

CGA M-5—2013

**GUIDE FOR HOME RESPIRATORY
CARE FIRMS FILLING OR
DISTRIBUTING LIQUID OXYGEN USP**

SECOND EDITION



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NOTE—Technical changes from the previous edition are underlined.

NOTE—Appendices A and B (Informative) are for information only.

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Contents	Page
1 Introduction.....	1
2 Scope	1
3 Definitions.....	2
4 Key laws, regulations, and guidelines	4
4.1 Overview.....	4
4.2 United States federal regulations	5
4.3 Canadian federal regulations.....	6
4.4 Canadian provincial regulations	7
5 Health and safety considerations	8
5.1 General requirements for health and safety	8
5.2 Personal protective equipment	8
6 Standard operating procedures.....	8
7 Organization/personnel	8
7.1 Organization	8
7.2 Personnel qualifications.....	9
7.3 Personnel responsibilities.....	10
7.4 Consultants.....	10
8 Buildings, facilities, and vehicles	10
8.1 General requirements.....	10
8.2 Design and construction features	11
8.3 Lighting.....	11
8.4 Maintenance	11
8.5 Security and limited access areas.....	11
8.6 Washing and toilet facilities	12
8.7 Sanitation.....	12
9 Equipment	12
9.1 Equipment design, size, location, and construction.....	12
9.2 Product filling equipment	13
9.3 Control systems.....	14
9.4 Equipment cleaning and maintenance, and cleaning procedures.....	14
9.5 Automatic, mechanical, and electronic equipment.....	14
9.6 Computers and electronic equipment.....	14
9.7 Analytical equipment	15
10 Control of components	15
10.1 General requirements.....	15
10.2 Liquid oxygen USP in storage tanks.....	15
10.3 Vehicle mounted vessel and portable liquid cryogenic containers filled from an on-site home respiratory care storage tank	16
10.4 Third party filled portable liquid cryogenic containers and vehicle mounted vessels	16
10.5 Certificate of analysis for vendor supplied product.....	17
10.6 Rejected liquid oxygen USP	17
11 Control of containers and closures	17
11.1 General requirements.....	17
11.2 Inspection and approval of containers and closure system.....	17
11.3 Vehicle mounted vessel.....	18
11.4 Portable liquid cryogenic containers.....	18
11.5 Cryogenic home vessels	19
11.6 Rejected drug product containers and closures	19

12	Control of the packaging and labeling of vessels and containers intended for liquid oxygen	19
12.1	Label receipt, storage, and inventory records	19
12.2	Label inspection, application, and batch records.....	20
12.3	Lot number	20
12.4	Expiration dating.....	20
13	Production and process controls	20
13.1	Control of the filling, testing, and release of supply vessels by the home respiratory care firm	20
13.2	Control of the filling, testing, and release of portable liquid cryogenic containers and cryogenic home vessels filled by the home respiratory care firm for patient use	21
13.3	Control and release of vehicle mounted vessel, portable liquid cryogenic containers, and cryogenic home vessel filled for the home respiratory care firm by a third party	22
14	Warehousing and distribution of homecare oxygen	22
14.1	Warehousing	22
14.2	Distribution.....	22
15	Laboratory controls.....	23
15.1	General requirements.....	23
15.2	Specifications	23
15.3	Sampling and testing plans	23
15.4	Calibration of testing equipment.....	24
15.5	Testing and release for distribution	25
15.6	Stability testing and expiration dating.....	25
16	Records and reports.....	25
16.1	General requirements.....	25
16.2	Complaint records	25
16.3	Record retention.....	26
16.4	Annual product review/internal audit	26
17	References	26

Appendices

Appendix A—Sample PLCC liquid oxygen filling log (Informative)	28
Appendix B—Sample vehicle mounted vessel filling record (Informative)	30
Appendix C—Sample cryogenic home vessel filling log (Informative)	32

Appendices Tables

Table A-1—Sample PLCC liquid oxygen filling log	29
Table B-1—Sample vehicle mounted vessel filling record	31
Table C-1—Sample cryogenic home vessel filling log	33

1 Introduction

The information in this guide is an aid for complying with the applicable regulations of the U.S. Food and Drug Administration (FDA) and Health Canada for filling, packaging, testing, labeling, and holding liquid oxygen USP by home respiratory care (HRC) firms to ensure that product is manufactured and distributed in accordance with United States and Canadian current good manufacturing practices (CGMP) and meets all United States Pharmacopoeia (USP) specifications. See the *United States Pharmacopoeia* and *National Formulary (USP–NF)* [1].¹

This publication describes the processes, procedures, and documentation typically recognized by the HRC industry as the minimum regulatory requirements needed for compliance.

