# COMPRESSED MEDICAL GASES

# GUIDELINE

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## INTRODUCTION

This guideline, issued under 21 CFR 10.90, states principles and practices of general applicability that are not legal requirements but are acceptable to the Food and Drug Administration (FDA). A person may rely upon it with assurance of its acceptability to FDA or may follow different procedures. Any person who chooses different procedures may, but is not required to, discuss the matter in advance with FDA to preclude expending money and effort on activity that FDA may later determine is unacceptable.

This guideline describes practices and procedures for compressed medical gas (CMG) fillers (including companies engaged in home respiratory services) that constitute acceptable means of complying with certain sections of the current good manufacturing practice (CGMP) regulations for drug products (21 CFR Parts 210 and 211).

Previous editions of this guideline were dated June 1981 and December 1983.

The guideline has been revised to include the home respiratory segment of the industry. Also included is an appendix containing questions and answers

addressing various laws and regulations as they pertain to the CMG industry. As in the previous editions, the guideline states specific sections of the CGMP regulations followed by a discussion of practices and procedures that FDA considers acceptable as a means of meeting those requirements. Although all sections of the CGMP regulations are applicable to CMG fillers unless specifically exempted, the guideline addresses only those sections that prompted significant questions concerning acceptable ways of compliance.

## EQUIPMENT DESIGN, SIZE, AND LOCATION

### Requirement

Section 211.63 requires that equipment used in the manufacture, processing, packing, or holding of a drug product be of appropriate design and suitably located to facilitate operations for its intended use.

### Guidance

One aspect of this requirement as related to the CMG industry is that the equipment must be designed to assure that the proper gas is put into the correct container. FDA considers acceptable elements of design in this regard to include the following:

1. The CMG manifolds used are dedicated to a single gas (e.g., oxygen). For mixtures of two or more gases, the mixture is produced by filling the cylinders on manifolds dedicated to mixtures (e.g., nitrogen/oxygen).

2. The manifolds are equipped with fill connections that correspond only to the container valve connection for that particular gas or mixture of gases so that the wrong containers cannot be attached to the manifold. Other than for laboratory functions, adapters should be used only when filling containers on manifolds dedicated to the filling of mixtures. The use of manifold and container valve connections recommended in the Compressed Gas Association (CGA) pamphlet V-1 (ANSI B57.1; CSA-B96), Compressed Gas Cylinder Valve Outlet and Inlet Connections is an acceptable system for this purpose.

3. Filling of industrial and medical CMG containers (concurrently) on the same line is acceptable, provided that the gas used for industrial purposes is equal to or higher in quality than the medical gas and that containers have been prepared in accordance with the "Testing and Approval or Rejection of Drug Product Containers and Closures" and the "Drug Product Containers" sections of this guideline.

## TESTING AND APPROVAL OR REJECTION OF COMPONENTS

### Requirements

Section 211.84(a) requires that each lot of components be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use.

Section 211.84(b) requires that representative samples of each shipment of each lot

be collected for testing or examination.

Section 211.84(d)(1) requires that at least one test be conducted to verify the identity of each component.

Section 211.84(d)(2) requires that each component be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of doing the testing itself, the manufacturer may accept a report of analysis from the supplier of a component, provided the manufacturer (1) conducts at least one specific identity test on the component, and (2) establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

## Guidance

Questions have been raised on how to meet the above types of testing requirements in situations involving bulk deliveries of components that upon receipt are then commingled in bulk storage tanks with other lots of the same component. For instance, it may not be practical to sample a bulk liquefied gas directly from a tank truck or from a bulk storage tank.

As an alternative to actually sampling and performing all required testing on each shipment of the component gas (i.e., either testing for all appropriate specifications or receiving a report of analysis covering all such specifications and conducting an identity test) before it is released and added to bulk storage tanks, the following

procedures may be used to achieve compliance with these requirements:

1. With a component that will be put in the final container as a single gas, the sample is taken either directly from the commingled lots in the bulk storage tank or indirectly by sampling from the first container filled from the commingled lots in the bulk storage tank after a new shipment has been added to the bulk tank. In the latter instance, testing the first container filled serves both as a component test and as a finished product test (as long as all appropriate tests are performed).

2. With separate components that will be used to produce a mixture of two or more gases, each component is tested before the mixture is put into containers. Samples are taken separately from the bulk storage tanks or from cylinders containing a single component.

## TESTING AND APPROVAL OR REJECTION OF DRUG PRODUCT CONTAINERS AND CLOSURES

### Requirements

Section 211.160(b) requires that laboratory controls include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug product containers and closures conform to appropriate standards of identity, strength, quality, and purity.

Section 211.84(d)(3) requires that containers and closures be tested for conformance with all appropriate written procedures.

### Guidance

Drug product containers and closures for CMG's are typically reused numerous times. This presents some special considerations regarding appropriate specifications and testing for containers that customers return for refilling. Specifications and testing procedures for CMG drug product container/closure systems should include the following each time the container/closure system is refilled:

1. Before refilling, an odor test of each CMG cylinder to detect foreign odors (exceptions to this area are for anesthetic gases and carbon dioxide).

