Good manufacturing practices for medical gases

GUI-0031

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Canada

Good manufacturing practices for medical gases (GUI-0031)

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Disclaimer

This document does not constitute part of the *Food and Drugs Act* (the Act) or its regulations and in the event of any inconsistency or conflict between the Act or regulations and this document, the Act or the regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the regulations and the applicable administrative policies.

Ce document est aussi disponible en français.

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About this document

1. Purpose

This guide is for people who work with **medical gases** as:

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

It will help you understand and comply with Part C, Division 2 of the Food and Drug Regulations, which is about good manufacturing practices (GMP).

This guide is intended for people who are required to hold an establishment licence under Part C, Division 1A of the Food and Drug Regulations. Additionally — whether a license is required or not — any person storing a medical gas (i.e. wholesaling) is required to comply with GMP. Refer to Health Canada's *Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002)* for more information on establishment licences.

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 package medical gases for their own use or administration to a patient.

For the purpose of these guidelines, these 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

These operations are considered a "packaging / labelling" activity:

- transfilling gases at a facility
- curbside filling

The scope of this document does not include establishment licensing. To understand how to comply with GMP requirements in order to get an establishment licence, see *Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002)*.

3. Introduction

These guidelines replace interpretations in the main *Good Manufacturing Practices (GMP) Guidelines (GUI-0001)* for medical gases. They were developed by Health Canada in consultation with stakeholders.

Medical gases have unique 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 used as a raw material, or it may be sold as a bulk drug or a finished packaged product.

Guidance documents like this one are meant to help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff, so that the rules are enforced in a fair, consistent and effective way across Canada.

Health Canada inspects establishments to assess their compliance with the Food and Drugs Act (the Act) and associated regulations. When we conduct an inspection, we will use this document as a guide in assessing your compliance with GMP requirements.

	To better understand how risk ratings are assigned during inspections, see *Risk Classification of Good Manufacturing Practices (GMP) Observations (GUI-0023)*.

These guidelines are not the only way GMP regulations can be interpreted, and are not intended to cover every possible case. Other ways of complying with GMP regulations will be considered with proper scientific justification. Also, as new technologies emerge, different approaches may be called for.

Guidance documents are administrative and do not have the force of law. Because of this, they allow for flexibility in approach. So use this guide to help you develop specific approaches that meet your unique needs.

About quality management

4. Pharmaceutical quality system

Guiding principles

Do you hold an establishment licence or run an operation governed by Part C, Division 2 of the Food and Drug Regulations? If you do, you must make sure that you comply with these requirements—and your marketing or clinical trial authorization—when you fabricate, package, label, import, distribute, test and wholesale medical gases. You must not place consumers at risk because of poor safety, quality or efficacy.

Your senior management is responsible for this quality objective. You will also need the help and commitment of your suppliers and personnel at all levels of your establishment.

To achieve this quality objective reliably, you must:

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

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 the production and control of drugs.

Pharmaceutical quality system

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

GMP applies to all lifecycle stages: from the manufacture of investigational drugs, to technology transfer, to commercial manufacturing, through to product discontinuation. The pharmaceutical quality system can even extend to the pharmaceutical development lifecycle stage (as described in *ICH Q10 Pharmaceutical Quality System*). While optional, this 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:

1. Design, plan, implement, maintain and continuously improve on your system to allow the consistent delivery of products with proper quality attributes.
2. Manage product and process knowledge throughout all lifecycle stages.
3. Design and develop drugs in a way that takes into account GMP requirements.
4. Clearly outline management responsibilities.
5. Make arrangements for:
    a. the manufacture, supply and use of the correct starting and packaging materials
    b. selecting and monitoring suppliers
    c. verifying that each delivery is from the approved supply chain
6. Ensure processes are in place to properly manage outsourced activities.
7. Establish and maintain a state of control by developing and using effective monitoring and control systems for process performance and product quality.
8. Take into account the results of product and process monitoring in batch release and in the investigation of deviations. This will allow you to take preventive action to avoid potential deviations in the future.
9. Carry out all needed controls on intermediate products, and any other in-process controls and validations.
10. Ensure continual improvement by making quality improvements appropriate to the current level of process and product knowledge.

11. Make arrangements to evaluate and approve planned changes before implementing them. Consider regulatory notification and approval where required.

12. After implementing any change, conduct an evaluation to confirm that your quality objectives were achieved and that there was no unintended negative impact on product quality.

13. Apply a proper level of root cause analysis when investigating deviations, suspected product defects and other problems. This can be determined using quality risk management principles. In cases where the true root cause(s) of the issue cannot be determined, identify the most likely root cause(s) and address those. Where human error is suspected or identified as the cause, this should be justified. Ensure that process, procedural or system-based errors or problems have not been overlooked, if present. 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.

14. Make sure Quality Control certifies each production batch of drugs before you sell or supply them. You must produce and control drugs according to marketing authorization requirements and any other regulations relevant to the production, control and release of drugs.

15. Ensure that drugs are stored, distributed and handled so that quality is maintained throughout their shelf life.

16. Implement a process for self-inspection and/or quality audit, to regularly appraise the effectiveness and applicability of your pharmaceutical quality system.

17. Your senior management's leadership and active participation in your pharmaceutical quality system is essential. Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place. They must ensure the system is properly resourced and that roles, responsibilities and authorities are defined, communicated and implemented throughout your organization. They should also ensure the support and commitment to your pharmaceutical quality system from staff at all levels and sites within your organization.

18. Your senior management should periodically conduct a management review of your pharmaceutical quality system operation to identify opportunities for continual improvement of products, processes and the system itself.

19. Your pharmaceutical quality system should be defined and documented. You should have a quality manual or equivalent documentation that contains a description of the system, including management responsibilities.

Good manufacturing practices for drugs

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

GMP is concerned with both production and quality control. To meet basic GMP requirements, you must:

1. Clearly define all manufacturing processes. Review them systematically in the light of experience. Show that they are capable of consistently manufacturing drugs of the required quality that comply with their specifications.

2. Validate critical steps of manufacturing processes and key changes to the process.

3. 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

4. Write instructions and procedures in an instructional form in clear and direct language, specifically applicable to the facilities provided.

5. Train operators to properly carry out procedures.

6. Create records (manually and/or by recording instruments) during manufacture that show that all the steps required by the defined procedures and instructions were in fact taken. Show that the quantity and quality of the drug was as expected.