2 Scope

This publication is intended to address operations typical to an HRC firm and is not all inclusive. It is primarily intended for firms engaged in the filling (manufacture) and distribution of liquid oxygen USP to patients at their residences. Portions of this publication may apply to those HRC firms that also distribute other compressed medical gases (CMG). This publication includes the minimum regulatory requirements that shall be described in an HRC firm's written standard operating procedures (SOP) for the firm to receive, fill, test, and distribute liquid oxygen USP and includes the following:

- establishment and responsibilities of the quality control unit (QCU);
- qualifications of the person(s) performing and supervising the receipt, filling, testing, release, and distribution of liquid oxygen USP;
- quality records;
- building and facility requirements (including vehicles);
- manufacturing equipment design and maintenance;
- test equipment;
- record and report requirements;
- use of computer and other electronic equipment;
- receipt and testing of vendor-supplied product into the HRC's storage tank;
- receipt and testing of vendor-supplied product into vehicle-mounted vessels (VMVs) or other large cryogenic containers;
- receipt and testing of vendor-supplied product into cryogenic home vessels (CHVs);
- HRC filling and testing of VMVs and/or large cryogenic containers from an HRC company's storage tank;
- HRC filling and testing CHVs; and
- labeling requirements.

This publication is not applicable to the receipt, testing, release, and distribution of high pressure oxygen filled by HRC firms. Firms engaged in filling high pressure medical gas cylinders (either gas-to-gas or liquid-to-gas) should refer to [CGA M-2, General Guide for the Manufacture of Medical Gases Classified as Drugs](#) [2].

This publication is typically not applicable to non-HRC firms unless those firms are engaged in activities similar to those of HRC firms. Non-HRC firms engaged in oxygen USP liquid-to-liquid filling for home care use should also refer to [CGA M-2](#) for additional guidance and potential additional regulatory requirements [2].

¹ References are shown by bracketed numbers and are listed in order of appearance in the reference section.

3 Definitions

For the purpose of this publication, the following definitions apply.

3.1 Air liquefaction

Process by which oxygen is manufactured, which consists of separating air into its component parts by cryogenic distillation.

3.2 Assay

Analytical test used to determine the strength of the component of interest.

NOTE—An example of an assay is testing for percent oxygen.

3.3 Batch

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

3.4 Bulk

CMG contained in stationary, fixed, or permanently mounted vessels.

NOTE—Bulk CMGs can be further processed into finished dosage forms.

3.5 Calibration

Process by which an instrument is checked against and/or adjusted to the known accuracy of a certified standard.

3.6 Certificate of analysis (COA)

Document supplied by the manufacturer that lists the specific analytical results of a shipment of drug product.

3.7 Closures

Portions of the liquid oxygen delivery system that prevent the escape of liquid oxygen from its container, e.g., valves.

3.8 Commingling

Condition that occurs when two or more batches or lots of medical gas product are blended together.

3.9 Compendial test

Specific analytical test contained or referenced in the official drug monograph compendia.

3.10 Component

Ingredient intended for use in the manufacture of a drug product.

3.11 Compressed medical gas (CMG)

Liquefied or vaporized gas alone or in combination with other gases, which is deemed a drug.

NOTE—CMGs include gas(es) recognized in the current, official *USP–NF* or their supplements and gas(es) intended for direct use or as a component of a gas used in the diagnosis, cure, mitigation, treatment, or prevention of diseases in man or animals that achieves its intended purpose through chemical rather than physical means [1].

3.12 Container

Vessel designed and constructed to retain a liquid or gas.

NOTE—A CMG container refers to an insulated vessel capable of storing oxygen in its liquid state at low pressure and at a temperature considerably below that of the ambient conditions.

3.13 Contamination

Matter that can adversely affect the purity and efficacy of oxygen.

3.14 Cryogenic liquid

Refrigerated, liquefied gas having a boiling point colder than -130°F (-90°C) at 14.7 psia (101.3 kPa, abs).²

² kPa shall indicate gauge pressure unless otherwise noted as (kPa, abs) for absolute pressure or (kPa, differential) for differential pressure. All kPa values are rounded off per [CGA P-11, Metric Practice Guide for the Compressed Gas Industry](#) [3].

3.15 Cryogenic home vessel (CHV)

Liquid oxygen containers with a capacity of 60 L or less that are typically used by patients at their residence.