2. A visual external inspection of each valve and container for dents, arc burns, other damage, and oil or grease.

3. For each aluminum cylinder, a visual check of the polyurethane coating or other heat-sensitive indicator, if provided, for evidence of exposure to heat or fire.

4. For each steel CMG cylinder manufactured to specifications under Department of Transportation (DOT) regulations (49 CFR Part 178), a dead ring test to determine if the gas cylinder walls have been weakened by interior rust. (Dead ring tests cannot be performed on cryogenic vessels, aluminum cylinders, or clustered cylinders [e.g., cradles that require special periodic hydrostatic testing].)

5. For each CMG cylinder, a check to determine that the hydrostatic test is conducted at the interval required by DOT regulations (49 CFR 173.34). The testing intervals vary for different types of containers and gases. The DOT regulations require that each cylinder be marked with the date of the last hydrostatic test.

6. A check to determine that each container is of the proper color to correspond to any color-coding system employed, such as that recommended by the CGA in its pamphlet C-9, Standard Color Marking of Compressed Gas Cylinders Intended for Medical Use in the United States.

7. A check of each cylinder or cryogenic vessel valve connection to determine that it is the proper type for the particular type of CMG involved.

## DRUG PRODUCT CONTAINERS

### Requirements

Section 211.94(c) requires that drug product containers be clean.

Section 211.94(d) requires that standards or specifications, methods of testing, and, where indicated, methods of cleaning be written and followed for drug product containers.

### Guidance

One factor to consider regarding the above requirements is the possible presence of foreign gas residues in CMG cylinders before filling. An acceptable method of assuring that cylinders do not contain foreign gas residues is to pull a vacuum on each cylinder equal to 25 or more inches of mercury prior to filling with the CMG. (Cryogenic vessels are seldom completely emptied and need not be evacuated before filling.)

## LABELING ISSUANCE AND PACKAGING AND LABELING OPERATIONS

### Requirements

Section 211.125(c) requires that procedures be used to reconcile the quantities of labeling issued, used, and returned.

Section 211.130 requires there be written procedures designed and followed to assure that correct labels, labeling, and packaging materials are used for drug products.

### Guidance

CMG containers are not always completely relabeled when they are refilled. For instance, a previous container label may be left on when the container is refilled, and the label need not be replaced unless it is outdated, damaged, or illegible. This practice has resulted in some questions concerning appropriate labeling controls and reconciliation procedures in such circumstances.

FDA considers it acceptable to continue to use existing labeling on CMG containers that are refilled if the procedures and controls provide for examining each container to assure that the labeling completely conforms to the currently approved master labeling and is otherwise suitable for continued use (i.e., it is undamaged, legible, and does not bear previous lot numbers or expiration dates).

Acceptable procedures for reconciling labeling in such circumstances would include

recording (1) the number of labels issued, (2) the number of containers actually relabeled and (3) the number of labels destroyed and/or returned to inventory.

If a home respiratory company (HRC) is distributing supplier filled cylinders only, and the HRC name is on the label, the HRC must be identified as the distributor in compliance with the labeling requirements of 21 CFR 201.1(h)(5).

If an HRC is transfilling gas cylinders, the HRC becomes the manufacturer according to 21 CFR 201.1(b). If an HRC does not issue its own labels and if the HRC transfills cylinders, the HRC's name and address must appear on the label as the filler or transfiller.

## TESTING AND RELEASE FOR DISTRIBUTION

### Requirements

Section 211.165(a) requires that for each batch of drug product, there be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, before release.

Section 211.165(c) requires that any sampling and testing plans be described in written procedures that include the method of sampling and the number of units per batch to be tested, and that the written procedure be followed.

Guidance

The following are acceptable types of plans for sampling and testing CMG's before release in certain types of filling operations. If nitrogen is a component of any mixture, a test for identity of the nitrogen is not required. Identity is assured by the filling procedure that introduces the nitrogen. If the filling procedure on the manifold makes possible an alternate gas, an identity test to establish the absence of that gas is to be performed.

1. For a single CMG put into cylinders on a multi-cylinder manifold, at least one cylinder of product from each manifold filling is tested for identity and strength each time the cylinders are changed on the manifold.

2. For a single CMG put into cylinders one at a time by individual filling operations, at least one cylinder of product for each uninterrupted filling operation cycle is tested for identity and strength. Examples of an uninterrupted filling operation cycle are one day's or one shift's production using the same personnel, equipment, and lot or commingled lots of component.

3. For a finished CMG produced by combining two different gases in a cylinder,

every cylinder is tested for the identity and strength of one of the gases, and at least one cylinder from each manifold filling is tested for identity of the other gas in the mixture.

4. For a finished CMG produced by combining three different gases in a cylinder, every cylinder is tested for the identity and strength of two of the gases and at least one cylinder from each manifold filling is tested for the identity of the third gas in the mixture.

5. For liquefied gas put into cryogenic home units at the plant for delivery to users, each home unit is tested for identity and strength.

