation of relevant production documentation, as well as an assessment of deviations from specified procedures

Note: Do not release medical gases for sale or distribution before they are approved by your quality control department.

4.5 Quality risk management

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

The principles of quality risk management are that:

- an evaluation of the risk to quality is based on scientific knowledge and experience with the process, and ultimately links to the protection of the patient
- the level of effort, formality and documentation of the quality risk management process is in keeping with the level of risk



For examples of the processes and applications of quality risk management, please refer to the following:

- [ICH Q9 Quality risk management](#)

5. The regulations

For each of the following sections, the exact text from Part C, Division 2 of the [Food and Drug Regulations](#) is provided first. The rationale (why the rule is important) and Health Canada's interpretation (what you need to do to be compliant) follow (if applicable).

5.1 Division 2: GMP (C.02.002, C.02.002.2)

C.02.002

In this Division:

- *medical gas* means any gas or mixture of gases manufactured, sold or represented for use as a drug
- *packaging material* includes a label
- *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.

C.02.002.2

In this Division,

- (a) a reference to specifications is — in respect of a drug intended for consumption or use outside Canada, the raw material used in such a drug or the packaging material for such a drug — a reference to the specifications with which the drug, raw material or packaging material is required to comply in the country in which the drug is intended to be consumed or used; and



- (b) the definition *expiration date* in subsection C.01.001(1) does not apply in respect of a drug intended for consumption or use outside Canada.

5.2 Sale (C.02.003, C.02.003.1, C.02.003.2)

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, including during transportation, in accordance with the requirements set out in this Division.

C.02.003.1 No person shall sell a drug that they have fabricated, packaged/labelled, tested or stored unless they have fabricated, packaged/labelled, tested or stored the drug, including during transportation, in accordance with the requirements set out in this Division.

C.02.003.2

(1) No person shall import an active ingredient into Canada for the purpose of sale unless they have in Canada a person who is responsible for its sale.

(2) No person who imports an active ingredient into Canada shall sell any lot or batch of it unless the following appear on its label:

- (a) the name and civic address of the person who imports it; and
- (b) the name and address of the principal place of business in Canada of the person responsible for its sale

5.3 Use in fabrication (C.02.003.3)

C.02.003.3 No person shall use an active ingredient in the fabrication of a drug unless the ingredient has been fabricated, packaged/labelled, tested and stored, including during transportation, in accordance with the requirements set out in this Division.

5.4 Premises (C.02.004)

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

If you run a medical gas fabricating or packaging establishment:

- having clean work areas allows you to achieve sanitary conditions
- maintaining order helps to prevent mix-up
- controlling airborne and other contaminants protects product integrity

Good building design and continuing maintenance lead to cleanliness, orderliness and prevention of contamination. Regular maintenance is also needed to prevent building decline. The main objective of these efforts is product quality.

Interpretation

Buildings where medical gases are fabricated or packaged should be located in an environment that presents a minimal risk of contaminating materials or medical gases. Also take measures to protect manufacturing processes.

Make sure your premises are suitable for the operation performed there. The layout of the site should be designed to avoid mix-ups and prevent contamination. Make sure:

- there is enough space for receiving and production activities
- working spaces for materials and equipment (including parts and tools) are placed in an orderly and logical fashion
- physical quarantine areas are well marked and access is restricted to designated staff
 - where electronic quarantine is used, electronic access should be restricted to designated staff
- working areas are lit well

Segregate and designate areas to distinguish:

- containers set aside for cleaning, testing or maintenance from those that have been released for filling
- different gases
- medical gases from non-medical gases
- empty containers from full containers
- quarantined finished medical gases from those available for distribution

Also:

- clearly identify the content of fixed distribution systems at their outlets
- minimize “dead legs” where circulation may be restricted



- identify pipelines carrying medical gases between areas by colour or by standard markings at suitable intervals and show direction of flow
- locate air intakes used in the production of medical gas in a way that avoids contamination with waste gases and other pollutants
- make sure filters, especially those used to trap desiccants after driers, are of suitable construction, and examined and changed as needed
- separate rest, change, wash-up and toilet facilities from production areas and make sure they are spacious, well-ventilated and allow good sanitary practices
- ensure fabrication and filling areas are lit well
- maintain premises in a good state of repair
- secure premises and vehicles used to store medical gases from unauthorized entry
- store filled cylinders and cryogenic vessels in a way that ensures they will be delivered in a clean state, compatible with the environment where they will be used

5.5 Equipment (C.02.005)

C.02.05 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 material to the drug; and
- (c) permits it to function in accordance with its intended use

Rationale

These requirements are meant to prevent the contamination of medical gases by:

- dust
- other gases
- foreign materials from the equipment, like:
 - rust
 - lubricant
 - particles

Contamination can be caused by poor maintenance, misusing equipment, exceeding the capacity of the equipment and using worn-out equipment.



Arranging your equipment in an orderly way makes it easier to clean nearby areas. It also avoids interference with other processing operations, minimizes circulation of people and improves the flow of material. To fabricate medical gases of consistent quality, you must make sure your equipment performs the way it is meant to be used.

Interpretation

Make sure that:

- parts in contact with medical gases are designed, constructed and located in a way that allows them to be cleaned and avoids contamination
 - fittings and accessory assemblies should be designed for easy dismantling (if required)
- tankers and trailers and their equipment (for example, hoses, valves, pumps) are well constructed and maintained
 - includes tankers and trailers owned by a contracting firm

You should also have bulk tanks and tankers use a single and defined quality of gas. You may store or transport medical gases in the same bulk tanks, containers used for intermediate storage or tankers as the same non-medical gas if:

- the quality of the non-medical gas is at least equal to the quality of the medical gas and
- you maintain GMP standards

In these cases, you should:

- perform and document quality risk management
- have a procedure that describes the measures to be taken when a tanker is returned to medical gas service (after transporting non-medical gas or after a maintenance operation)
 - this procedure should include analytical testing

Use proper filling and storage equipment for medical gases, by ensuring that:

- materials for product contact surfaces are non-toxic, non-reactive to medical gases and corrosion-resistant
- gas filling equipment prevents the possibility of making a wrong connection

Containers may be connected either to different valves through an adapter or to a manifold that is connected to different medical gas outlets. Fully validate and document the procedure to ensure no cross-contamination, as either procedure prevents the possibility of connecting a container to the wrong line.



Also:

- perform installation and operational qualification on equipment used during the critical steps of fabrication, packaging and testing (including computerized systems)
 - document the equipment qualification (for guidance, please refer to the [validation guidelines for pharmaceutical dosage forms \(GUI-0029\)](#))
- use a common system to supply gas to medical and non-medical gas manifolds if there is a validated way to prevent backflow from the non-medical gas line to the medical gas line
- check and maintain equipment used to fabricate, package/label and test medical gases regularly, including computerized equipment, by:
 - calibrating measuring devices according to a written program
 - not using temporary devices for repairs
 - keeping records of maintenance and calibration
 - have a system in place to support identification of calibration status (may use labelling or other means)
- calibrate vacuum gauges used during the essential evacuation of residual gas from high-pressure cylinders
 - do this regularly
 - at routine intervals, calibrate vacuum gauges to standards established by the National Institute of Standards and Technology or another recognized standard
 - follow manufacturer's recommendations for frequency of calibration or determine intervals based on usage and experience
 - check vacuum gauges before use (with no vacuum present) to make sure that the needle on the gauge returns to "zero"
 - keep calibration records

When it comes to repair and maintenance of equipment (includes cleaning and purging):

- make sure this does not adversely affect the quality of medical gases
- describe in your procedures the measures to be taken after repair and maintenance operations if the system's integrity is ever breached
- check there are no contaminants before using the equipment
- keep records of use and maintenance operations

Also:

- protect openings for connections on lines supplying medical gases from contamination



- perform regular checks to ensure that check valves used to prevent contamination are working properly

You may use a sampling cylinder to sample gases from a storage bulk tank, if you have validated the process. In particular, you must validate the time it takes to fully purge the cylinder, which provides proof that the cylinder has been fully evacuated.

5.6 Personnel (C.02.006)

C.02.06 Every lot or batch of a drug shall be fabricated, packaged/labelled, tested and stored, including during transportation, under the supervision of personnel who, having regard to the duties and responsibilities involved, have had any technical, academic or other training that the Minister considers satisfactory in the interests of the health of the consumer or purchaser.

Rationale

Who you hire is very important. Staff should have a quality mindset and the right training. Without this, it will be impossible to fabricate, package/label, test or store good quality medical gases.

You must only hire qualified staff to supervise the fabrication and packaging of medical gases. Making medical gases can be highly technical in nature. It requires constant vigilance, attention to detail and a high degree of competence. The reason many products fail to meet required standards is because of poorly trained staff or a lack of understanding of the importance of production control.

Senior management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness.