3.16 Cylinder

Pressure vessel designed and constructed to retain a gas or liquid under pressure.

NOTE—For the purpose of this publication, a cylinder refers to an uninsulated vessel capable of storing a CMG at high pressures.

3.17 Distributor

HRC firm that receives fully labeled CMGs including liquid oxygen USP in cryogenic home vessels (CHVs) and does not manipulate this product or the labeling in any way.

3.18 Drug

Substance recognized in the official *USP–NF* or any supplement thereof; substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; substance (other than food) intended to affect the structure of or any function of the body of man or other animals; or substance intended for use as a component of any substances specified in preceding clauses [1].

3.19 Guideline

Nonbinding interpretation of regulations.

3.20 Hand-held oxygen analyzer

Analyzer that operates on the fuel, electrochemical, galvanic, or polarographic cell principle.

NOTE—When properly calibrated, hand-held analyzers only provide a specific oxygen identification test result.

3.21 Home respiratory care (HRC) firm

Company that supplies liquid or gaseous oxygen to patients at their residences.

NOTE—Although HRC firms may also perform various manufacturing steps via liquid-to-liquid, gas-to-gas, or liquid-to-gas filling, HRC firm refers to a firm filling or distributing liquid oxygen.

3.22 Identity (test)

Test to determine that the product is oxygen.

3.23 In-process

Manufacturing operations that are not yet complete.

3.24 Leak check

Method for determining the integrity of a CMG closure system.

3.25 Lot

Batch or a specific identified portion of a batch having uniform character and quality within specified limits.

3.26 Lot number

Distinctive combination of letters, numbers, or symbols from which the complete history of the manufacture and distribution can be determined.

3.27 Manufacturer

Individual or firm that fills liquid oxygen USP via liquid-to-liquid filling operations.

3.28 Misbranded

Condition in which the label or labeling of the CMG does not clearly identify the CMG, does not bear all required information, bears the required information in an inconspicuous manner, or gives information that is misleading, inaccurate, incomplete, or dangerous.

NOTE—For additional information see Section 502 of the Federal *Food, Drug and Cosmetics Act* [4].

3.29 Monograph

Specifications and test methods for CMGs found in the *USP–NF* [1].

3.30 Out of specification (OOS)

Test result that falls outside the acceptance criteria established in either an official compendia or by the manufacturer.

3.31 Portable liquid cryogenic container (PLCC)

TC/DOT 4L insulated liquid container specified for over-the-road shipments of product that exceeds 25.3 psi (174.4 kPa) in accordance with Title 49 of the U.S. *Code of Federal Regulations* (49 CFR) Part 173.320 [4].

3.32 Prescription

Written or oral order provided by a licensed practitioner.

3.33 Production record

Quality record used to record significant CGMP process steps.

3.34 Quality control unit (QCU)

Person or organizational element designated by the firm as responsible for the duties relating to quality control.

3.35 Quarantine

Segregation and identification of CMGs or materials pending a decision on their subsequent disposition.

3.36 R

Symbol signifying a prescription is required and may also be represented by the statement, "Rx only".

3.37 Residual

CMG product that remains in a container.

3.38 Segregated

Set apart and uniquely identified.

NOTE—Segregation can be by product type, quality control status, quarantine, etc.

3.39 Storage tank (stand tank)

Container mounted on a stationary foundation that is designed to store refrigerated liquid or cryogenic liquid.

3.40 Tare weight

Weight of an empty cylinder and associated valve components.

3.41 Strength

Concentration and/or potency of a drug.

3.42 Validation

Documented evidence providing a high degree of assurance that a specific process consistently produces a product that meets its predetermined specifications and quality attributes.

3.43 Vehicle mounted vessel (VMV)

Vessel that is permanently mounted to a vehicle, e.g., inside a van.

NOTE—VMVs do not include bulk cryogenic trailers.

3.44 Vent

Process of releasing product from a container or filling system.

4 Key laws, regulations, and guidelines**4.1 Overview**

The Federal *Food, Drug and Cosmetics Act* (United States) and the *Food and Drugs Act* (Canada) define prohibited acts and penalties and contain specific information for drugs and devices as well as general administrative provisions [5, 6]. All CMG manufacturers shall comply with these Acts.

4.2 United States federal regulations

4.2.1 Title 21, *Code of Federal Regulations* (21 CFR)

Title 21 of the U.S. *Code of Federal Regulations* (21 CFR) is a body of specific regulations for medical drugs and devices and other products regulated by the FDA. It is important that manufacturers of liquid oxygen be familiar with the following sections of 21 CFR [7].