7. Document any significant deviations. Investigate them to determine the root cause. Ensure proper corrective and preventive action is taken.

8. 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.

9. Distribute products in a way that minimizes any risk to their quality and takes account of good distribution practice.

10. Control storage, handling and transportation of drugs to minimize any risk to their quality.

11. Have a system in place for recalling drugs from sale.

12. Examine complaints about drugs. Investigate the causes of quality defects. Take appropriate measures to prevent problems from happening again.

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 products for use or sale if their quality is satisfactory. Quality control ensures that you carry out the necessary and relevant tests to ensure quality. It is not only done in labs—you must incorporate quality control into all activities and decisions about the quality of your products.

To meet basic quality control requirements, you must:

1. Ensure you have adequate facilities, trained personnel, and approved procedures for sampling and testing raw materials, packaging materials, intermediate bulk and finished products, and—where appropriate—for monitoring environmental conditions for GMP purposes.

2. Take samples of raw materials, packaging materials, and intermediate, bulk, and finished products according to procedures approved by the quality control department.

3. Validate test methods.

4. 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.

5. Ensure finished products contain active ingredients complying with the qualitative and quantitative composition of your marketing or clinical trial authorization. Ensure they are of the purity required, enclosed within their proper containers, and correctly labelled.

6. Document the results of your inspection and testing of intermediate, bulk and finished products and materials against specification.

7. Include in your product release procedures a review and evaluation of relevant production documentation, as well as an assessment of deviations from specified procedures.

8. Do not release drugs for sale or supply before they are approved by your quality control department.

9. Keep sufficient samples of raw material and finished product to allow future examination if needed.

Quality risk management

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

The principles of quality risk management are that:

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

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

Guidance

5. Regulations

For each section below, the exact text from Part C, Division 2 of the Food and Drug Regulations is provided first. This is followed by the rationale (why the rule is important) and Health Canada's interpretation (what you need to do to be compliant), where needed.

Division 2 – Good manufacturing practices

C.02.002

In this Division,

- "medical gas" means any gas or mixture of gases manufactured, sold, or represented for use as a drug; (*gaz médical*)
- "packaging material" includes a label; (*matériel d'emballage*)
- "specifications" means a detailed description of a drug, the raw material used in a drug, or the packaging material for a drug and includes:

  (a) a statement of all properties and qualities of the drug, raw material or packaging material that are relevant to the manufacture, packaging, and use of the drug, including the identity, potency, and purity of the drug, raw material, or packaging material,

  (b) a detailed description of the methods used for testing and examining the drug, raw material, or packaging material, and

  (c) a statement of tolerances for the properties and qualities of the drug, raw material, or packaging material. (spécifications)

229 ## Sale

230 ### C.02.003

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

231 ### 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 it in accordance with the requirements of this Division.

232 ### 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.

233 ## Use in fabrication

234 ### C.02.003.3

No person shall use an active ingredient in the fabrication of a drug unless it is fabricated, packaged/labelled, tested and stored in accordance with the requirements of this Division.

Premises

C.02.004

The premises in which a lot or batch of a drug is fabricated, packaged/labelled or stored shall be designed, constructed and maintained in a manner that

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

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

(c) prevents the contamination of the drug and the addition of extraneous material to the drug.

Rationale

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

1. Locate buildings where medical gases are fabricated or packaged in an environment that presents a minimal risk of causing any contamination of materials or medical gases. Measures taken to protect manufacturing processes will be considered along with location.

2. Make sure your premises are suitable for the operation performed there. Design site layout to avoid mix-ups and prevent contamination. Make sure:

    a. There is enough space for receiving and all production activities.

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

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

d. Working areas are well lit.

3. Segregate and designate areas to distinguish:

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

   b. different gases

   c. medical gases from non-medical gases, including their respective empty containers

   d. empty from full containers

   e. quarantined finished products from those available for distribution

4. Clearly identify the content of fixed distribution systems at their outlets.

5. Minimize “dead legs” where circulation may be restricted.

6. Identify pipelines carrying medical gases between areas by colour or by standard markings at suitable intervals. Show direction of flow.

7. 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 the ones used to trap desiccants after driers—are of suitable construction, and examined and changed as needed.

8. Separate rest, change, wash-up and toilet facilities from production areas. Make sure they are spacious, well ventilated and allow good sanitary practices.

9. Ensure fabrication and filling areas are well lit.

10. Maintain premises in a good state of repair.

11. Secure premises and vehicles used to store medical gases from unauthorized entry.

12. Store empty and filled cylinders/home cryogenic vessels under cover, protected from adverse weather conditions. Store filled cylinders/cryogenic vessels in a way that ensures they will be delivered in a clean state, compatible with the environment where they will be used.

Equipment

C.02.005

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

(a) permits the effective cleaning of its surfaces;

(b) prevents the contamination of the drug and the addition of extraneous 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:

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

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

Arranging your equipment in an orderly way makes cleaning nearby areas easier and avoids interference with other processing operations. It also minimizes circulation of personnel and optimizes 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

1. Make sure parts in contact with medical gases are designed, constructed and located in a way that allows cleaning and avoids contamination. Where required, fittings and accessory assemblies are designed for easy dismantling.

2. Make sure tankers and trailers and their equipment (hoses, valves, pumps, etc.) are well constructed and maintained. Pay special attention to tankers and trailers owned by a contracting firm.

3. In general, dedicate bulk tanks and tankers to 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** you ensure 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. You should also have a procedure that describes the measures to be taken when a tanker is returned back into medical gas service (after transporting non-medical gas or after a maintenance operation). This procedure should include analytical testing.

4. Use proper filling and storage equipment for medical gases.

    a. Use materials that are non-toxic, non-reactive to medical gases and corrosion-resistant.

    b. Use gas filling equipment that prevents wrong connections: it should be impossible to fill a container with the wrong gas.

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

5. Perform installation and operational qualification on equipment used during the critical steps of fabrication, packaging and testing (including computerized systems). Document equipment qualification. You can find more guidance in the Health Canada document: *Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)*.

6. You should only 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.

7. Check and maintain equipment used to fabricate, package/label and test medical gases regularly, including computerized equipment.

    a. Calibrate measuring devices according to a written program.

    b. Avoid using temporary devices for repairs.

c. Keep records of maintenance and calibration. Ensure a system is in place to support identification of calibration status, and you may use means other than labelling.

d. Calibrate vacuum gauges used during the essential evacuation of residual gas from high pressure cylinders 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 the "zero." Keep calibration records.