Interpretation

If you are a fabricator, the person in charge of your company's quality control department and the person in charge of your manufacturing department:

- must have proper professional or technical qualifications
 - may include a respiratory therapist under provincial legislation governing health professionals or someone qualified by pertinent training
- must have practical experience in their area of responsibility
- must directly control and personally supervise on site for each working shift when activities under their control are being conducted



- may delegate duties and responsibility (for example, to cover all shifts) to a person who has proper professional or technical qualifications, while remaining accountable for those duties and responsibility

The person in charge of your company's quality control department (whether you are a packager/labeller, tester, importer or distributor of medical gases):

- must have proper professional or technical qualifications
 - may include a respiratory therapist under provincial legislation governing health professionals or someone qualified by pertinent training
- must have practical experience in their responsibility area
- may delegate their duties and responsibilities to a person who has proper professional or technical qualifications

Note: At medical gas filling stations, staff performing simple analytical tests and quality control functions (following standard company procedures) may have practical experience only.

The person in charge of your filling/packaging operations (including control over printed packaging materials and withdrawal of bulk gases for the purpose of filling):

- must be qualified by training and experience
- may delegate their duties and responsibilities to a person who is qualified by training and experience

Ensure you have enough staff available on site and that they have the proper qualifications and practical experience appropriate to their responsibilities:

- do not place so many responsibilities on any one individual that quality is put at risk
- list duties relating to medical gases for all responsible staff in written work descriptions
- ensure staff have authority to carry out their responsibilities
- appoint qualified replacements to carry out their duties and functions when key staff are absent

Your staff must be aware of the principles of GMP that affect them. They must receive initial and continuing training relevant to their job responsibilities. Make sure to:

- provide training by qualified staff
- have in place a written training program for all staff involved in fabricating, packaging/labelling, testing, importing or storing a medical gas
 - including technical, maintenance and cleaning staff



- assess the effectiveness of continuing training from time to time
- provide training before implementing new or revised standard operating procedures (SOPs)
- keep training records
- give specific training to staff working in areas where highly active, toxic, infectious or sensitizing materials are handled
- review staff performance from time to time

Make sure any consultants and contractors you hire have the necessary qualifications, training and experience to offer advice on those matters for which they are retained. Staff of subcontractors who could influence the quality of medical gases (for example, those in charge of maintaining cylinders or valves) should be appropriately trained.

5.7 Sanitation (C.02.007, C.02.008)

C.02.07 (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) 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 quality mindset, influences the quality of medical gases. Medical gases must be fabricated and packaged free from contamination.

A written sanitation program provides some assurance that:

- levels of cleanliness in your facility are maintained
- the provisions of sections 8 and 11 of the [Food and Drugs Act](#) are satisfied

Interpretation

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

You must have a written sanitation program available on site for every facility that fabricates or packages/labels a medical gas.



Include procedures in your sanitation program that describe:

- cleaning requirements for the facility
- cleaning requirements for processing equipment

Follow written procedures for cleaning critical equipment you use to fabricate, transport, store and fill medical gases. Use written procedures also for cleaning and purging pipelines that carry medical gases. Include checks for the absence of cleaning agents or other contaminants. Validate and document all procedures (includes those for tankers and trailers owned by contracting firms).

C.02.08 (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. The potential for environmental contamination of the product is minimal.

The hygiene requirements for staff who help produce medical gases are similar to those for staff involved with other dosage forms. However, the extent to which they are applied will depend on the operation and procedures.

Interpretation

Make minimum health requirements available in writing, including that:

- no person affected by an infectious disease or having open lesions on an exposed surface of the body will engage in the manufacture and packaging of medical gases
- people responsible for performing odour tests do not have ailments that can adversely affect test results
- people responsible for performing inspections involving distinguishing colours can distinguish colours properly



Clearly define clothing requirements and hygiene procedures for company staff and visitors in your written hygiene program. For example:

- people must wear clean clothing and protective covering anywhere there is a possibility that medical gas can be contaminated
- operators must avoid touching any parts of equipment that come in direct contact with the medical gas
- unsanitary practices are not allowed in processing areas
- requirements for personal hygiene should be outlined when important to the quality of the product

5.8 Raw material testing (C.02.009, C.02.010)

Sections C.02.009 and C.02.010 apply only to batches of gases used to fabricate medical gas mixtures. For testing bulk gases that are not used to produce gas mixtures, refer to sections C.02.011, C.02.018 and C.02.019.

- C.02.09 (1) Each lot or batch of raw material shall be tested against the specifications for that 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) If any property of a raw material is subject to change during storage of the material, including during transportation, no lot or batch of that raw material shall be used in the fabrication of a drug after the lot or batch has been stored, including during transportation, unless the raw material is retested after an appropriate interval and meets the specifications for that material.
- (5) Where the specifications referred to in subsections (1), (2) and (4) are not prescribed, they shall
- (a) be in writing;
 - (b) be acceptable to the Minister 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

Testing raw materials before using them has 3 objectives:



1. confirm the identity of the raw materials
2. provide assurance that the quality of the medical gas in dosage form will not be changed by raw material defects
3. confirm that the raw materials have the characteristics that will provide the desired quality in a given manufacturing process

Interpretation

For fabricators:

- test raw materials to specification before use and after you receive them
- make sure your specifications comply with your marketing authorization
 - check to see if a monograph exists in a pharmacopeia listed in Schedule B to the act
 - if so, make sure your specifications meet the monograph
- validate test methods and document the results of validation studies
 - full validation is not needed for methods included in any standard listed in Schedule B to the act
 - if you use one of these methods, you must establish its suitability under actual conditions of use
 - conduct method transfer studies when applicable

For guidance on validating particular types of methods, please refer to any standard listed in Schedule B to the act or to the following International Conference on Harmonization (ICH) document:

- [ICH Q2 Validation of analytical procedures: Text and methodology](#)

You may add deliveries of raw material to a bulk storage tank containing the same gas from previous deliveries. In this case:

- you must test a sample of the delivered raw material and find it to be satisfactory
- when the raw material is a single gas accompanied by a certificate of analysis, you may take the sample and test it after:
 - allowing for sufficient mixing of the delivery in the bulk storage tank, and
 - adequately purging the sampling line
- when the raw material is a mixture, your testing must verify each component

C.02.10 (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 Minister 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 Minister, 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 for when you should carry out testing as per section C.02.009. Sourcing raw materials is an important operation that requires specific and in-depth knowledge of the raw materials and their fabricator in order to maintain consistency and quality when fabricating medical gases. Raw materials should come from reliable fabricators.

Interpretation

Before use and after receiving the raw material at your facility that fills medical gas into containers, take a sample and test. Conduct specific identity testing on all lots of any raw material (section C.02.009, interpretation 2). When the raw material is a bulk gas accompanied by a certificate of analysis, you may take the sample after allowing for comingling of the delivery in the bulk storage tank.

For tests other than identity tests, paragraph C.02.010 (1) (b) outlines conditions you must meet if you rely on test results provided by the vendor.

Evidence satisfactory to the Minister should include either:

- evidence of ongoing GMP compliance (including process control and validation in accordance with these guidelines) or
- an audit report issued by a qualified authority
 - should demonstrate that the raw material fabricator complies with the [ICH Q7 Good manufacturing practice guide for active pharmaceutical ingredients](#) or any standard or system of equivalent quality)



Evidence should also include:

- a certificate of analysis for all lots, showing actual numerical results and the product specification and validated test methods used
- complete confirmatory testing on a minimum of 1 lot each year of a raw material received from each vendor, with the raw material chosen on a rotational basis
- where multiple raw materials are received from the same vendor, confirmatory testing must be carried out for each raw material at least once every 5 years

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

Conditions when transporting and storing raw materials should prevent changes to the potency and purity of the raw material. To show that these conditions have been met, you must have standard operating procedures and records for shipping and receiving that contain:

- the type of packaging to be used
- labelling requirements
- mode of transportation
- seal of package
- verification to ensure that each package has not been tampered with and there are no damaged containers
- evidence that shipping requirements have been met

5.9 Manufacturing control (C.02.011, C.02.012)

C.02.11 (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 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

You must take measures to maintain the integrity of a medical gas, from the moment the raw materials or bulk gases enter your plant to when you release the finished product for sale and distribution. These measures:



- ensure that all of your manufacturing processes are clearly defined and systematically reviewed
- demonstrate that your manufacturing processes can consistently produce medical gas products that comply with their established specifications for quality

Interpretation

You must:

- handle all raw materials, packaging materials and medical gases according to pre-approved written procedures or instructions
 - includes when receiving, quarantining, sampling, storing, tracking, labelling, processing, packaging and distributing
 - keep records as required
- validate all critical production processes and conduct validation studies according to predefined protocols
 - prepare, evaluate, approve and keep a written report that summarizes recorded results and conclusions
- approve changes to production processes, systems or equipment that may affect product quality and/or process reproducibility before implementing them
 - validate these changes where applicable
- avoid deviating from instructions or procedures
 - if deviations happen, have qualified staff investigate and write a report that describes the deviation, the investigation, the rationale for disposition and any follow-up activities required
 - your quality control department must approve the report and keep records
- store bulk gases under conditions and in distribution systems that prevent product mix-ups, deterioration or contamination
- check measuring devices regularly for accuracy and precision and keep records of these checks
- make written procedures available on site to ensure that raw materials and bulk gases:
 - are identified by lot number, receiving number or laboratory control number
 - are released for production or filling operations according to written procedures approved by the quality control department
 - meet Schedule B standards (if applicable) and make sure Certificates of Analysis are reviewed and available on site for each lot of source gas received



- are stored under conditions that will preserve their quality and avoid their inadvertent use

Written procedures must be approved by the quality control department. These should be available to ensure that containers are checked or tested and meet their specifications before being filled.