4.2.1.1 Labeling (Part 201)

U.S. label and labeling requirements are found in 21 CFR Part 201 [7]. Where appropriate, liquid oxygen USP labels shall comply with U. S. Department of Transportation (DOT) and Transport Canada (TC) regulations on proper shipping name, hazard class, and UN number.

CGA C-7, *Guide to the Preparation of Precautionary Labeling and Marking of Compressed Gas Containers*, provides guidance for the preparation of labels for compliance with FDA and DOT/TC regulations including wording addressing hazards, precautions, and first aid statements as well as the required dimensions for markings and required height for certain letters and numbers [8].

4.2.1.2 Guidelines for state licensing of wholesale prescription drug distributors (Part 205)

21 CFR Part 205 provides the minimum standards, terms, and conditions including but not limited to:

- licensing of wholesale prescription drug distributors by state licensing authorities;
- minimum qualifications of firms being licensed;
- minimum qualifications required of personnel employed by a firm engaged in wholesale distribution;
- storage, security, and handling of prescription drugs; and
- establishment and maintenance of prescription drug distribution records.

Typically a state's board of pharmacy or department of health defines licensing requirements. Some states also have additional CGMP requirements.

4.2.1.3 Registration (Part 207)

Part 207 contains the requirements for drug establishment registration and drug product listings.

As of June 1, 2009, FDA no longer accepted drug establishment registration and drug listing information in paper format. For more information regarding the electronic registration and listing system go to the FDA website to obtain the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Drug Establishment Registration and the Drug Listing*, and also consult the Electronic Drug Registration and Listing Instructions (eDRLS) website, www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation [9].

4.2.1.4 Current good manufacturing practices (Parts 210 and 211)

21 CFR Parts 210 and 211 contain the CGMP, which specify the minimum requirements for the manufacture, processing, packaging, or holding of a drug to ensure product safety, identity, strength, quality, and purity [7].

4.2.2 United States Pharmacopoeia and National Formulary

The *USP–NF* contains specifications and official test methods for determining the identity, strength, quality, and purity of medical gases [1].

4.2.3 State regulations

Manufacturers and distributors should contact the appropriate agencies to ascertain any regulations applicable to liquid oxygen USP transfilling or distribution operations.

4.2.4 Hazardous materials transportation

Liquid oxygen USP is considered a hazardous material. It therefore shall be handled and transported in compliance with DOT regulations contained in 49 CFR Parts 300-399 [4].

4.3 Canadian federal regulations

4.3.1 *Food and Drug Regulations, Part C Drugs* [10]

Oxygen is a drug per the definition in the Canadian *Food and Drugs Act* which includes any substance or mixture of substances manufactured, sold or represented for use in the diagnosis, treatment, mitigation, or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals [6].

4.3.1.1 Part C, Division 1, Drug labeling (C.01.003 – C.01.013)

Oxygen sold as a drug in Canada shall be labeled in accordance with the applicable requirements in C.01.003 – C.01.013, which include:

- The proper name of the drug immediately preceding or following the brand name (if there is a one) in a font size not less than one-half the brand name font size. If there is no proper name, use the common name of the drug;
- The standard used for the drug;
- The name and address of the manufacturer of the drug;
- The lot number of the drug unless filled at the patient's residence;
- Adequate directions for use of the drug;
- A quantitative list of the medicinal ingredients of the drug by their proper names or, if they have no proper names, by their common names;
- The expiration date of the drug; and
- The net amount of the drug in the container in terms of weight, measure, or number.

4.3.1.2 Part C, Division 1, Drug identification number (C.01.014)

No manufacturer shall sell a drug in dosage form unless a drug identification number has been assigned for that drug.

4.3.1.3 Part C, Division 1a, Establishment licenses (C.01A.001)

A firm shall have an establishment license to fabricate, package/label, distribute, import a drug; or perform tests including examinations, required under Division 2 of the regulations. No distributor and no importer shall sell a drug unless it is fabricated, packaged/labeled, tested or stored in accordance with the requirements of this division.

- An HRC firm transfilling liquid oxygen USP from one container to another either at the firm's site or at a patient's residence is classified as a drug packager and must obtain a drug establishment license for each of its sites with the Health Products and Food Branch Inspectorate (HPFBI) on an annual basis.
- An HRC firm distributing liquid oxygen USP, under its own name, that is packaged by another company is classified as a distributor and must obtain a drug establishment license as a distributor for each of its sites with the HPFBI on an annual basis.

