



CGA M-2—2021 STANDARD FOR THE MANUFACTURE OF MEDICAL GASES CLASSIFIED AS DRUGS

THIRD EDITION



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NOTE—Technical changes from the previous edition are underlined.

NOTE—Appendix A (Informative) is for information only.

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1 Introduction

This publication is a standard for compliance with the applicable regulations of the U.S. Food and Drug Administration (FDA) for the manufacture of compressed medical gases (CMG) classified as drugs as described in Title 21 of the U.S. *Code of Federal Regulations* (21 CFR) [1].¹ It outlines the requirements for manufacturing CMGs classified as drugs; however it may not contain all information necessary to comply with FDA regulations. It is the responsibility of each CMG manufacturer to ensure that their standard operating procedures (SOP) comply with all applicable federal, state, and local regulations.

2 Scope

This publication applies to firms that engage in the filling, repackaging, transfilling, mixing, and/or re-labeling of CMG classified as drugs by the FDA and applicable state agencies. Although it is primarily intended for firms engaged in the CMG manufacturing processes, portions may apply to firms that only distribute CMG classified as drugs.

This publication is intended to address current good manufacturing practice (CGMP) requirements for:

- designated medical gases as defined in Section 575(1) of the Federal *Food Drug and Cosmetic Act* (Act) or combinations thereof; and
- other medical gases as defined in Section 575(2) of the Act that may be approved via a new drug application (NDA) or abbreviated new drug application (ANDA) for which the sponsor has shown through a science based risk management plan that this publication provides appropriate CGMPs [2].

Throughout this standard, the terms CMG, medical gas or medical gases are used to refer to these categories of products.

This publication does not apply to:

- bulk air separation (oxygen, USP and nitrogen, NF) manufacturing and distribution facilities;
- bulk carbon dioxide USP manufacturing and distribution facilities;
- bulk helium USP manufacturing and distribution facilities;
- bulk nitrous oxide USP manufacturing and distribution facilities;

NOTE—For information about bulk medical gases classified as drugs, See CGA M-3, *Standard for the Manufacturer of Bulk Medical Gases* [3].

- refrigerated liquid oxygen USP that is filled at a patient's residence or is filled, repackaged, transfilled, and/or relabeled by home respiratory care companies;
- medical gases classified by FDA as medical devices as defined by the Act [2]; or
- drugs that are defined as Investigational New Drug Applications, e.g., a gas or gas mixture that has never been previously used as a drug, NDAs, or ANDAs by the Act [2].

See the *United States Pharmacopeia and National Formulary (USP–NF)* for information on the USP and NF designations for medical gases [4].

NOTE—Gases such as, diving gases, U.S. Occupational Safety and Health Administration (OSHA) regulated breathing air, aviator's breathing oxygen, although inhaled are not medical gases.

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 **Publication terminology**

3.1.1 **Shall**

Indicates that the procedure is mandatory. It is used wherever the criterion for conformance to specific recommendations allows no deviation.

3.1.2 **Should**

Indicates that a procedure is recommended.

3.1.3 **May**

Indicates that the procedure is optional.

3.1.4 **Will**

Is used only to indicate the future, not a degree of requirement.

3.1.5 **Can**

Indicates a possibility or ability.

3.2 **Technical definitions**

3.2.1 **Adulterated**

Drug product that does not meet all required or claimed standards of purity, strength, identity, or quality, or that contains a foreign substance that can be injurious to health.

NOTE—A drug product not manufactured in accordance with CGMP may also be considered adulterated. See Section 501 of the Act [2].

3.2.2 **Air liquefaction**

Process by which air is separated into its component parts by cryogenic distillation.

3.2.3 **Alternate test method**

Analytical method that is different from those described in the official USP/NF monograph and has been validated to produce results that meet or exceed those achieved using the official USP/NF monograph method.

3.2.4 **Assay**

Analytical test used to determine the strength of the component of interest in either a pure gas or mixture of gases, e.g., percent oxygen.

3.2.5 **Automated analysis**

System in the medical gas filling or testing process that provides for automatic sampling, analysis, recording, and/or storage of required quality control data.

NOTE—An automated analysis system may be considered an electronic record keeping system under 21 CFR Part 11 [1]. It may or may not contain provisions for electronic signatures.

3.2.6 **Balance gas**

Gas used to dilute other gas components.

NOTE—A balance gas can also be defined as a substance or substances other than the active drug that are included in a drug delivery system.

3.2.7 **Batch**

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

NOTE—In a continuous process, a batch corresponds to a defined portion of the production based on time or quantity.

3.2.8 Bulk

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

NOTE—Bulk CMG may be further processed into finished dosage forms.