8. Make sure repair and maintenance of equipment (including cleaning and purging) does not adversely affect the quality of medical gases.

   a. Describe in your procedures the measures to be taken after repair and maintenance operations if there are breaches of the system’s integrity.

   b. Check for the absence of contaminants before releasing equipment for use.

   c. Maintain records of use and maintenance operations.

9. Protect openings for connections on lines supplying medical gases from contamination.

10. Verify check valves used to prevent contamination at regular intervals, to ensure they work properly.

11. You may use a sampling cylinder, such as a hoke bomb (a stainless steel cylinder with a valve on each end that allows a gaseous product to flow through) 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.

Personnel

C.02.006

Every lot or batch of a drug shall be fabricated, packaged/labelled, tested and stored under the supervision of personnel who, having regard to the duties and responsibilities involved, have had such technical, academic, and other training as the Director considers satisfactory in the interests of the health of

the consumer or purchaser.

Rationale

Who you hire is one of the most important element in any medical gases operation. Without the proper staff with the right attitude and training, it is almost impossible to fabricate, package/label, test or store good quality medical gases.

It is essential that you 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

1. If you are a fabricator, the person in charge of your quality control department, and the person in charge of your manufacturing department:

    a. must have proper professional or technical qualifications (this may include a respiratory therapist under provincial legislation governing health professionals, or someone qualified by pertinent training)

    b. must have practical experience in their area of responsibility

    c. must directly control and personally supervise on site for each working shift when activities under their control are being conducted

    d. may delegate duties and responsibility (for example, to cover all shifts) to a person who meets the requirements defined under 1.a, while remaining accountable for those duties and responsibility

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

    a. must have proper professional or technical qualifications (this may include a respiratory therapist under provincial legislation governing health professionals, or someone qualified by pertinent training)

    b. must have practical experience in their responsibility area

394 c. may delegate their duties and responsibilities to a person who meets the
395 requirements defined under 2.a

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

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

398 a. must be qualified by training and experience

399 b. may delegate their duties and responsibilities to a person who meets the
400 requirements defined under 3.a

401 4. Ensure you have enough staff available on site, with proper qualifications and
402 practical experience appropriate to their responsibilities.

403 a. Do not place so many responsibilities on any one individual that quality is put at
404 risk.

405 b. Record duties relating to medical gases for all responsible staff in written work
406 descriptions.

407 c. Ensure personnel have authority to carry out their responsibilities.

408 d. When key personnel are absent, appoint qualified replacements to carry out
409 their duties and functions.

410 5. Your personnel must be aware of the principles of GMP that affect them. They must
411 receive initial and continuing training relevant to their job responsibilities.

412 a. Provide training by qualified personnel. Follow a written training program for all
413 staff involved in fabricating, packaging/labelling, testing, importing, or storing a
414 medical gas (including technical, maintenance and cleaning staff).

415 b. Assess the effectiveness of continuing training periodically.

416 c. Provide training before implementing new or revised standard operating
417 procedures (SOPs).

418 d. Maintain records of training.

419 e. Give specific training to personnel working in areas where highly active, toxic,
420 infectious or sensitizing materials are handled.

421 f. Review performance of personnel periodically.

6. Make sure any consultants and contractors you hire have the necessary qualifications, training and experience to advise on the subjects for which they are retained. Personnel of subcontractors that could influence the quality of medical gases (for example, personnel in charge maintaining cylinders or valves) should be appropriately trained.

Sanitation

C.02.007

(1) Every person who fabricates or packages/labels a drug shall have a written sanitation program that shall be implemented under the supervision of qualified personnel.

(2) The sanitation program referred to in subsection (1) shall include:

(a) cleaning procedures for the premises where the drug is fabricated or packaged/labelled and for the equipment used in the fabrication or packaging/labelling of the drug; and

(b) instructions on the sanitary fabrication and packaging/labelling of drugs and the handling of materials used in the fabrication and packaging/labelling of drugs.

Rationale

Sanitation in a medical gas fabricating and packaging facility, as well as employee attitude, influences the quality of medical gas products. 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 and that the provisions of sections 8 and 11 of the *Food and Drugs Act* are satisfied.

Interpretation

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

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

3. Include procedures in your sanitation program that describe:
    a. cleaning requirements for the facility
    b. cleaning requirements for processing equipment
4. 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. Give special attention to the tankers and trailers owned by contracting firms.

C.02.008

(1) Every person who fabricates or packages/labels a drug shall have, in writing, minimum requirements for the health and the hygienic behaviour and clothing of personnel to ensure the clean and sanitary fabrication and packaging/labelling of the drug.

(2) No person shall have access to any area where a drug is exposed during its fabrication or packaging/labelling if the person

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

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

Rationale

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

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

Interpretation

1. Make minimum health requirements available in writing, including:
    a. 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.

b. People responsible for performing odour tests do not have ailments that can adversely affect test results.

c. People responsible for performing inspections involving distinguishing colours can distinguish colours properly.

2. Clearly define clothing requirements and hygiene procedures for company personnel and visitors in your written hygiene program.

   a. People must wear clean clothing and protective covering anywhere a potential for contaminating a medical gas exists.

   b. Operators must avoid direct contact between their hands and any parts of equipment that come in direct contact with the medical gas.

   c. Unsanitary practices are not allowed in processing areas.

   d. Requirements for personal hygiene should be outlined when important to the quality of the product.

Raw material testing

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

C.02.009

(1) Each lot or batch of raw material shall be tested against the 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) Where any property of a raw material is subject to change on storage, no lot or batch of that raw material shall be used in the fabrication of a drug after its storage unless the raw material is retested after an appropriate interval and complies with its specifications for that

property.

(5) Where the specifications referred to in subsections (1), (2) and (4) are not prescribed, they shall

(a) be in writing

(b) be acceptable to the Director who shall take into account the specifications contained in any publication mentioned in Schedule B to the Act; and

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

Rationale

Testing raw materials before using them has three 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 quantity or yield in a given manufacturing process.

Interpretation

1. For fabricators, test raw materials to specification when you receive them.
2. 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.
3. 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. But if you use one of these methods, you must establish its suitability under actual conditions of use. Conduct method transfer studies when applicable.