You must also:

- ensure processing operations are covered by master formulas
 - must be prepared and subject to independent checks by people with the qualifications described in section C.02.006
- write master formulas, master production documents and/or master filling documents to provide not less than 100% of label claim and include:
 - the name of the product
 - the name and concentration of components, including acceptable tolerances
 - the filling sequence of components
 - the fill pressure or weight of components
 - in-process and final quality control requirements
- take and document all necessary steps to ensure that your work area and equipment are clean before you start any processing operation
 - should be free from any raw materials, medical gases, product residues, labels or documents not required for the current operation
- make sure manufacturing and filling records contain all information related to the manufacturing and filling of each batch of medical gas, including:
 - in-process quality control requirements
 - equipment used (if multiple systems are used for same product)
 - a mark that is unique to the individual or the initials of staff involved in the activity
 - a name for each raw material in a mixture and references to the relevant specification(s)

Include the following in completed manufacturing documents:

- appropriate checks to ensure the containers have been filled
- actual results of the quality checks performed
- batch or lot number, receiving number or laboratory control number for each raw material in a mixture
- a mark that is unique to the individual or the initials of staff involved in preparing the mixture



You may add deliveries of bulk gas to bulk storage tanks containing the same gas from previous deliveries. In this case, do 1 of the following:

- test a sample of the delivered bulk gas before adding it to the storage tank and make sure it is satisfactory
- if the bulk gas is a single gas accompanied by a certificate of analysis, allow for sufficient mixing of the delivery in the bulk storage tank, then take the sample
 - 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 properly purged before sampling
- if the bulk gas is a mixture, test to verify each component

You may:

- combine residual batches or lots in cryogenic containers or trailers or
- add product from the bulk storage tank to the containers or trailers if you perform purity testing after mixing

The written instructions should ensure that you:

- have quality control staff or qualified replacements record their initials in the filling logs
- assign a lot number for each medical gas, which must appear on each container
 - no need to include the lot number on each bulk transport container, storage tank filled and container filled at curbside as long as you document traceability
- control the filling of high-pressure cylinders either by mass or by monitoring the pressure and the temperature on the wall of cylinders
 - verify correct fill by referring to either a temperature/pressure chart or a target mass chart
- perform a heat of compression check on the exterior surface of each cylinder to demonstrate proper filling during the manifold filling sequences of high-pressure non-liquefied compressed gases
 - conduct a leak test on each container during filling
 - use an appropriate method, such as applying leak detection solution to the valve to detect valve packing leaks, safety plug leaks and other valve leaks
 - conduct a second leak test on each container after filling to detect valve outlet leaks
 - do not use leak test solutions that can cause corrosion or leave films, such as soap



- properly quarantine filled containers until released by the quality control department

Note: The leak test does not apply to refrigerated or cryogenic liquids.

Make sure to also:

- follow filling as quickly as possible by labelling (if labelling is delayed, take measures to ensure that no mix-ups or incorrect labelling can occur) by:
 - documenting and reconciling label withdrawals
 - controlling labelling operations through 100% verification
 - documenting labelling operations
 - attaching samples of the printed packaging materials used whenever possible (include specimens bearing the batch number) and any additional overprinting to packaging orders
- label and identify all containers to make their content easy to distinguish
 - identify containers using predetermined and well-recorded procedures under the supervision of qualified staff
 - may segregate medical gases by cylinder colour if the staff are well trained
 - have other measures in place to segregate quarantined and released cylinders
- fit cylinder post valves with covers after filling to protect the outlets from contamination
- store materials and medical gas labels used to identify containers in a limited access area, restricted to designated staff
- destroy outdated or obsolete materials and labels, and record their disposal
- release medical gases only after your quality control department has approved them
- monitor water used for cooling during compression of air for microbial quality when in contact with the medical gas

Annual product quality review

Conduct an annual product quality review (APQR) of all medical gases. Verify the consistency of your existing process and the appropriateness of current specifications for both raw materials and medical gas. Highlight any trends and identify product and process improvements.

You should usually conduct and document these reviews every year, taking into account previous reviews. Include at least a review of the following:



- critical in-process controls, finished product testing results and specifications
- all batches that failed to meet established specification(s) and their investigation
- all significant deviations or non-conformances, their related investigations, and the effectiveness of corrective and preventative actions taken
- all changes carried out to processes, analytical methods, raw materials, packaging materials or critical suppliers
- the results of the continuing stability program and any adverse trends (if applicable)
- all product quality-related returns, complaints and recalls, and the investigations performed at the time
- the adequacy of any other previous product process or equipment corrective actions
- the qualification status of relevant equipment used for fabricating and packaging medical gases
- agreements (to ensure that they are up to date)

Your quality control department should ensure that the APQR is accurate and done in a timely manner. If you are a medical gas company that has implemented a uniform quality assurance system across all sites (including periodic on-site self-audits of all sites), you can perform 1 annual product quality review instead of 1 at each individual site. APQR reports must be available at each site.

Where required, you should have an agreement in place between the various parties involved in the APQR (for example, importer and fabricator). This agreement should define each of their responsibilities in producing and assessing the quality review and taking any corrective and preventative actions.

Your quality control department should:

- evaluate the results of this review
- assess whether corrective and preventative action or any revalidation should be undertaken

Also:

- document reasons for any corrective actions
- complete corrective and preventative actions in a timely and effective manner
- have procedures in place for the ongoing management and review of these actions
- review how effective your procedures are during self-inspection



C.02.12 (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 paragraph C.01A.003(b) and importer of a drug shall maintain a system 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) Subsection (2) does not apply to a distributor if the drug is fabricated, packaged/labelled and tested in Canada by a person who holds an establishment licence that authorizes those activities in respect of that drug.

(4) Subsection (2) does not apply to a distributor or importer if the drug is fabricated or packaged/labelled in an MRA country at a recognized building and both of the following requirements are met:

- (a) the address of the building is set out in their establishment licence; and
- (b) they retain a copy of the batch certificate for each lot or batch of the drug that they receive.

Rationale

A recall removes from the market a medical gas that either:

- does not conform to the act or regulations
- presents a risk to consumer health

Medical gases that have left the premises of a fabricator, packager/labeller, distributor, importer or wholesaler may end up in a number of locations. Depending on the non-compliance and how serious the health risk is, you may need to recall a product from the market. If you are a fabricator, packager/labeller, distributor, importer or wholesaler, you must have a mechanism in place to recall the product at the consumer level if needed.

For more guidance on recalls, please refer to the [Recall Policy \(POL-0016\)](#).

This regulation also requires fabricators, packagers/labellers, distributors, importers and wholesalers to have a self-inspection program. The purpose of self-inspection is to evaluate if all aspects of production and quality control comply with GMPs. A self-inspection program should be designed to detect any shortcomings in the implementation of GMPs if they occur and recommend corrective actions.



Whether they are produced in Canada or imported, medical gases offered for sale in Canada must meet the requirements of Part C, Division 2 of the [Food and Drug Regulations](#) (regulations). If production and analysis are contracted out, they must be correctly defined, agreed upon and controlled to avoid misunderstandings that could result in a product, work or analysis of poor quality. There should be a written agreement between all the parties. The agreement should establish the duties of each party.

Interpretation

Recall

You must have a written recall system in place to comply with section C.01.051 of the regulations. The system must include the following steps:

- notify Health Canada of the recall
 - include an assessment of the impact that any recall action may have on the market availability of the medical gas
- notify all Canadian and foreign establishments involved in fabricating, distributing or importing the recalled medical gas
- take prompt action to recall a medical gas suspected or known to be defective, according to a predetermined plan
 - procedures to be followed are to be in writing and known to all concerned
- identify the person(s) responsible for initiating and coordinating all recall activities

You must be able to carry out your recall procedure at any time, during and outside normal working hours. You may use a voice mail system or electronic means as part of your off-hours product recall activation, with appropriate contact information. Include the functions and monitoring requirements of the system you are using in your written procedures.

Your recall procedure must outline the way to decide a recall's extent, notify about a recall and implement a recall.

Your distribution records must make it possible to trace medical gases, including any medical gases that are in transit and any samples that have been removed by the quality control department.