3.2.9 Calibrate

To check, adjust, or determine by comparison with a certified standard.

3.2.10 Calibration

Process by which an instrument is checked or adjusted to a certified standard.

3.2.11 Calibration check

Process by which an instrument readout is compared to that of a known standard and no adjustment is necessary.

3.2.12 Certificate of analysis (COA)

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

3.2.13 Closures

Element of the drug delivery system that holds the CMG within the containers, i.e., valves.

3.2.14 Commingled

Condition occurring when two or more noncontinuous batches or lots of medical gas products are blended together.

3.2.15 Compendia

Official compilation of drug monographs, which includes medical gases, containing minimum drug product specifications and testing methods.

3.2.16 Compendial method

Specific analytical method contained or referenced in a monograph in an official compendia.

3.2.17 Compressed medical gas (CMG)

Medical liquefied or vaporized gas, alone or in combination with other gases, that is a drug as defined by Federal Food, Drug and Cosmetic Act, 21 USC Section 321 (2)(g)(1) [2].

NOTE—CMG includes the following:

- gas(es) recognized in the current *USP–NF* and its supplements;
- gas(es) intended for direct use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in man or animals that achieves its intended purpose through chemical rather than physical means [4].

3.2.18 Container

Vessel designed and constructed to retain a liquid or gas.

NOTE—A CMG container refers to a high pressure cylinder or an insulated vessel capable of storing the CMG.

3.2.19 Contaminant

Any substance that can significantly affect the purity and physical attributes of CMGs.

3.2.20 Cross-contamination

Inadvertent mixing of one gas with another.

3.2.21 Cryogenic liquid

Refrigerated, liquefied gas having a boiling point less than $-130\text{ }^{\circ}\text{F}$ at 14.7 psia ($-90\text{ }^{\circ}\text{C}$ at 101.3 kPa, abs).²

3.2.22 Cryogenic home vessels

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

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, *Guideline for Metric Practice in the Compressed Gas Industry* [5].

3.2.23 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.

3.2.24 Dewar

Pressurized or unpressurized vessel used for the storage of cryogenic liquids.

3.2.25 Distributor/reseller

Firm that receives fully labeled, finished drug product and does not change the product or the labeling in any way.

NOTE—Product can be received as either liquid in large cryogenic vessels, i.e., 4Ls, and/or as gas in high pressure cylinders.

3.2.26 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 previously specified substance.

3.2.27 Emergency use

Initial use of oxygen by properly trained personnel to treat a condition in which the patient experiences respiratory distress.

3.2.28 Evacuation

Process of removing residual product by mechanical means, creating a negative atmospheric pressure.

3.2.29 Gas component

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

3.2.30 Heat of compression

Heat generated by increasing the pressure of a gas in a confined space.

NOTE—Heat of compression verifies that a container is being filled.

3.2.31 Identity

Determination of whether or not a CMG is what it is purported to be.

3.2.32 In-process

An intermediate stage within the CMG filling operation.

3.2.33 Label

Written, printed, or graphic material on or accompanying a CMG container.

3.2.34 Labeling

- (Noun) Labels and other written, printed, or graphic material on a CMG container or wrapper, or the written, printed, or graphic material accompanying a CMG.
- (Verb) The act of applying labels as described in the firms' SOP.

3.2.35 Leak check

Test to determine the integrity of a CMG closure system.

3.2.36 Lot

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

3.2.37 Lot number

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

3.2.38 Manufacturer

Person or firm that produces CMG, fills CMG containers via liquid-to-liquid, liquid-to-gas, or gas-to-gas, or re-labels filled containers of CMG.

3.2.39 Master label

A firm's quality control (QC) approved label specimen or copy of a current label used to approve other labels for CMG containers.

3.2.40 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 Act [2].

3.2.41 Monograph

Specifications and test methods for CMG found in the *USP–NF* [4].

3.2.42 Out of specification (OOS)

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

3.2.43 Pigtail

Flexible piping used to connect the CMG container to the filling system.

NOTE—A pigtail is equipped with a CGA fitting that is specific for the CMG being filled.

3.2.44 Portable liquid cryogenic cylinders

TC/DOT–4L insulated liquid container specified for over-the-road shipments of product that exceeds 25 psi (172 kPa).

3.2.45 Prescription

Written or oral order provided by a licensed practitioner.

NOTE—The only exception allowed to the prescription requirement for oxygen USP is oxygen for emergency use by rescue squads, fire departments, or other first aid-type service.

3.2.46 Production record

Quality record used to record significant CGMP process steps.

3.2.47 Quality control unit (QCU)

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

3.2.48 Quarantine

Physical isolation, segregation or identification of CMG or materials pending a decision on their subsequent disposition.