You can find guidance for validating particular types of methods in the International Conference on Harmonization (ICH) document *ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology*, or in any standard listed in Schedule B to the Act.

4. You may add deliveries of raw material to a bulk storage tank containing the same gas from previous deliveries. In this case:
    a. You must test a sample of the delivered raw material and find it to be satisfactory.
    b. When the raw material is a single gas accompanied by a Certificate of Analysis, you may take the sample and test it after:
        i. allowing for sufficient mixing of the delivery in the bulk storage tank, and
        ii. adequately purging the sampling line
    c. When the raw material is a mixture, your testing must verify each component.

C.02.010

(1) The testing referred to in section C.02.009 shall be performed on a sample taken

(a) after receipt of each lot or batch of raw material on the premises of the fabricator; or

(b) subject to subsection (2), before receipt of each lot or batch of raw material on the premises of the fabricator, if

i. the fabricator

(A) has evidence satisfactory to the Director to demonstrate that raw materials sold to him by the vendor of that lot or batch of raw material are consistently manufactured in accordance with and consistently comply with the specifications for those raw materials, and

(B) undertakes periodic complete confirmatory testing with a frequency satisfactory to the Director, and

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

(2) After a lot or batch of raw material is received on the premises of the fabricator, the lot or batch of raw material shall be tested for identity.

Rationale

Section C.02.010 outlines options for when you should carry out testing as per section C.02.009. Buying raw materials is an important operation. You must have in-depth knowledge of the raw materials and their vendor.

Interpretation

1. After receiving the raw material at your facility that fills medical gas into containers, take a sample and perform testing. Conduct specific identity testing on all lots of any raw material (see 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.

2. 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.

    a. Evidence satisfactory to the Director should include:

        i. 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 (demonstrating that the raw material fabricator complies with the ICH document *ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* or with any standard or system of equivalent quality)

        ii. an authentic certificate of analysis for all lots, showing actual numerical results and the product specification and validated test methods used

        iii. complete confirmatory testing on a minimum of one lot each year of a raw material received from each vendor, with the raw material chosen on a rotational basis

        iv. where multiple raw materials are received from the same vendor, confirmatory testing must be carried out for each raw material at least once every five years

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

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

    a. the type of packaging to be used

    b. labelling requirements

    c. mode of transportation

    d. seal of package

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

    f. evidence that special shipping requirements have been met

Manufacturing control

C.02.011

(1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003 *(b)* and importer of a drug shall have written procedures prepared by qualified personnel in respect of the drug to ensure that the drug meets the specifications for 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 the time you release the finished product for sale and distribution. These measures ensure that all of your manufacturing processes are clearly defined and systematically reviewed in light of experience. They also demonstrate that your manufacturing processes can consistently produce medical gas products that comply with their established specifications for quality.

Interpretation

1. Handle all raw materials, products and packaging materials according to pre-approved written procedures or instructions. This includes when receiving, quarantining, sampling, storing, tracking, labelling, processing, packaging and distributing. You must keep records as required.

2. Validate all critical production processes. Conduct validation studies according to predefined protocols. Prepare, evaluate, approve and maintain a written report summarizing recorded results and conclusions.

3. Approve changes to production processes, systems or equipment that may affect product quality and/or process reproducibility before implementing them. Where applicable, you should also validate these changes.

4. Avoid any deviation from instructions or procedures. If deviations happen, have qualified personnel 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 maintain records.

5. Store bulk gases under conditions and in distribution systems that prevent product mix-up, deterioration or contamination.

6. Check measuring devices regularly for accuracy and precision. Maintain records of such checks.

7. Make written procedures available on site to ensure that raw materials and bulk gases:
    a. are identified by lot number, receiving number or laboratory control number
    b. are released for production or filling operations according to written procedures approved by the quality control department
    c. meet Schedule B standards (if applicable) and Certificates of Analysis are reviewed and available on site for each lot of source gas received
    d. are stored under conditions that will preserve their quality and avoid their inadvertent use

8. Make written procedures—approved by the quality control department—available to ensure that containers are checked or tested and meet their specifications before being filled.

9. Ensure processing operations are covered by master formulae. These must be prepared by, and subject to independent checks by, people having the qualifications described under section C.02.006.

10. Write master formulae, master production documents and/or master filling documents to ensure 100% of label claim and include:
    a. the name of the product
    b. the name and concentration of components, including acceptable tolerances
    c. the filling sequence of components
    d. the fill pressure or weight of components (compressed gases)
    e. in-process and final quality control requirements

11. Before you start any processing operation, take and document all necessary steps to ensure that your work area and equipment are clean. They should be free from any raw materials, products, product residues, labels or documents not required for the current operation.

12. Make sure manufacturing and filling records contain all information related to the manufacturing and filling of each batch of medical gas, including:
    a. in-process quality control requirements
    b. equipment used (if multiple systems are used for same product)
    c. a mark that is unique to the individual, or the initials of personnel involved in the activity
    d. a name for each raw material in a mixture, and references to the relevant specification(s)
13. Include the following in completed manufacturing documents:
    a. appropriate check to ensure the containers have been filled
    b. actual results of the quality checks performed
    c. batch or lot number, receiving number or laboratory control number for each raw material in a mixture
    d. a mark that is unique to the individual, or the initials of personnel involved in the preparation of the mixture
14. You may add deliveries of bulk gas to bulk storage tanks containing the same gas from previous deliveries. In this case, do one of the following:
    a. Test a sample of the delivered bulk gas before adding it to the storage tank and ensure it is satisfactory.
    b. 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. You may take the sample from a sampling line or from the first container filled, provided that the sampling, distribution and filling lines have been properly purged before sampling.
    c. If the bulk gas is a mixture, test to verify each component.
15. 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.
16. Make sure your written instructions ensure that:
    a. Your quality control personnel or qualified replacements record their initials in the filling logs.
    b. You assign a lot number for each medical gas, and it appears on each container. You don’t have to include the lot number on each bulk transport container,

storage tank filled, and container filled at curbside as long as you document traceability.

c. You control the filling of high pressure cylinders either by mass, or by monitoring the pressure and the temperature on the wall of cylinders. You may verify correct fill by referring to either a temperature/pressure chart or a target mass chart.

d. During manifold filling sequences, you perform a heat of compression check on the exterior surface of each cylinder to demonstrate proper filling, where needed.

e. You conduct a leak test on each container during filling. You must 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. You must conduct a second leak test on each container after filling to detect valve outlet leaks. Leak test solutions that can cause corrosion or leave films—such as soap—should not be used.

f. You properly quarantine filled containers until released by the quality control department.