During a recall, you should:

- assess and record the progress and effectiveness of a recall at regular intervals, and issue a final report (including a final reconciliation)



- identify recalled medical gases and store them separately in a secure area until their disposition is determined
- have a written agreement in place that clearly describes each party's responsibilities during a recall
 - the agreement must provide information on and acknowledgement of the medical gas distribution supply chain

Self-inspection

You must have a self-inspection program appropriate to your establishment's activities. This program must ensure compliance with Part C, Division 2 of the regulations as it applies to medical gases. This program must include the following elements:

- a comprehensive written procedure that describes the functions of your self-inspection program
- staff on the self-inspection team who are suitably trained and qualified in GMP
- periodic self-inspections
- a review of reports on the findings of inspections and on corrective actions by senior management
 - corrective actions are to be taken in a timely manner

Outsourced activities

To ensure compliance of contractors performing fabrication and packaging/labelling, you must have a written agreement for all the parties involved in fabrication or packaging/labelling. The agreement must specify the responsibilities of each party relating to product fabrication, packaging/labelling or control. Technical aspects of the agreement must be drawn up by qualified staff who are knowledgeable in medical gas technology and GMP.

The agreement:

- permits the distributor or importer to audit the contractor's facilities
- describes, at a minimum, who is responsible for:
 - buying, sampling, testing and releasing materials
 - undertaking production, quality and in-process controls
 - validating processes
- specifies that no subcontracting of any work shall occur without written authorization
- specifies the way in which the distributor or importer's quality control department ensures that each lot or batch has been fabricated and packaged/labelled in compliance with marketing authorization requirements



- describes the handling of raw materials, packaging materials, in-process medical gas, bulk gas and finished medical gases if they are rejected

The contractor's complaint/recall procedures must 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.

Your responsibilities to the contractor include the following:

- provide all information needed to carry out the contracted operations correctly and according to the marketing authorization and any other legal requirements
- ensure the contractor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, staff, other materials or other products

You are responsible for assessing the continuing competence of the contractor to successfully carry out the work or tests required according to the GMP principles described in these guidelines.

If:

- you are a distributor of medical gases fabricated, packaged/labelled or tested at Canadian sites, you only need to have a copy of the relevant valid Canadian establishment licence held by the Canadian fabricator, packager/labeller or tester
- you are an importer of bulk gases and medical gases fabricated, packaged/labelled or tested at a foreign site, you must meet the requirements described in [How to demonstrate foreign building compliance with drug good manufacturing practices \(GUI-0080\)](#)
 - the foreign site must be listed on your establishment licence

5.10 Quality Control (C.02.012.1, C.02.013, C.02.014, C.02.015)

C.02.12.1 Every lot or batch of a drug shall be fabricated, packaged/labelled, tested and stored, including during transportation, in a manner that assures the quality of the drug.

C.02.13 (1) Every fabricator, packager/labeller, wholesaler, distributor referred to in section C.01A.003 and importer of a drug 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 or a distributor referred to in paragraph C.01A.003(a), 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

The regulations and this guideline use the term “quality control” to refer to any quality unit that satisfies this role. A quality unit independent of production fulfills both quality assurance and quality control responsibilities. It can be made up of separate units, a single individual or a group, depending upon the organization’s size and structure. Quality control is the part of GMP concerned with sampling, specifications and testing. It also includes organization, documentation and release procedures.

This regulation provides for a quality control department that helps to ensure that:

- proper production steps and product tests are carried out
- raw materials and packaging materials are not released for use
- products are not released for sale until their quality has been judged to be satisfactory

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

Manufacturing and quality control staff share the same goal, and that is to make sure that high-quality medical gases are fabricated. But 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 staff in various departments using a matrix organization. For quality control issues, these people are responsible to the individual in charge of quality control. The independence of quality control from fabricating and packaging is fundamental. The rationale for the requirement that the quality control department be supervised by qualified staff is outlined under the section C.02.006.

Interpretation

If you are a fabricator, packager/labeller, distributor, importer or wholesaler, you must have a person on site or fully accessible to on-site quality staff who can make decisions about quality control requirements. At locations with 2 or fewer operations staff available, the manufacturing and quality control person may be the same as long as:

- it is impractical to have distinct organizational units on site
- chances of error are minimized



- the reporting relationship is different when the employee performs quality control functions and when they perform fabrication or packaging/labelling activities
- the employee is fully aware of their dual role, clearly understands responsibilities and line authority, and acts accordingly

The quality control department must have true and effective access to equipment and facilities for inspecting and testing.

C.02.14 (1) Except in the case of a wholesaler or a distributor referred to in paragraph C.01A.003(a), no lot or batch of a drug shall be made available for further use in fabrication or for sale unless the person in charge of the quality control department approves the sale or the further use.

(2) A drug that is returned to its fabricator, packager/labeller, wholesaler, distributor referred to in section C.01A.003 or importer shall not be made available for further use in fabrication or for further sale unless the person in charge of the quality control department approves the further sale or further use.

(3) No lot or batch of a raw material or packaging/labelling material shall be used in the fabrication or packaging/labelling of a drug unless the person in charge of the quality control department approves the use.

(4) No lot or batch of a drug shall be reprocessed unless the person in charge of the quality control department approves the reprocessing.

Rationale

Your quality control department is responsible for approving all raw materials, packaging materials and finished medical gases. This department must implement adequate controls 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

The head of your quality control department (or a designated alternate person who meets the requirements described in section C.02.006) must sign and date all decisions made by the quality control department. This is outlined in section C.02.014.

Your quality control department must:



- ensure that raw materials, bulk gases and packaging materials are effectively quarantined, sampled, tested and released before being used to fabricate or package/label a medical gas
- evaluate deviations and borderline conformances according to a written procedure, and document the decision and rationale
 - conduct trend analysis on batch deviations where appropriate
- assess any non-conformances, malfunctions or errors (including those related to premises, equipment, sanitation and testing) that may have an impact on the quality and safety of batches pending release or released, and document the rationale
- destroy finished medical gases returned from the market, unless your quality control department determines that their quality is satisfactory
 - to consider returned goods for resale only after they have been assessed according to a written procedure in your assessment, you must examine:
 - the reason for the return
 - the nature of the product
 - the storage and transportation conditions
 - the product's condition and history
 - the time elapsed since it was originally sold

Keep records of any action taken.

C.02.15 (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 any complaint or information that is received respecting the quality of a drug or its deficiencies or hazards and cause any necessary 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 must be designed and developed in a way that takes into account GMP requirements. 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 may indicate problems related to quality. By tracing their causes, you can determine which corrective measures to take, to prevent them from happening again. Having tests carried out by a competent lab provides assurance that test results are genuine and accurate.

You must have written agreements for consultants and contract laboratories that describe the education, training, experience and types of services provided, and make agreements available for examination and inspection. You must also maintain records of their activities.

Interpretation

Your quality control department must ensure that:

- the person in charge of the department (or a designated alternate who meets the requirements described in section C.02.006, as applicable to the activity) signs and dates all decisions made pursuant to section C.02.015
- 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 and delivered to customers in a clean state, compatible with the environment in which they will be used
- tests are performed by a lab that meets all relevant GMP requirements, which means ensuring the following:
 - lab facilities are designed, equipped and maintained to suit the testing and approval (or rejection) of raw materials, medical gases and containers
 - the person in charge of the lab is qualified as set out in section C.02.006 of this guide or reports to a person who has these qualifications
 - there are enough lab staff who are qualified to carry out the work



- lab control equipment and instruments are suited to the testing procedures undertaken, and equipment and records are kept as set out in section C.02.005 of this guide
- all lab data are created, maintained, processed and reviewed as outlined by the firm's data governance system

Note: Data integrity is an important consideration. For other requirements relating to a data governance system, please refer to sections C.02.020 to C.02.024.

The data governance system (as it applies to lab data) must include enough detail to allow accurate and complete reporting and interpretation of all lab test data and to ensure data integrity. This system should include the following:

- validate computerized systems for their intended use, with special attention to any that are used to create, process and store laboratory data (qualify spreadsheets used in the lab)
- put in place systems and procedures to ensure that lab records are reliable, complete and accurate
 - these must require that all test results that could affect the quality, safety or efficacy of a medical gas are reported, reviewed and assessed appropriately
- organize and store data in a way that is interpretable and traceable to the execution and purpose of test procedures (for instance, use of defined and meaningful naming conventions for samples, test sequences and data storage locations/folders)
- put controls in place to ensure that test data are not deleted and that changes to testing records are documented and justified where required (for example, audit trails must be enabled and reviewed)
- keep data in its original format, as original records (or a true copy), including electronic records, may be reviewed by qualified staff
- protect and back up data for all computerized systems
- keep written procedures for operating and maintaining computer systems

Also ensure that Out of Specification (OOS) test results are investigated in accordance with a defined procedure:

- for a clearly identified lab or statistical error, you may invalidate the original results, then repeat the test and report the results
 - keep the original results and record an explanation
- when there is no clearly identified lab or statistical error and retesting is performed, specify the number of retests to be performed on the original sample



and/or a new sample (and the statistical treatment of the resultant data) in advance of the procedure

- report all valid test results (both passing and suspect) and fully consider them in batch release decisions
- if the original OOS result is valid, raise a deviation against the batch and conduct a complete investigation, according to written procedures

Also ensure systems and procedures are in place so that lab records are reliable, complete and accurate:

- these systems and procedures should require that all test results that could affect the quality, safety or efficacy of a drug be reported, reviewed and assessed appropriately

Also:

- review and assess all complaints and other information about potentially defective medical gases according to written procedures
 - record the complaint with all the original details and thoroughly investigate
 - take appropriate follow-up action after investigating and evaluating the complaint
 - record all decisions and measures taken as a result of the complaint, and reference them to the corresponding batch records
 - review complaint records regularly for any indication of specific or recurring problems that need attention
- establish a change control system to provide for ongoing process optimization and a continuing state of control
 - have the quality control department document, evaluate and approve all changes, identifying them with the appropriate effective date
 - any significant change may require re-validation

5.11 Packaging material testing (C.02.016, C.02.017)

C.02.16 (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 subsections (1) and (2) shall
- (a) be in writing;
 - (b) be acceptable to the Minister 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

Medical gas quality is directly dependent on packaging quality. When a medical gas is placed in an improper container, the entire effort put into manufacturing control is wasted.