3.2.49 R_x

Symbol that indicates a prescription is required.

3.2.50 Residual

CMG product that remains in a container upon return to the manufacturer.

3.2.51 Segregated

Set apart and uniquely identified.

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

3.2.52 Storage tank

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

NOTE—A storage tank is also called a stand tank.

3.2.53 Tamper resistant

Gas-specific use outlet connections that are attached to the valve body so that they cannot be readily removed or replaced (without making the valve inoperable and preventing the containers' use) except by the manufacturer.

3.2.54 Tare weight

Weight of an empty cylinder and associated valve components.

3.2.55 Uninterrupted filling cycle

Continuous filling process that uses the same personnel, equipment, and lot of bulk material.

3.2.56 Vacuum

See evacuation.

3.2.57 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.

3.2.58 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.

3.2.59 Vent

Process of releasing product from a container or filling system.

4 Health and safety considerations

Individuals associated with filling or handling of CMGs shall be trained in applicable health and safety considerations.

5 Key laws, regulations, and guidelines

5.1 Federal

5.1.1 Federal Food, Drug, and Cosmetic Act (the Act)

The Act is a law enacted by Congress that includes definitions, prohibited acts and penalties, specific information for drugs and devices, and general administrative provisions [2]. All CMG manufacturers shall comply with the Act.

5.1.2 Health Canada Food and Drug Act and Regulations

Although this publication contains information on industry practice that is used to ensure compliance to the U.S. FDA requirements for drugs, the practices for the fabrication, packaging/labelling and testing of medical gases that are detailed in this document are also intended to demonstrate a firm's ability to comply with the general interpretation of the Health Canada guidance document GUI-0031, *Good Manufacturing Practices (GMP) for Medical Gases* [6].

5.1.3 Title 21, U.S. Code of Federal Regulations (21 CFR)

21 CFR is a body of regulations promulgated under the Act and enforced by the FDA. All manufacturers of CMG are required to comply with applicable drug regulations contained in 21 CFR [1].

5.1.3.1 Labeling (Part 201)

Each CMG shall have an intact, approved, legible, compliant label that is specific to the product.

The product label shall include the name and address of the manufacturer or distributor. Only the business name, city, state, and zip code are required if the place of business is listed in a city directory. If the distributor's name appears on the label, the name requires a qualifying phrase, e.g., "distributed by."

In addition to FDA regulations, labels shall comply with U.S. Department of Transportation (DOT) regulations regarding proper shipping name, hazard class, and UN/NA numbers. See CGA M-15, Standard for Appropriate and Effective Regulations for Medical Gases within 21 CFR Parts 201, 205, and 210/211, for the proposed changes to the FDA labeling regulations impacting CMG manufacturers [7].

CGA C-7, *Guide to Classification and Labeling of Compressed Gases*, provides guidance for the preparation of labels that comply with FDA and DOT regulations. CGA C-7 includes the wording used to address hazards, precautions, and first aid statements as well as the required dimensions for markings and required height for certain letters and numbers [8].

Also see 12.2 for additional labeling requirements.

5.1.3.2 Prescription drug marketing (Part 203) and State licensing of wholesale prescription drug distributors (Part 205)

21 CFR Parts 203 and 205 provide 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
- establishing and maintaining prescription drug distribution records.

See CGA M-15 for the proposed changes to the wholesale drug distribution regulations impacting CMG manufacturers [7].

5.1.3.3 Registration (Part 207)

A firm engaged in the manufacture of CMG shall register electronically each of its manufacturing sites with the FDA on an annual basis. In addition, a firm shall provide the FDA with a current list of the CMG manufactured. The FDA requires an electronic submission of a renewal registration each year to verify the status of a firm's operation.

Distributors as defined in 3.2.25 are not required to register as manufacturers with FDA.

See 5.2 for state registration requirements.

5.1.3.4 Current good manufacturing practices (Parts 210 and 211)

21 CFR Parts 210 and 211 contain the CGMPs. CGMPs specify the minimum requirements for the manufacturing, processing, packaging, or holding of a drug to ensure product safety, identity, strength, quality, and purity. These requirements include packaging and labeling operations, testing, and quality control of the drug product. The CGMP regulations are general in nature, not specific for CMG manufacturers.

Failure to comply with the CGMP regulations render the drug as adulterated under section 501 of the Act [2]. The drug, as well as the person who is responsible for the failure to comply with the CGMP regulations, may be subject to regulatory action.

See CGA M-15 for the proposed changes to the current good manufacturing practices regulations impacting CMG manufacturers [7].