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

17. Follow filling as quickly as possible by labelling. If labelling is delayed, take measures to ensure that no mix-ups or mislabelling can occur.

    a. Document and reconcile labels withdrawal.

    b. Control labelling operations by 100% verification. Document verifications.

    c. Document labelling operations.

    d. Whenever possible, attach samples of the printed packaging materials used (including specimens bearing the batch number) and any additional overprinting to packaging orders.

18. 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 personnel. You may segregate products by cylinder colour if the personnel involved are well trained. You must have other measures in place to segregate quarantined and released cylinders.

19. After filling, fit cylinder post valves with covers to protect the outlets from contamination. Fit cylinders and cryogenic vessels with tamper-evident seals or devices.

20. Store materials and labels used to identify containers in a limited access area, restricted to designated personnel.

21. Destroy outdated or obsolete materials and labels. Record their disposal.

22. Only release medical gases after your quality control department has approved them.

23. Monitor water used for cooling during compression of air for microbial quality when in contact with the medical gas.

Annual product quality review

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

25. Your quality control department should ensure that the annual product quality review is performed in a timely manner and is accurate. 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 one annual product quality review instead of one at each individual site. APQR reports must be available at each site.

26. Where required, you should have an agreement in place between the various parties involved in the annual product quality review (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.

27. Your quality control department should evaluate the results of this review, and assess whether corrective and preventative action or any revalidation should be undertaken. Document reasons for any corrective actions. Complete corrective and preventative actions in a timely and effective manner. You should have procedures for the ongoing management and review of these actions, and review how effective your procedures are during self-inspection.

C.02.012

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

(a) a system of control that permits complete and rapid recall of any lot or batch of the drug that is on the market; and

(b) a program of self-inspection.

(2) Every fabricator and packager/labeller and, subject to subsections (3) and (4), every distributor referred to in 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) 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 are expected to be able to recall to the consumer level if needed. More guidance on recalls can be found in *Recall Policy (POL-0016)*.

This regulation also requires fabricators, packagers/labellers, distributors, importers, and wholesalers to maintain a program of self-inspection. The purpose of self-inspection is to evaluate whether all aspects of production and quality control comply with GMPs. A self-inspection program detects any shortcomings in the implementation of GMPs and recommends corrective actions.

Medical gases offered for sale in Canada—whether they are produced in Canada or imported—must meet the requirements of Part C, Division 2 of the Food and Drug Regulations (the 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 the parties involved, clearly establishing the duties of each party.

Interpretation

1. You must have a written recall system in place to comply with section C.01.051 of the Regulations. It must include the following:
    a. Notify Health Canada of the recall.
    b. Take prompt action to recall a medical gas suspected or known to be defective, according to a pre-determined plan. The procedures to be followed are in writing and known to all concerned.

c. Identify the person(s) responsible for initiating and co-ordinating all recall activities.

d. You must be able to carry out your recall procedure at any time, during and outside normal working hours.

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

f. Your distribution records must enable tracing of medical gases, including any medical gases that are in transit.

g. Assess and record the progress and effectiveness of a recall at regular intervals, and issue a final report (including a final reconciliation).

h. Identify recalled medical gases and store them separately in a secure area until their disposition is determined.

i. Notify all Canadian and foreign establishments involved in the fabrication, distribution, or importation of the recalled medical gas.

2. 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.

   a. You must have a comprehensive written procedure that describes the functions of the self-inspection program.

   b. Your self-inspection team must include personnel who are suitably trained and qualified in GMP.

   c. You must carry out periodic self-inspections.

   d. Senior company management must review reports on the findings of the inspections and on corrective actions. Corrective actions are implemented in a timely manner.

3. To ensure compliance of contractors performing fabrication and packaging/labelling:

   a. You must have a written agreement covering the fabrication or packaging/labelling arranged among the parties involved. The agreement must specify the responsibilities of each party relating to the fabrication or packaging/labelling and control of the product.

      i. Technical aspects of the agreement must be drawn up by qualified personnel who are knowledgeable in pharmaceutical technology and GMP.

      ii. The agreement permits the distributor or importer to audit the facilities of the contractor.

      iii. The agreement clearly describes, as a minimum, who is responsible for:

- buying, sampling, testing and releasing materials
- undertaking production, quality and in-process controls
- validating processes

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

v. The agreement 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.

vi. The agreement describes the handling of raw materials, packaging materials, in-process medical gas, bulk medical gas, and finished products if they are rejected.

b. 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.

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

d. 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.

i. 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.

ii. If you are an importer of bulk gases and finished products fabricated, packaged/labelled or tested at a foreign site, you must meet the requirements described in Health Canada's document: *Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080)*. The foreign site must be listed on your establishment licence.

Quality control department

C.02.013

(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

Quality control is the part of GMP concerned with sampling, specifications and testing. It also includes the organization, documentation and release procedures that ensure that the proper tests are actually carried out. This ensures that raw materials and packaging materials are not released for use—and products are not released for sale or supply—until their quality has been judged to be satisfactory.

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

Manufacturing and quality control personnel share the same goal of assuring 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 considered fundamental. The rationale for the requirement that the quality control department be supervised by qualified personnel is outlined under the section C.02.006.

Interpretation

1. If you are a fabricator, packager/labeller, distributor, importer or wholesaler, you must have a person on site responsible for making decisions about quality control requirements. At locations with two or fewer operations staff available, the manufacturing and quality control person may be the same, as long as:
    a. it is impossible to have distinct organizational units on site
    b. chances of error are eliminated
    c. the reporting relationship is different when the employee performs quality control functions and when they perform fabrication or packaging/labelling activities
    d. the employee is fully aware of his/her dual role, clearly understands responsibilities and line authority, and acts accordingly
2. The quality control department must have true and effective access to equipment and facilities for inspecting and testing.

C.02.014

(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 may be made available for further use in fabrication or for sale unless the person in charge of the quality control department approves the further use or the sale.

(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 use or further sale.