Packaging materials must be tested or examined to ensure they are of good quality before they are used to package medical gases. Because medical gas containers are returned and reused, inspection and testing is even more important.

Interpretation

Ensure each packaging material used to package and label a medical gas is covered by specifications (defined in section C.02.002). These specifications must be approved and dated by the person in charge of your quality control department (or by a designated alternate who meets the requirements described in section C.02.006).

In addition to the definition of specification described in C.02.002, specifications for any primary and printed packaging material should include (or provide reference to, if applicable):

- a description of materials, including:
 - the designated name and the internal code reference
 - the reference (if any) to a pharmacopeial monograph
 - the approved suppliers
 - a specimen of printed materials
- qualitative and quantitative requirements with acceptance limits
- storage conditions and precautions

Note: You do not need to remove old labels if they are identical to the labels currently used, in good condition and correct for the product being filled.

Examine containers carefully against their specifications before filling.

For high-pressure containers returned for filling, perform checks and tests on every container. These checks and tests should include:



- 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
- a check to determine that old batch labels (with lot numbers and identification) and other damaged labels have been removed
- venting or blowing down to atmospheric pressure if any gas is present (or inverting and draining the gas)
- an odour or sniff test to check for foreign gas or odour, except in cases where this presents a safety hazard (for example, nitrous oxide or carbon dioxide)
- a check to see if the container requalification has been conducted as required, with each container coded (cylinder marking) to show the date of the last requalification:
 - steel cylinders must be requalified every 5 years, unless an asterisk (*) follows the testing date (which means the cylinder may be requalified every 10 years)
 - aluminum cylinders must be requalified every 5 years
 - water used for hydrostatic testing must be at least of drinking water quality
 - the interior of cylinders must be visually examined if the valve is removed during periodic requalification (usually when re-qualification is performed)
- evacuation of each cylinder (at least to a remaining pressure of 150 millibar) or purging by a suitable method before any medical gas is introduced into the cylinder
 - data should be available demonstrating the suitability of the evacuation or purge

Note: As an alternative to evacuation, conduct a full analysis of the remaining gas for each cylinder.

You must perform checks on cryogenic vessels before filling. The required prefill checks are usually outlined in the manufacturer's manual supplied with each cryogenic vessel. At a minimum, you must do:

- an external vessel check
- a check of all inlet and outlet connections
- a label check

You must also:

- examine cryogenic vessels for Transport Canada markings and ensure that the pressure relief device on the unit is the right kind for its intended use



- make sure your specifications state that each container must be dedicated for a specific type of medical gas and be uniquely identified (for example, using a specific colour) unless a specific change of grade or service procedure is followed
- check gauges on containers that show volume or quantity to ensure proper operation
- quarantine containers that fail these checks and tests
- document the examination and tests performed

For specific testing information, please refer to the following standard:

- [Selection and use of cylinders, spheres, tubes and other containers for the transportation of dangerous goods, Class 2 \(CAN/CSA B340\)](#)

C.02.17 (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, if
 - (i) that person
 - (A) has evidence satisfactory to the Minister 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 Minister,
 - (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 for when you may carry out the testing or examination outlined in regulation C.02.016. As with raw materials, buying packaging materials is an important operation that must involve staff who have thorough knowledge of the packaging materials and vendor.

Packaging materials must come only from vendors named in the relevant specification. All aspects of the production and control of packaging materials should be discussed between the manufacturer and vendor. Particular attention should be paid to printed packaging materials. Labels must be examined or tested after receipt on the premises of the person who packages a medical gas.

Interpretation

This section applies if your containers are tested at a location other than where the filling takes place.

Make sure transportation and storage conditions do not affect the characteristics of the packaging material. To show these conditions have been met, you must have standard operating procedures and records that indicate:

- the type of packaging used
- labelling requirements
- mode of transportation
- the type and seal of package
- verification to ensure the package has not been tampered with and there are no damaged containers

5.12 Finished product testing (C.02.018, C.02.019)

C.02.18 (1) Each lot or batch of a drug shall, before it is made available for further use in fabrication or for sale, be tested against the specifications for that drug.

(2) No lot or batch of a drug shall be made available for further use in fabrication or for sale unless it complies with the specifications for that drug.

(3) The specifications referred to in subsections (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 used during manufacturing. As a fabricator, packager/labeller, distributor or importer, you must have acceptable specifications and test methods. This helps ensure that all medical gases sold are safe and meet applicable standards.

Interpretation

The person in charge of your quality control department must approve any written specifications (or a designated alternate who meets the requirements described in section C.02.006).

Written specifications for any finished medical gas must include (or provide reference to, if applicable):

- a description of the medical gas, including all properties and qualities (such as identity, purity and potency)
- tolerances and a description of all tests or analyses used to measure compliance with the established tolerances (in enough detail to allow qualified staff to perform them)
- the name or identification mark that will be used for each medical gas throughout the processing operation

Specifications must be equal to or exceed a recognized standard, as listed in Schedule B to the act. They must also comply with your marketing authorization.

You must validate test methods and document the results. You should conduct method transfer studies when needed.

Compendial methods cannot include all possible formulations. For this reason, you must demonstrate that the particular compendial method you are using applies to your specific formulation of a medical gas.

You must show there is nothing in the product that interferes with the compendial method or affects the method's performance.

You must also prove that the impurities that would be expected from the active ingredient route of synthesis or finished product formulation are detected by the compendial method.

Note: For guidance on validating particular types of methods, please refer to any standard listed in Schedule B to the act or to the following International Conference on Harmonization (ICH) document:



- [Q2 Validation of analytical procedures: Text and methodology](#)

You must test each medical gas to ensure it meets its specifications. You must record test results in a proper document, clearly and concisely:

- for a given filling operation of a single gas, you must test a representative number of containers to specification (usually 1 filled container from each manifold filling sequence)
- for high-pressure containers filled individually and manually, you must test 1 filled container per uninterrupted filling sequence
 - if the filling sequence is interrupted, you must perform additional tests
- for mixtures of 2 gases, you must test every cylinder to its specification for 1 gas, then perform an identity test for the other gas on 1 cylinder from the manifold filling sequence
- for mixtures containing more than 2 gases, you should test every cylinder to specification for all but 1 of the gases, then test 1 cylinder from each manifold filling sequence for the identity of the remaining gas
- for a mixture of 2 or more gases first filled into a series of storage buffer tanks, if the mixing process of the gases can be validated to show that the mixture remains homogenous within the buffer tanks and during the filling process, you may perform full testing on 1 cylinder per filling sequence or manifold

You do not have to analyze vessels filled at curbside if a certificate of analysis is available for the medical gas in the tank used to make the delivery.

For deliveries of liquid nitrogen NF in an unpressurized open-top Dewar, you do not need to perform additional testing if the source container was tested, met appropriate specifications and was released. A certificate of analysis must be available for the bulk tank used to make the delivery.

When filling homecare units with liquid oxygen USP on company premises, if a certificate of analysis is available for the source container, you only need to conduct identity testing.

Ethylene oxide is carcinogenic. As an importer, you do not need to perform an identity test on any medical gas mixtures of ethylene oxide, as long as you:

- sell the gas mixture "as is, in the same container"
- do not perform any other fabricating and/or packaging operations for this gas mixture

You must get a certificate of analysis from the fabricator of the gas mixture.



You must quarantine any lot or batch of medical gas that does not comply with specifications. Do not make it available for sale while waiting for final disposal.

C.02.19 (1) A packager/labeller of a drug, a distributor referred to in paragraph C.01A.003(b) and an importer of a drug other than an active ingredient shall perform the finished product testing on a sample of the drug that is taken either

- (a) after receipt of each lot or batch of the drug on their premises in Canada; or
- (b) before receipt of each lot or batch of the drug on their premises in Canada if the following conditions are met:
 - (i) the packager/labeller, distributor or importer
 - (A) has evidence satisfactory to the Minister to demonstrate that drugs sold to them by the vendor of that lot or batch 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 Minister, and
 - (ii) the drug has not been transported or stored under conditions that may affect its compliance with the specifications for that drug.