4.3.1.4 Part C, Division 2, Good manufacturing practices

Health Canada's guidance document, *Good Manufacturing Practices for Medical Gases* (GUIDE-0031), provides interpretation of the good manufacturing practices requirements in the Food and Drug Regulations for medical gases [11].

Good manufacturing practices (GMP) are the part of quality assurance that ensures that drugs are consistently produced and controlled to meet the quality standards appropriate to their intended use, as required by the marketing authorization.

GMP are concerned with both production and quality control. Their basic requirements are as follows:

- Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications;
- Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary;
- All necessary key elements for GMP are provided including:
 - Qualified and trained personnel
 - Adequate premises and space
 - Suitable equipment and services
 - Correct materials, containers and labels
 - Approved procedures and instructions
 - Suitable storage and transport;
- Instructions and procedures are written in clear and unambiguous language;
- Operators are trained to carry out and document procedures;
- Records are made, manually or by instruments, during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented;
- Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form;
- The distribution of the drugs minimizes any risk to their quality;
- A system is available for recalling any batch of drug from sale or supply; and
- Complaints about marketed drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.

4.3.2 *Transportation of Dangerous Goods Act [13]*

Liquid oxygen USP is considered a dangerous good. It therefore must be handled and transported in compliance with the *Transportation of Dangerous Goods Regulations* with respect to proper labeling, shipping name, classification, UN number, vehicle safety marks, and employee training.

VMVs shall meet the requirements of CSA B620, *Highway Tanks and Portable Tanks for the Transportation of Dangerous Goods*, and portable liquid cryogenic containers (PLCCs) shall meet the requirements of CSA B339, *Cylinders, Spheres, and Tubes for the Transportation of Dangerous Goods* [14, 15].

4.4 Canadian provincial regulations

Manufacturers and distributors should contact the appropriate agency to ascertain any regulations applicable to their liquid oxygen USP transfilling or distribution operations.

5 Health and safety considerations

5.1 General requirements for health and safety

Personnel associated with filling or handling liquid oxygen USP shall be trained in the applicable health and safety considerations. The following CGA publications contain relevant health and safety information:

- [CGA P-2.6](#), *Transfilling of Liquid Oxygen Used for Respiration* [16];
- [CGA P-2](#), *Characteristics and Safe Handling of Medical Gases* [17];
- [CGA P-12](#), *Safe Handling of Cryogenic Liquids* [18];
- [CGA AV-8](#), *Characteristics and Safe Handling of Cryogenic Liquid and Gaseous Oxygen* [19];
- [CGA SB-9](#), *Recommended Practice for the Outfitting and Operation of Vehicles Used in the Transportation and Transfilling of Liquid Oxygen Used for Respiration* [20]; and
- [CGA SB-26](#), *Cylinder Connections on Portable Liquid Cryogenic Cylinders* [21].

5.2 Personal protective equipment

To minimize exposure and facilitate response to exposure, a company policy shall be developed to address the use of personal protective equipment (PPE) when handling cryogenic liquids, e.g., gloves, boots, aprons, and face shields, in addition to other precautions regarding suitable wearing apparel. Proper PPE shall be worn while handling liquid oxygen.

6 Standard operating procedures

HRC firms shall develop, approve, implement, periodically review, and maintain SOPs. SOPs shall be in writing and appropriately approved by the firm's quality control unit (QCU). A firm's SOP are the master production and control records for all operations associated with liquid oxygen USP manufacturing and distribution activities.

SOPs shall be current, accessible, and followed by the applicable personnel.

SOPs shall include all medical gas manufacturing procedures, documentation, and quality control activities necessary to meet CGMP requirements. Manufacturing includes processing, labeling, testing, packing, holding, and distributing a CMG. A firm shall comply with its own approved and issued SOP. Any changes or deviations from the SOP shall be documented and justified.

7 Organization/personnel

7.1 Organization

An HRC firm shall maintain a current organizational chart describing the line authority for operations and the QCU reporting structure.

7.1.1 Quality control unit

HRC firms shall establish and maintain a list of current, qualified QCU personnel. The QCU shall have the responsibility and authority to:

- Approve or reject procedures or specifications that have an impact on the identity, strength, quality, and purity of the liquid oxygen USP;
- Approve or reject deviations from approved procedures or specifications;
- Approve or reject suppliers providing components or materials critical to product quality;
- Approve or reject components (liquid oxygen used as a supply for filling containers), containers (vessels) and closures (valves), and any in-process materials critical to product quality;