(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 products. It is very important that adequate controls be exercised by this department in order to guarantee the quality of the end product. To maintain this level of quality, it is also important to examine all returned medical gases.

Interpretation

1. The head of your quality control department (or an authorized alternate) must sign and date all decisions made by the quality control department, pursuant to section C.02.014.

2. 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.

3. Evaluate deviations and borderline conformances according to a written procedure. Document the decision and rationale. Where appropriate, conduct trend analysis on batch deviations.

4. 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. Document the rationale.

5. Destroy finished products returned from the market, unless your quality control department determines that their quality is satisfactory. You may consider returned goods for resale only after they have been assessed according to a written procedure. In your assessment, you must consider the reason for the return, the nature of the product, the storage and transportation conditions, the product's condition and history, and the time elapsed since it was originally sold. Maintain records of any action taken.

C.02.015

(1) All fabrication, packaging/labelling, testing, storage, and transportation methods and procedures that may affect the quality of a drug shall be examined and approved by the person in charge of the quality control department before their implementation.

(2) The person in charge of the quality control department shall cause to

be investigated 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 are an indicator of 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 laboratory 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 is responsible for the following:

1. The person in charge of your quality control department (or a designated alternate who meets the requirements described under section C.02.006, as applicable to the activity) must sign and date all decisions made pursuant to section C.02.015.

2. You must ensure that guidelines and procedures are in place and implemented for storage and transportation conditions. Filled gas cylinders and home cryogenic vessels should be protected during transportation and delivered to customers in a clean state, compatible with the environment in which they will be used.

3. Tests must be performed by a lab that meets all relevant GMP requirements. Ensure that:

    a. Lab facilities are designed, equipped and maintained to suit the testing and approval (or rejection) of raw materials, medical gases and containers.

    b. The individual in charge of the lab is qualified in accordance with C.02.006, or reports to a person having these qualifications.

    c. There are enough lab personnel who are qualified to carry out the work they undertake.

    d. Lab control equipment and instruments are suited to the testing procedures undertaken. Equipment and records are maintained as per the interpretations under C.02.005.

    e. Computerized systems are validated, and spreadsheets are qualified.

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

        i. Have procedures in place to describe the steps to be taken as part of the investigation.

        ii. In the case of a clearly identified lab or statistical error, you may invalidate the original results and repeat the test. Keep the original results and record an explanation.

        iii. 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 in the procedure.

        iv. Report all valid test results (both passing and suspect) and consider them in batch release decisions.

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

    g. Ensure systems and procedures are in place so that lab records are reliable, complete and accurate.

    h. Ensure that all test results that could affect the quality, safety or efficacy of the drug are reported, reviewed and assessed appropriately.

4. Review all complaints and other information about potentially defective products 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.

5. Establish a change control system to provide for ongoing process optimization and a continuing state of control. Your quality control department must document, evaluate and approve all changes, identifying them with the appropriate effective date. Any significant change may require re-validation.

Packaging material testing

C.02.016

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

(2) No lot or batch of packaging material shall be used in the packaging of a drug unless the lot or batch of packaging material complies with the specifications for that packaging material.

(3) The specifications referred to in subsections (1) and (2) shall

(a) be in writing;

(b) be acceptable to the Director who shall take into account the specifications contained in any publication mentioned in *Schedule B* to the *Act*; and

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

Rationale

Medical gas quality is directly dependent on packaging quality. When a medical gas is presented in an improper container, the entire effort put into manufacturing control is wasted. Packaging materials must be tested or examined to ensure materials are of good

quality before being used to package medical gases. Because medical gas containers are returned and reused, inspection and testing becomes even more important.

Interpretation

1. Examine containers carefully against their specifications before filling.

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

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

    b. a check to determine that old batch labels (with lot numbers and identification) and other damaged labels have been removed

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

    c. venting or blowing down to atmospheric pressure if any gas is present (or inverting and draining the gas)

    d. an odour or sniff test to check for foreign gas or odour

    e. a check to see if the container re-qualification has been conducted as required Each container must be coded (cylinder marking) to show the date of the last hydrostatic test:

        i. Steel cylinders must be re-qualified every five years, unless a "*" follows the testing date (meaning the cylinder may be re-qualified every 10 years).

        ii. Aluminum cylinders must be re-qualified every five years.

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

        iv. The interior of cylinders must be visually examined at regular intervals (usually when re-qualification is performed).

    f. 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)

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

3. Perform checks on cryogenic vessels before filling. The required pre-fill checks are usually outlined in the manufacturer's manual supplied with each cryogenic vessel. At a minimum, you must do:
    a. an external vessel check
    b. a check of all inlet and outlet connections
    c. a label check
4. Examine cryogenic vessels for Transport Canada markings. Ensure that the pressure relief device on the unit is the right kind for its intended use.
5. Make sure your specifications state that each container must be reserved for a specific type of medical gas and be uniquely identified (for example, using a specific colour).
6. Check gauges on containers that show volume or quantity to ensure proper operation.
7. Quarantine containers failing above checks and tests to prevent their use.
8. Document examination and testing.

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

9. Have a system to ensure the traceability of cylinders, cryogenic vessels and valves.

C.02.017

(1) The examination or testing referred to in section C.02.016 shall be performed on a sample taken

(a) after receipt of each lot or batch of packaging material on the premises of the person who packages a drug; or

(b) subject to subsection (2), before receipt of each lot or batch of packaging material on the premises of the person who packages a drug, if

i. that person

(A) has evidence satisfactory to the Director to demonstrate that packaging materials sold to him by the vendor of that lot or batch of packaging material are consistently manufactured in accordance with and consistently comply with the specifications for those packaging materials; and

(B) undertakes periodic complete confirmatory examination or testing with a frequency satisfactory to the Director,

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

1. This section applies in the event that your containers are tested at a location other than where the filling takes place.

2. Make sure conditions of transportation and storage prevent changes to the characteristics of the packaging material. To show these conditions have been met, you must have standard operating procedures and records available that contain the following:

    a. the type of packaging to be used

    b. labelling requirements

    c. mode of transportation

    d. the type and seal of package

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

Finished product testing

C.02.018

(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 and/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

1. 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).
    a. Written specifications must include:
        i. a description of the medical gas, including all properties and qualities (such as identity, purity and potency)
        ii. 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)
        iii. the name or identification mark that will be used for each medical gas throughout the processing operation
    b. 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.
2. You must validate test methods, and document the results. You should conduct method transfer studies when needed.