(2) If the packager/labeller, distributor or importer receives a lot or batch of a drug on their premises in Canada the useful life of which is more than 30 days, the lot or batch shall be tested for identity and the packager/labeller shall confirm the identity after the lot or batch is packaged/labelled.

(3) Subsections (1) and (2) do not apply to a distributor if the drug is fabricated, packaged/labelled and tested in Canada by a person who holds an establishment licence that authorizes that activity.

(4) Subsections (1) and (2) do not apply to a distributor or importer if the drug is fabricated, packaged/labelled and tested in an MRA country at a recognized building and they retain a copy of the batch certificate for each lot or batch of the drug that they receive.

(4.1) Subsections (1) and (2) do not apply to a distributor or importer of a COVID-19 drug if it is the subject of a written request made under section C.04.015.

(4.2) Subsection (1) does not apply to a packager/labeller, distributor or importer if the following conditions are met:

- (a) the drug is a radiopharmaceutical or a *radionuclide generator*, as defined in section C.03.001, and has a useful life of no more than 30 days; and



- (b) the packager/labeller, distributor or importer maintains evidence satisfactory to the Minister to demonstrate that
 - (i) the drug has been tested against the specifications for that drug, and
 - (ii) the drug has not been transported or stored under conditions that may affect its compliance with those specifications.

(4.3) Subsections (1) and (2) do not apply to a packager/labeller, distributor or importer if the following conditions are met:

- (a) the drug is
 - (i) for human use,
 - (ii) in dosage form,
 - (iii) listed in Schedule D to the Act,
 - (iv) not a vaccine, and
 - (v) composed of genetically modified autologous human nucleated cells or is delivered to cells using an adeno-associated virus vector; and
- (b) the packager/labeller, distributor or importer maintains evidence satisfactory to the Minister to demonstrate that
 - (i) the drug has been tested against the specifications for that drug, and
 - (ii) the drug has not been transported or stored under conditions that may affect its compliance with those specifications.

(5) Subsections (1) and (2) do not apply to a distributor or importer of a drug that is not a prescription drug and that is part of a class of drugs that is set out in column 1 of the List of Non-prescription Drugs Not Subject to Certain Testing Requirements if all of the following conditions are met:

- (a) the drug contains, as its only active ingredients, one or more of those set out in column 2, each of which corresponds to that class, in the corresponding quantity set out in column 3, and the drug is consistent with the descriptive information set out in columns 4 to 6;
- (b) the drug is
 - (i) fabricated in Canada or in a recognized country or region,
 - (ii) packaged/labelled in Canada or in a recognized country or region, and
 - (iii) tested in a recognized country or region;
- (c) the distributor or the importer retains a copy of the batch certificate for each lot or batch of the drug that is distributed or imported, as the case may be.

(6) A drug that is referred to in subsection (4.2), (4.3) or (5) and that is imported may be shipped directly to a person other than the importer if the following conditions are met:

- (a) before importing the drug, the importer receives a document that demonstrates that the drug complies with the specifications for that drug;
- (b) the importer and the distributor have measures in place to ensure that all the requirements of these Regulations in respect of the importation of the drug are met.



Rationale

Section C.02.019 outlines conditions and exemptions for when you must perform finished product testing. Paragraph C.02.019 (1) (b) outlines requirements you must meet as a packager/labeller, distributor or importer of medical gas if testing is done before receipt on your site. Paragraphs C.02.019 (3) and C.02.019 (4) outline exemptions to finished product testing.

Interpretation

If you are a distributor (C.01A.003 (b)) or importer of a medical gas, you must test a sample taken after you receive it on your site. The exception is if you choose to rely on test results provided by the supplier.

Buildings holding a Canadian establishment licence

If you are a distributor of medical gases that are fabricated, packaged/labelled and tested at Canadian sites, you only need to have a copy of the authentic certificate of analysis from the licensed Canadian establishment to show you comply with specifications. This certificate must show actual numerical results and refer to the product specifications and test methods used. Retesting, including identity testing, is not required.

Buildings recognized by a regulatory authority in an MRA country

If you are an importer of medical gases fabricated, packaged/labelled and tested at recognized buildings authorized by a regulatory authority (listed in section C.01A.019 and identified on your establishment licence), you only need to have a batch certificate for each lot or batch of the medical gas received to show you comply with specifications. The batch certificate must be in the format agreed on by Mutual Recognition Agreement (MRA) partners in the [International Harmonized Requirements for Batch Certification](#). Retesting, including identity testing, is not required when the medical gas is fabricated, packaged/labelled and tested in an MRA country.

Buildings in non-MRA countries

As an importer, you must meet the following conditions for testing (other than identity testing) if you choose to rely on test results provided by an establishment in a non-MRA country:

- You must provide evidence of ongoing GMP compliance, according to a system described in the interpretation of section C.02.012. This can be indicated by ensuring the site is listed on your establishment licence.
 - For more information, please refer to [How to demonstrate foreign building compliance with drug good manufacturing practices \(GUI-0080\)](#).



- Each lot must come with an authentic certificate of analysis or a copy of it (an electronic copy with an electronic signature is fine). The certificate must show actual numerical results and refer to the product specifications and test methods used.
- You must perform complete confirmatory testing on at least 1 lot per year per fabricator. You must choose medical gases on a rotational basis.
- You may release for sale a lot or batch of a finished product undergoing periodic confirmatory testing before all tests are complete, as long as a specific identity test is performed and your quality control department approves.

If any product from a non-MRA site fails to conform to finished product testing requirements, you must conduct an investigation of the extent of the non-compliance. This may include:

- re-evaluating GMP compliance
- adding complete confirmatory testing, based on the risk associated with the non-compliance

As an importer, you must carry out positive identification on a sample of each lot or batch in a shipment of medical gas that arrives on your site. Acceptable identity test methods could include chemical testing or physical testing (in cases where the product has unique identifiers). Unique identifier principles can be used for labelled dedicated bulk tanks of imported medical gas if the following criteria are met:

- the foreign site is listed on your drug establishment licence
- only labelled dedicated bulk tanks with traceability identification are used (an attestation must be available to declare tank dedication)
- you verify the certificate of analysis and certificate of manufacture before quality control review for release to customer
- the foreign supplier is qualified by a vendor certification program
- periodic confirmatory testing is done

Note: Unique identifier principles do not apply to mixed gases.

5.13 Records (C.02.020 – C.02.024.1)

C.02.20 (1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer shall maintain all of the following records on their premises in Canada for each drug that they fabricate, package/label, distribute or import:

- (a) except in the case of an importer of an active pharmaceutical ingredient or an active ingredient that is used in the fabrication of a drug that is of non-biological



origin and that is listed in Schedule C to the Act, master production documents for the drug

- (b) evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and stored including during transportation, 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, including during transportation, meet the requirements set out in this Division
- (d) evidence that establishes the period during which the drug in the container in which it is sold or made available for further use in fabrication will meet the specifications for that drug; and
- (e) evidence that the finished product testing referred to in section C.02.018 was carried out, and the results of that testing

(2) Every distributor referred to in paragraph C.01A.003(b) and importer shall make available to the Minister, on request, the results of testing performed on raw materials and packaging/labelling materials for each lot or batch of drug that it distributes or imports.

(3) Every fabricator shall maintain on their premises written specifications for all raw materials and adequate evidence of the testing of those raw materials referred to in section C.02.009 and of the test results.

(4) Every person who packages a drug shall maintain on their premises written specifications for all packaging materials and adequate evidence of the examination or testing of those materials referred to in section C.02.016 and of any test results.

(5) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada detailed plans and specifications of each building in Canada where they fabricate package/label or test drugs and a description of the design and construction of those buildings.

(6) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada personnel records in respect of each person who is employed to supervise the fabrication, packaging/labelling and testing of drugs, including the person's title, responsibilities, qualifications, experience and training.

C.02.21 (1) All records and evidence on the fabrication, packaging/labelling, finished product testing referred to in section C.02.018 and storage, including storage during transportation, of a drug in dosage form that are required to be maintained under this Division shall be retained for 1 year after the expiration date of the drug unless the person's establishment licence specifies some other period.



(2) Subject to subsection (4), all records and evidence of the fabrication, packaging/labelling, finished product testing referred to in section C.02.018 and storage, including during transportation, of an active ingredient that are required to be maintained under this Division shall be retained in respect of each lot or batch of the active ingredient for the following period unless the person holds an establishment licence that specifies some other period:

- (a) in the case of an active ingredient that has a retest date, three years after the lot or batch has been completely distributed and
- (b) in any other case, one year after the expiration date of the lot or batch

(3) Subject to subsection (4), all records and evidence of the raw material testing referred to in section C.02.009 and of the testing of packaging/labelling materials that are required to be maintained under this Division shall be retained for five years after the raw materials and packaging/labelling materials were last used in the fabrication or packaging/labelling of a drug unless the relevant establishment licence specifies some other period.