5.1.4 United States Pharmacopeia and National Formulary (USP–NF)

The *USP–NF* and its supplements contain specifications and official test methods for the following CMG:

- carbon dioxide USP;
- medical air USP;
- helium USP;
- nitrogen NF;
- nitrogen, 97%, NF;
- nitrous oxide USP;
- oxygen USP; and
- oxygen, 93%, USP.

Alternate test methods may be used if they are validated and documented to meet or exceed the official test method. Methods and standards to validate equivalency are contained in the *USP–NF* and other publications [4].

5.1.5 Guidance documents

Guidance documents have been developed that define acceptable principles and practices of general applicability. These are not legal requirements but are acceptable to the FDA for compliance.

5.2 State/local

Firms should contact the appropriate state agency (Board of Pharmacy, etc.) to ascertain state and local regulations that are applicable to medical gases.

State CGMPs may be more stringent than the Federal model. The more stringent CGMPs should be followed.

6 Standard operating procedures

CGMPs require each firm to develop, approve, implement, periodically review, and maintain its own SOP. SOP shall be in writing and approved by the quality control unit (QCU). CGMP outline the areas that should be addressed in SOP and suggest minimum requirements. SOPs are a firm's master production and control record as stated in 21 CFR Part 211.186 [1].

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

SOP shall be in writing, appropriately approved, and should include all medical gas manufacturing procedures, documentation, and quality control activities necessary to meet CGMP requirements including quality responsibilities and medical release procedures. Manufacturing includes processing, labeling, testing, packing, holding, and distributing a CMG.

7 Organization and Personnel (21 CFR Part 211 Subpart B)

7.1 Quality control unit (21 CFR Part 211.22)

7.1.1 Responsibilities

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

- approve or reject all procedures and specifications that have an impact on the identity, strength, quality, and purity of CMG;
- approve or reject all components, supply gases, containers (cylinders), closures (valves), labeling, and suppliers of materials used in the manufacture of CMG;
- approve or reject all in-process and finished CMG manufactured by a firm or by another firm under contract;
- review production and test records to ensure that no errors have occurred, or if errors have occurred that they have been fully investigated;
- ensure that any out of specification (OOS) results have been adequately investigated; and
- ensure that adequate laboratory facilities are available for the testing and approval/rejection of supply gases, cylinders, valves, labels, and in-process and finished CMG.

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

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

7.1.2 Delegation of responsibilities and authorities

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

Although not required by regulation, multisite companies may wish to designate an individual to head the QCU (corporate quality control unit) for the entire firm. This head or corporate quality control can delegate certain functions of the QCU.

7.2 Personnel qualifications (21 CFR Part 211.25)

There shall be an adequate number of qualified individuals to perform and supervise CMG operations. Personnel engaged in or supervising CMG operations shall have adequate education, training, experience, or any combination thereof to ensure that a CMG has the purported safety, identity, strength, quality, and purity characteristics.

7.2.1 Education/experience

To perform CMG operations, personnel should have the ability to read, write, and understand the language in which a firm's applicable SOP are written as well as the ability to perform simple arithmetic operations that could be required for certain job functions. A firm should establish its own educational/experience requirements based on the specific job function.

NOTE—Individual states may have additional requirements for employee education/experience.

7.2.2 Training

The CGMP regulations require that personnel be trained in the operations they perform as well as in the portions of the CGMP regulations that apply to their job functions. Training content and frequency shall be defined in

writing and shall occur at intervals that ensure employees remain familiar with the regulations and procedures applicable to their job functions.

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

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

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

All training should be documented and may include the following as applicable:

- name(s) and signature(s) of the trainer(s);
- name(s) and signature(s) of the trainee(s);
- date of the training;
- duration of training; and
- specific topic(s) covered.

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

7.3 Personnel responsibilities (21 CFR Part 211.28)

Personnel should observe good health, safety, and sanitation practices; however health and sanitation habits are not critical to protect CMG from contamination.

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

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

7.4 Consultants (21 CFR Part 211.34)

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

8 Buildings and Facilities (21 CFR Part 211 Subpart C)

8.1 General

Any buildings or facilities used in the manufacture, processing, packaging, or holding of a CMG shall be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operation.

Systems controlling HVAC, plumbing, sewage and refuse, washing and toilet facilities, or sanitation facilities as specified in 21 CFR Parts 211.46, 211.48, 211.50, 211.52, and 211.56 are not typically critical to the manufacturing of CMG. CMG firms should provide adequate washing and toilet facilities. CMG firms should also ensure that buildings and facilities are maintained in a clean condition and have an appropriate pest control program. If an HVAC system is required to provide heating and cooling to analytical equipment, it should be of adequate size and maintained to ensure proper performance. This system should be designed to ensure that equipment operates within manufacturer's design specifications.