You can find guidance for validating particular types of methods in the International Conference on Harmonization (ICH) document *Q2(R1) Validation of Analytical Procedures: Text and Methodology*, or in any standard listed in Schedule B to the Act.

3. You must test each medical gas to ensure it meets its specifications. You must record test results in a proper document, clearly and concisely.
    a. For a given filling operation of a single gas, you must test a representative number of containers to specification (usually one filled container from each manifold filling sequence).

b. For high pressure containers filled individually and manually, you must test one filled container per uninterrupted filling sequence. If the filling sequence is interrupted, you must perform additional testing.

c. For mixtures of two gases, you must test every cylinder to its specification for one gas (usually the active ingredient). Then you must also perform an identity test for the other gas on one cylinder from the manifold filling sequence.

d. For mixtures containing more than two gases, you should test every cylinder to specification for all but one of the gases. Then you should test one cylinder from each manifold filling sequence for the identity of the remaining gas.

e. For a mixture of two 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 one cylinder per filling sequence or manifold.

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

5. 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.

6. 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.

7. Ethylene oxide is carcinogenic. So 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" and 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.

8. 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.

1069

C.02.019

(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 Director 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 Director, and

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

(2) 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 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

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

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

Sites holding a Canadian establishment licence

2. If you are a distributor of finished products 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

3. If you are an importer of finished products fabricated, packaged/labelled and tested at recognized buildings authorized by a Regulatory Authority (as 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 drug received to show you comply with specifications. The batch certificate must be in the format agreed on by Mutual Recognition Agreement (MRA) partners. Re-testing, including identity testing, is not required when the drug is fabricated, packaged/labelled and tested in an MRA country.

Sites in non-MRA countries

4. 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:
    a. 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 see *Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080)*.

b. 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 of analysis must show actual numerical results and refer to the product specifications and test methods used.

c. You must perform complete confirmatory testing on at least one lot per year per fabricator. You must choose products on a rotational basis.

d. 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.

5. 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:

   a. re-evaluation of GMP compliance

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

6. 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 labeled dedicated bulk tanks of imported medical gas if the following criteria are met. :

   a. Ensure the foreign site is listed on your Drug Establishment Licence.

   b. Use only labeled dedicated bulk tanks with traceability identification. An attestation must be available to declare tank dedication.

   c. Ensure that:

      i. you verify the certificate of analysis and certificate of manufacture before Quality Control review for release to customer

      ii. the foreign supplier is qualified by a vendor certification program

      iii. periodic confirmatory testing is performed

Unique identifier principles are not applicable for mixed gases.

Records

C.02.020

(1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(*b*) and importer shall maintain 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, master production documents for the drug;

(b) evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and stored in accordance with the procedures described in the master production documents;

(c) evidence that the conditions under which the drug was fabricated, packaged/labelled, tested and stored are in compliance with the requirements of this Division;

(d) evidence 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 Director, 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.

1136

C.02.021

(1) All records and evidence on the fabrication, packaging/labelling, finished product testing referred to in section C.02.018 and storage of a drug in dosage form that are required to be maintained under this Division shall be retained for one 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 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 person's 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.

1137

1138

C.02.022

(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 one 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 and 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; or

(b) in any other case, one year after the expiration date of the lot or batch.

1139

C.02.023

(1) On receipt of a complaint or any information respecting the quality of a drug or its deficiencies or hazards, every fabricator, packager/labeller, wholesaler, distributor referred to in paragraph C.01A.003 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.

1140

C.02.024

(1) Every fabricator, packager/labeller, distributor referred to in section C.01A.003, importer and wholesaler shall

(a) maintain records of the results of the self-inspection 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.

1141

C.02.024.1

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.

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Rationale (C.02.020 to C.02.024.1)

Good documentation is a key part of any quality assurance system. GMP documentation aims to define the specifications for all materials and methods of fabrication, packaging/labelling and control. This ensures authorized staff have all the information they need to decide whether or not to release a lot of a medical gas for sale. It also provides an audit trail that will allow investigation of the history of any lot or batch suspected to be defective.

Developing good record systems allows you to maintain evidence that medical gases have been produced and packaged/labelled under proper conditions. For medical gases imported from another country, information and evidence must show they are produced and packaged/labelled as carefully as those in Canada are required. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. The various types and documents used should be fully defined in the pharmaceutical quality system. Records must be reliable, complete, accurate and consistent.

Interpretation (C.02.020 to C.02.024.1)

1. 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.

2. 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 change should still allow the original information to be read. Where appropriate, record the reason for the change.

3. You may maintain records 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.

4. You may use an electronic signature instead of a handwritten signature. But this system must be evaluated and tested for security, validity and reliability. You must keep records of those evaluations and tests, and document validation of electronic signature identification systems.

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

6. Your records must include a copy of master filling and/or master production documents that are verified, dated and signed. Each step of the process must be documented, as it 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.

7. 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.

8. You must have documentation to support the expiry date of a medical gas. For very stable gases that have been used for a long time and packaged in containers that have also been used for a long time, bibliographic data is enough. For gas mixtures, the expiry date should be based on validation studies related to physical aspects (such as the rate of stratification).

9. The following documents must be maintained by the fabricator, packager/labeller, wholesaler, distributor (C.01A.003) and importer of a medical gas, as they relate to operations in Canada:

    a. distribution records for all sales of medical gas, including professional samples (records must be easily accessible to allow a complete and rapid recall of any lot or batch of a drug, but you do not have to track by lot number)

    b. records of complaints or other information you receive relating to quality, deficiencies or hazards of a medical gas, and any follow-up investigations and corrective actions taken

    c. records of the results of your self-inspection program, and any actions taken

10. The fabricator of medical gas mixtures must maintain these documents:

    a. written specifications for the raw materials

    b. results of the raw material testing

    c. sources of the raw materials supplied

11. The packager/labeller must maintain these documents:

    a. written specifications for the packaging materials

    b. results of the packaging material examinations or testing

    c. sources of the packaging materials supplied

d. 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 before filling
    - checks for functionality on valves on cylinders
    - records of any checks

12. The fabricator and packager of medical gases must maintain records about the operation of the sanitation program required under section C.02.007.