(4) If a fabricator is required to maintain records and evidence in respect of the same active ingredient under subsections (2) and (3), they shall maintain them for the longest period that is applicable.

C.02.22 (1) Every wholesaler, distributor referred to in C.01A.003 and importer of a drug in dosage form shall retain records of sale of each lot or batch of the drug, which enable them to recall the lot or batch from the market, for 1 year after the expiration date of that lot or batch, unless their establishment licence specifies some other period.

(2) Every distributor of an active ingredient referred to in paragraph C.01A.003(a) and every wholesaler and importer of an active ingredient shall retain records of sale of each lot or batch of the active ingredient, which enable them to recall the lot or batch from the market, for the following period unless the person holds an establishment licence that specifies some other period:

- (a) in the case of an active ingredient that has a retest date, 3 years after the lot or batch has been completely distributed or
- (b) in any other case, 1 year after the expiration date of the lot or batch

C.02.23 (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 and importer of the drug shall make a record of the complaint or information that contains the following:

- (a) the results of any investigation carried out under subsection C.02.015(2) and, if applicable, the corrective action taken or



- (b) the name and business address of the person in charge of the quality control department to whom the complaint or information was forwarded under subsection C.02.015(2.1) and the date on which it was forwarded

(2) Records referred to in subsection (1) shall be retained for the following period unless the person holds an establishment licence that specifies some other period:

- (a) in the case of a drug in dosage form, one year after the expiration date of the lot or batch of the drug and
- (b) in the case of an active ingredient
 - (i) if the active ingredient has a retest date, three years after the lot or batch has been completely distributed
 - (ii) in any other case, one year after the expiration date of the lot or batch of the active ingredient

C.02.24 (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 program required by section C.02.012 and of any action taken in connection with that program 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 program required to be implemented under section C.02.007 and
- (b) retain those records for a period of at least three years

C.02.24.1 Every distributor of an active ingredient referred to in paragraph C.01A.003(a) and every fabricator, packager/labeller, wholesaler and importer of an active ingredient shall add all of the following information to the documentation that accompanies the active ingredient, immediately after any like information that has been added by another person:

- (a) their establishment licence number, or if there is none, their name, address, telephone number, fax number and email address
- (b) an indication whether they have fabricated, packaged/labelled, wholesaled, distributed or imported the active ingredient and the date on which that activity was carried out
- (c) the expiration date and
- (d) the lot number

Rationale (C.02.020 to C.02.024.1)

Good documentation is a key part of a pharmaceutical quality system and promotes compliance with GMP requirements. Documentation may be paper-based, electronic or



photographic media. You should define the types of documents and media used in your pharmaceutical quality system.

The documentation system's main goal is to establish, control, monitor and record all activities that directly or indirectly impact all aspects of the quality of medical gases. This includes information from all stages of the product lifecycle and all records related to the quality of medical gases.

Records must be reliable, complete, consistent and accurate.

You must establish a data governance system to ensure controls are in place to prevent and detect data integrity issues throughout the product lifecycle.

This includes:

- having policies and standard operating procedures that clearly indicate management's expectations for how data should be acquired, modified, reviewed and stored
- validating and maintaining equipment and associated computer systems
 - these are standard principles under a pharmaceutical quality system, regardless of whether paper or electronic records are used
- checking the preventative measures put in place periodically to verify their implementation and effectiveness

Interpretation (C.02.020 to C.02.024.1)

You must make any documentation requested by Health Canada for evaluation available in one of Canada's official languages (English or French).

For all sections of the GMP guidelines, you must keep standard operating procedures (SOPs) for reference and inspection. These SOPs must be regularly reviewed and kept up to date by qualified staff. You must document reasons for any revisions. You should have a system in place to ensure that only current SOPs are in use. Where needed, keep records of SOPs for all computer and automated systems as well.

Your quality control department must approve, sign and date all relevant SOPs and GMP documents (such as records of actions taken or conclusions reached). They must also approve any changes to these documents by signing and dating the change. All changes must also be signed and dated by the person making the change. Any changes should still allow the original information to be read. Where appropriate, record the reason for the change.

You may keep records (for example, specifications, instructions, procedures) either as originals or true copies in electronic format as long as you also keep backup copies.



Electronic data must be easy to print. Your records must be secured and you must be able to provide them within 48 hours.

You should establish a data governance system to ensure data integrity is maintained for all records required under GMP. The general principles of good documentation practices apply to the management of records, regardless of the media used, throughout their lifecycle. This includes from the time data is first generated and any modifications made after.

Records:

- should be traceable to their source
 - use techniques such as initials/signatures, secure user identification and change history/audit trails to capture relevant information (for example, processing parameters, method settings, acquisition details or reasons for changes/reprocessing)
- should be legible, with no parts of the data obscured or removed
 - you must be able to retrieve archived records quickly
 - any changes to records must be documented and traceable data should be recorded, documented or saved at the time it is generated, with reliable evidence that this was done
- must be kept in an original format as an original record or as a true copy which has undergone a qualified conversion process that maintains data integrity
- must be generated and kept under the oversight of a pharmaceutical quality system that ensures their accuracy

Note: Cloud computing services are to be treated as a contracted service. Risks should be identified and addressed, and responsibilities clearly outlined in a contract or service agreement.

An electronic signature is an acceptable alternative to a handwritten signature.

Appropriate controls must be in place as follows:

- validate electronic signature systems to show that the systems are suitably secure and reliable (and document this validation)
 - have a procedure for creating electronic signatures
 - put controls in place to ensure the uniqueness of all electronic signatures
- ensure all electronic signatures include a time and date stamp and are subject to audit trail requirements
- inform users that electronic signatures are equal to hand-written signatures
 - keep records to show that users are aware of their responsibilities and accountability relating to the use of electronic signatures



Note: Find more information on electronic records in [Annex 11 to the good manufacturing practices guide: Computerized Systems: GUI-0050](#).

If you use an electronic system to create, modify or store records required under these regulations, you should evaluate and test the system for security, validity and reliability. You should keep records of those evaluations and tests.

Also:

- ensure all access and user rights in electronic systems are properly controlled to prevent system users from compromising data integrity
- control electronic records in a way that ensures the records:
 - can only be created and modified by authorized staff
 - are protected against intentional or accidental deletion
 - are named and organized in a way that makes them easy to trace
 - are tracked through an audit trail when created or modified
 - the audit trail should include changes made to the record, who made the change, the time and date the record was changed and, if applicable, the reason the record was modified
 - are backed up regularly to protect against potential data loss due to system issues or data corruption
 - are available for review during an inspection and can be easily retrieved in a suitable format
 - include all necessary metadata

Your records must include a copy of master filling and/or master production documents that are verified, dated and signed. Document all the steps of the process required by the defined procedures and instructions, as the step is performed. However, instead of repeating in detail each operation in the manufacturing orders, you may refer to the master filling documents that contain these details.

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 a medical gas.

You must have documentation to support the expiration date of a medical gas mixture. The expiration date should be based on validation studies related to physical aspects (such as the rate of stratification).

Health Canada is no longer requiring expiration dates on product labels by medical gas manufacturers of:



- oxygen
- helium
- nitrogen
- carbon dioxide
- medical air
- nitrous oxide and
- their medically appropriate mixtures

The following documents for operations in Canada must be kept by the fabricator, packager/labeller, wholesaler, distributor (C.01A.003) and importer of a medical gas:

- distribution records for all sales of medical gas
 - must be easily accessible in the event of a complete and rapid recall of any lot or batch of a medical gas
 - do not have to track by lot number
- records of complaints or other information you receive on the quality, deficiencies or hazards of a medical gas and any follow-up investigations and corrective actions taken
- records of the results of your self-inspection program and any actions taken

The fabricator of medical gas mixtures must keep the following documents:

- written specifications for the raw materials
- results of the raw material testing
- sources of the raw materials supplied
- records about the operation of the sanitation program required under section C.02.007

The packager/labeller must keep the following documents:

- written specifications for packaging materials
- results of examinations or tests on a packaging material
- sources of the packaging materials supplied
- documentation for cylinders and valves that include:
 - certification issued according to Transport Canada's requirements for new cylinders
 - written specifications that outline the checks to be performed on empty cylinders and valves before filling and other requirements
 - checks on the functionality of valves on cylinders
- records of any checks
- records about the operation of the sanitation program required under section C.02.007



Keep records required under sections C.02.021(1), C.02.022 and C.02.023 for either:

- at least 1 year after the expiration date of the medical gas or
- at least 5 years from the date of fabrication or packaging/labelling for medical gases that do not require an expiration date

For GMP purposes, you must keep records giving details on the qualifications/experience of any consultant employed, along with the services that each consultant provides.

Note: Gas chromatogram charts are considered records or evidence of testing. They must be kept for 5 years from the date of filling.

Keep records of all staff employed in GMP activities, such as:

- organization charts
- person's title, job description, responsibilities, qualifications, experience and training
- name of each person's designated alternate

5.14 Medical gases (C.02.030)

Sections C.02.025, C.02.026, C.02.027, C.02.028 and C.02.029 do not apply to medical gases.