13. You must generally retain records required under sections C.02.021(1), C.02.022 and C.02.023 for at least one year past the expiration date of the drug. For medical gases that do not require an expiration date, you must retain records required under sections C.02.021(1), C.02.022 and C.02.023 for at least five years from the date of fabrication or packaging/labelling. Gas chromatogram charts are considered to be records/evidence of testing and must be maintained for five years from the date of filling.

14. You must maintain records detailing the qualifications/experience of any consultant employed for GMP purposes, along with the services that each consultant provides.

15. Maintain records of all personnel employed in GMP activities, including:
    a. organization charts
    b. each person's title, job description, responsibilities, qualifications, experience and training
    c. the name(s) of each person's designated alternate(s)

Medical gases

C.02.030

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

Sections C.02.026 and C.02.029 also do not apply to medical gases.

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Appendices

Appendix A – Glossary

Acronyms

DIN: Drug Identification Number

GMP: Good Manufacturing Practices

ICH: International Council on Harmonization

MRA: Mutual Recognition Agreement

NF: National Formulary

PIC/S: Pharmaceutical Inspection Cooperation/Scheme

SOP: Standard Operating Procedure

USP: United States Pharmacopeia

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/Regulations prevails.

Batch – 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 exported within the framework of a mutual recognition agreement and in which the fabricator:

a. identifies the master production document for the drug and certifies that the lot or batch has been fabricated, packaged/labelled and tested in accordance with the procedures described in that document;
b. provides a detailed description of the drug, including
    i. a statement of all properties and qualities of the drug, including the identity, potency and purity of the drug, and
    ii. a statement of tolerances for the properties and qualities of the drug;
c. identifies the analytical methods used in testing the lot or batch and provides details of the analytical results obtained;
d. sets out the addresses of the buildings at which the lot or batch was fabricated, packaged/labelled and tested; and
e. certifies that the lot or batch was fabricated, packaged/labelled and tested in accordance with the good manufacturing practices of the regulatory authority that has recognized those buildings as meeting its good manufacturing practices standards." (Food and Drug Regulations, 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 (a) to facilities, materials, equipment and/or processes used in the fabrication, packaging and testing of drugs, or (b) that may affect the operation of the quality or support system.

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

Cryogenic vessel – A static or mobile 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 – "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." (Food and Drug Regulations, A.01.010)

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

a. a distributor of an active ingredient or of a drug in dosage form that is listed in *Schedule C* to the Act
b. a distributor of a drug for which the distributor holds the drug identification number (Food and Drug Regulations, C01A.003)

Dosage form – A drug product that has been processed and is now in a form that can be administered in individual doses, unless otherwise defined in the Food and Drug Regulations.

Fabricate – "To prepare and preserve a drug for the purposes of sale." (Food and Drug Regulations, 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.

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." (Food and Drug Regulations, C.01A.001)

Liquefied gas – A gas that has a critical temperature above 20^0C, which remains as a liquid in the container when under pressure.

Lot – See Batch.

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

Manifold filling sequence – A filling sequence of many containers at one 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), a device licence for classes II, III and IV medical devices, a natural product number (NPN), or a homeopathic DIN (DIN-HM).

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

Master formula – A document or set of documents specifying the raw materials with their quantities and the packaging materials, a detailed description of the procedures and precautions required to produce a specified quantity of a finished product, and the processing instructions (including in-process controls).

Master production documents – Documents that include specifications for raw material, for packaging material and for packaged dosage form; master formula (including composition and instructions as described in the definition above), sampling procedures, and critical processing related standard operating procedures (SOPs), whether or not these SOPs are specifically referenced in the master formula.

Medical gas – "Any gas or mixture of gases manufactured, sold or represented for use as a drug." (Food and Drug Regulations, C.02.002)

MRA country – "A country that is a participant in a mutual recognition agreement (MRA) with Canada." (Food and Drug Regulations, C.01A.001)

Mutual recognition agreement – "An international agreement that provides for the mutual recognition of compliance certification for good manufacturing practices for drugs." (Food and Drug Regulations, C.01A.001)

Package/label – "To put a drug in its immediate container or to affix the inner or outer label to the drug." (Food and Drug Regulations, C.01A.001)

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 and 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.

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.

Reconciliation – A comparison between the amount of product or materials theoretically produced/used and the amount actually produced/used, with allowance for normal variation.

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 that may take enforcement action to ensure that drugs marketed within its jurisdiction comply with legal requirements. (Food and Drug Regulations, C.01A.001)

Standard operating procedure – A written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (for example: equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documents.

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

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

Validation – A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance 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) 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); (b) an active ingredient; or (c) a narcotic as defined in the Narcotic Control Regulations." (Food and Drug Regulations, C.01A.001(1)). As per the new definition of wholesaler in Part C, Division 1A of the Food and Drug Regulations, agents, brokers and traders are considered wholesalers.

Appendix B – References

Food and Drugs Act
http://laws-lois.justice.gc.ca/eng/acts/f-27/

Food and Drug Regulations
http://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html

Good Manufacturing Practices Guidelines (GUI-0001)
www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php

Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002)
www.hc-sc.gc.ca/dhp-mps/compli-conform/licences/directives/gui-0002-eng.php

Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080)
www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0080-eng.php

ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology
www.ich.org/products/guidelines/quality/quality-single/article/validation-of-analytical-procedures-text-and-methodology.html

ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
www.ich.org/products/guidelines/quality/quality-single/article/good-manufacturing-practice-guide-for-active-pharmaceutical-ingredients.html

Narcotic Control Regulations
http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.%2C_c._1041/

PIC/S GMP Annexes – Annex 6 – Manufacture of Medicinal Gases
http://www.picscheme.org/publication.php?download&file=cGUtMDA5LTEyLWdtcC1ndWlkZS14YW5uZXhlcy5wZGY_

Product Recall Procedures
www.hc-sc.gc.ca/dhp-mps/compli-conform/recall-retrait/proces-eng.php

Selection and Use of Cylinders, Spheres, Tubes and Other Containers for the Transportation of Dangerous Goods, Class 2 (CAN/CSA B-340)
www.tc.gc.ca/eng/tdg/moc-cylinder-csab340-351.html

Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)
www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui_29-eng.php

Appendix C – Frequently asked questions

C.02.018

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

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

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

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

   You should have documentation available showing that the specific lot of oxygen has been produced by the air liquefaction process.

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

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

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

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