6. Glossary and Terms

6.1 Glossary

DIN: drug identification number

GMP: good manufacturing practices

ICH: International Council on Harmonization

MRA: mutual recognition agreement

NF: national formulary

OOS: out of specification

PIC/S: Pharmaceutical Inspection Cooperation/Scheme

SOP: standard operating procedure

USP: United States Pharmacopeia



6.2 Terms

These definitions explain how terms are used in this document. Definitions quoted from other documents are noted in brackets at the end of the definition. If there is a conflict with a definition in the *Food and Drugs Act* or *Food and Drug Regulations*, the definition in the act or regulations prevails.

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

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

- 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
- provides a detailed description of the drug, including:
 - a statement of all properties and qualities of the drug, including the identity, potency and purity of the drug and
 - a statement of tolerances for the properties and qualities of the drug
- identifies the analytical methods used in testing the lot or batch and provides details of the analytical results obtained
- sets out the addresses of the buildings at which the lot or batch was fabricated, packaged/labelled and tested and

certifies that the lot or batch was fabricated, packaged/labelled and tested in accordance with the good manufacturing practices of the regulatory authority that has recognized those buildings as meeting its good manufacturing practices standards. (C.01A.001)

Bulk gas: A medical gas (either a single gas or a mixture of gases) that does not need more processing to be administered, but is not in its final package (for example, liquefied oxygen).

Bulk tank: A static container that is used to store liquefied or cryogenic gas and is thermally insulated (to keep temperatures stable). Also called “stationary cryogenic vessels.”

Certificate of manufacture: A document issued by a vendor to a distributor or importer that attests that a specific lot or batch of drug has been produced in accordance with its



master production documents. Such certificates include a detailed summary of current batch documentation, with reference to respective dates of revision, manufacture and packaging, and are signed and dated by the vendor's quality control department. For drugs that are fabricated, packaged/labelled and tested in MRA countries, the batch certificate is considered to be equivalent.

Change control: A written procedure that describes the action to be taken if a change is proposed:

- to facilities, materials, equipment and/or processes used in the fabrication, packaging and testing of drugs or
- that may affect the operation of the quality or support system

Critical process: A process that, if not properly controlled, may cause significant variation in the quality of the finished product.

Cryogenic vessel: A stationary or portable vacuum insulated container designed to contain liquefied gas at extremely low temperatures. Mobile vessels are also called "Dewars."

Curbside delivery: The filling of cryogenic vessels with cryogenic liquefied gas at the point of use.

Cylinder: Container usually cylindrical suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature. (PIC/S)

Distributor or manufacturer: A person, including an association or partnership, who under their own name (or under a trade, design or word mark, trade name or other name, word, or mark controlled by them) sells a food or drug. (A.01.010)

Divisions 1A and 2 to 4 apply to the following distributors:

- a distributor of an active ingredient or of a drug in dosage form that is listed in Schedule C to the act
- a distributor of a drug for which the distributor holds the drug identification number (C01A.003)

Fabricate: To prepare and preserve a drug for the purposes of sale." (C.01A.001)
Also referred to as "produce" or "manufacture."



Finished product: A product that has undergone all stages of production, including packaging in its final container and labelling.

Gas: Products in gaseous phase and products in liquid phase at cryogenic temperatures or liquefied compressed gases at 15 °C and 1 atmosphere.

Home cryogenic vessel: Mobile tanks designed to hold liquid oxygen (at very low temperatures) and dispense gaseous oxygen at patients' homes.

Hydrostatic pressure test: A test performed as required by national or international regulations, to ensure that containers are able to withstand pressures up to the container's design pressure. (PIC/S)

Immediate container: The receptacle/vessel that is in direct contact with a drug.

Import: To import into Canada a drug for the purpose of sale. (C.01A.001)

Liquefied gas: A gas that has a critical temperature above 200°C, which remains as a liquid in the container when under pressure.

Lot: Refer to Batch.

Manifold: Equipment or apparatus designed to allow 1 or more medical gas containers to be filled at a time.

Manifold filling sequence: A filling sequence of many containers at 1 time, using a multiple outlet manifold or rack.

Marketing authorization: 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 Drugs Act* and its regulations. The marketing authorization may be in the form of a:

- notice of compliance (NOC)
- drug identification number (DIN)
- device licence for classes II, III and IV medical devices
- natural product number (NPN) or
- homeopathic DIN (DIN-HM)

Master filling documents: A set of instructions for filling containers with a medical gas in dosage form. They contain a description of the filling operation, controls, procedures, specifications and methods of quality control of the medical gas.

Master formula: A document or set of documents specifying the raw materials with:

- their quantities and the packaging materials



- a detailed description of the procedures and precautions required to produce a specified quantity of a finished product
- the processing instructions (including in-process controls)

Master production documents (MPD): Documents that include:

- specifications for raw material, packaging material and packaged dosage form
- master formula (including composition and instructions as described in the definition above)
- sampling procedures and
- critical processing-related standard operating procedures (SOPs), whether or not these SOPs are specifically referenced in the master formula

Medical gas: Any gas or mixture of gases manufactured, sold or represented for use as a drug. (C.02.002)

MRA country: A country that is a participant in a mutual recognition agreement (MRA) with Canada. (C.01A.001)

Mutual recognition agreement (MRA): An international agreement that provides for the mutual recognition of compliance certification for good manufacturing practices for drugs. (C.01A.001)

Package/label: To put a drug in its immediate container or to affix the inner or outer label to the drug. (C.01A.001)

This includes the repackaging and relabelling of previously packaged and labelled drugs.

Packaging material: Includes a label. (C.02.002)

Note: For the purpose of these guidelines, this definition also includes:

- labels
- printed packaging materials
- any material intended to protect the intermediate or API or drug during storage and transport
- those components in direct contact with the final API or drug

Qualified authority: A member of the Pharmaceutical Inspection Cooperation/Scheme (PIC/S).

Quality control department: A unit in an establishment that:

- monitors the quality of production operations and



- exercises control over the quality of materials required for and resulting from those operations

Quality manual: Document specifying the quality management system of an organization. (ISO 9000:2005)

Quarantine: The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection. (ICH Q7)

Raw material: The individual gases that are used in the production of medical gas mixtures.

Regulatory authority: A government agency or other entity in an MRA country that:

- has a legal right to control the use or sale of drugs within that country and
- may take enforcement action to ensure that drugs marketed within its jurisdiction comply with legal requirements (C.01A.001)

Specifications: A detailed description of a drug, the raw material used in a drug or the packaging material for a drug and includes 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
- detailed description of the methods used for testing and examining the drug, raw material or packaging material and
- statement of tolerances for the properties and qualities of the drug, raw material or packaging material (C.01A.001)

Standard operating procedure (SOP): A written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature, for example:

- equipment operation
- maintenance and cleaning
- validation
- cleaning of premises
- environmental control
- sampling and inspection



Certain SOPs may be used to supplement product-specific master and batch production documents.

Tanker: A thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas. (PIC/S)

Uninterrupted filling sequence: A single, continuous filling sequence with no breaks or shutdowns during filling and no change of staff, equipment or lots of raw materials. This procedure applies to the individual filling of high-pressure cylinders (1 cylinder at a time).

Validation: A documented program that provides a high degree of assurance that a specific process, method or system will consistently produce a result that meets pre-determined acceptance criteria. (ICH Q7)

Vendor: Any person or company that sells or supplies goods or services to another company. Also called “supplier.”

Wholesaler: A person who is not a distributor described in section C.01A.003 and who sells any of the following drugs other than at retail sale:

- a drug in dosage form that is listed in Schedule C or D to the act, a drug that is a prescription drug or a controlled drug, as defined in subsection G.01.001(1)
- an active ingredient or
- a narcotic as defined in the Narcotic Control Regulations (C.01A.001(1))



7. References

Legislation

- [Food and Drugs Act](#)
- [Food and Drug Regulations](#)
- [Narcotic Control Regulations](#)

Guidances and policies

- [Recall policy \(POL-0016\)](#)
- [Validation guidelines for pharmaceutical dosage forms \(GUI-0029\)](#)
- [Good manufacturing practices \(GMP\) guidelines for drug products \(GUI-0001\)](#)
- [Risk classification guide for drug good manufacturing practices observations \(GUI-0023\)](#)
- [Guidance on drug establishment licences and drug establishment licensing fees \(GUI-0002\)](#)
- [How to demonstrate foreign building compliance with drug good manufacturing practices \(GUI-0080\)](#)

International guidance

- [ICH Q9: Quality risk management](#)
- [ICH Q10: Pharmaceutical quality system](#)
- [PIC/S GMP annexes – Annex 6 – Manufacture of medicinal gases](#)
- [ICH Q2\(R1\) Validation of analytical procedures: Text and methodology](#)
- [ICH Q7 Good manufacturing practice guide for active pharmaceutical ingredients](#)

Other

- [Selection and use of cylinders, spheres, tubes and other containers for the transportation of dangerous goods, Class 2 \(CAN/CSA B340\)](#)