6. Home units that are retained by customers and are serviced in place periodically by refilling from vehicle mounted vessels need not be directly tested after filling if the filling firm has available suitable records of analysis covering the identity and strength testing performed on a sample taken from its vehicle mounted vessel, or has satisfied the conditions in 8 below.

7. Each filled CMG cylinder is tested for leaks using an appropriate method, such as a leak detection solution applied to the valve area.

8. For HRC firms dispensing liquid oxygen from vehicle mounted vessels, acceptable means of compliance with the identity and strength testing

requirements are as follows:

a. If the HRC obtains bulk liquid oxygen from a bulk supplier, the identity and strength test is performed by the bulk supplier and witnessed by the HRC. Documentation of this testing is maintained by the HRC.

b. If the HRC obtains bulk liquid oxygen from a bulk supplier who supplies a certificate of analysis but the test is not witnessed by the HRC, the HRC must perform an identity test on each lot received and establishes the reliability of the supplier's analyses at appropriate intervals.

c. If the HRC neither witnesses the identity and strength test nor receives a certificate of analysis, the HRC must test each vehicle mounted vessel filled by the bulk supplier for identity and strength.

9. If the HRC owns or leases a stand tank (stationary holding tank), the HRC must perform a test for identity and strength taken directly from the stand tank after each oxygen delivery before any vehicle mounted vessel is filled. Vehicle mounted vessels filled from this stand tank need not be tested if the HRC can demonstrate compliance with all of the following conditions:

(1) No other stand tanks are located at the facility;

(2) The vehicle mounted vessels filled from the stand tank are

dedicated to the delivery of oxygen by the HRC for home care use only; and

(3) The vehicle mounted vessels filled from the stand tank have not been completely emptied or have not been out of service.

## COMPONENT RECORDS

### Requirement

Section 211.184(c) requires that records include an individual inventory record of each component, a reconciliation of the use of each lot of the component, and sufficient information to allow determination of which batches or lots of drug product are associated with the use of each component.

### Guidance

The agency recognizes that accurate component inventory records, including reconciliation of the use of each lot, are difficult to maintain for bulk liquefied gases. Complications include normal loss of the gas through vaporization, which may amount to l0 percent or more, and the commingling of component lots in bulk storage tanks.

FDA does not expect in such circumstances that the reconciliation will allow 100 percent accountability. The procedures for reconciling the use of components can allow for normal storage and operating losses as long as the procedures require

further investigation in the event of unexplained discrepancies such as losses beyond established normal levels.

## BATCH PRODUCTION AND CONTROL RECORDS

### Requirement

Section 211.188 requires that batch production and control records be prepared for each batch of drug product produced and include complete information relating to the production and control of each batch. These records must include:

(a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed; and

(b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including all particular information specified in this section.

## Guidance

Questions have been raised on whether batch production and control records, which in the CMG industry are frequently in the form of a pumper's or filler's log, must contain a complete copy of all corresponding master production and control information.

It is acceptable for the batch production and control records to incorporate detailed production and control information by reference as long as significant processing steps are included in the batch records. As one example, it is suitable for the batch production and control record to provide an instruction such as "Evacuate cylinders per Standard Operating Procedure XYZ," if the details of Standard Operating Procedure XYZ appear in the master production and control records.

The requirement for supervising review of the batch production control records may be satisfied if the person in charge reviews these records daily and this review is noted on the records.

# LABORATORY RECORDS

## Requirement

Section 211.194(a)(2) requires that laboratory records include a statement of each method used to test the sample, indicating

the location of data establishing that the methods meet proper standards of accuracy and reliability for the product tested. If the method used is in a recognized standard reference, such as the current United States Pharmacopeia/National Formulary, and is not modified, a statement of the method and reference will suffice.

## Guidance

Several CMG's, being recognized in the United States Pharmacopeia/National Formulary, must meet the requirements contained in the official compendium. This does not mean, however, that the official tests must necessarily be used in testing for batch release purpose. Alternative methods may be used to demonstrate satisfactory conformance with the appropriate requirements, but if a nonofficial test method is used for an official article, the laboratory records must document that the method used is equal to or superior to the compendial method in terms of accuracy and reliability.

## GLOSSARY

For purposes of this guideline, the following definitions apply:

1. Compressed medical gas (CMG)--Any liquefied or vaporized gas alone or in combination with other gases which is a drug as defined by Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 321(g)(1)). NOTE: Calibration gases and lung diffusion mixtures are classed as devices (2l CFR 868.6400).

2. Container--A metal container designed to contain either liquefied or vaporized CMG.

3. Cryogenic vessel--A metal container designed to contain liquefied CMG at extremely low temperatures.

4. Cylinder--A metal container designed to contain CMG at a high pressure.

5. Dead ring test--Also called the "hammer test." A test used to determine the soundness of a cylinder by striking the side of the cylinder. If a clear bell-like sound results, the cylinder is considered satisfactory. If a dull sound results, the cylinder is not considered suitable for filling with a high pressure CMG (not applicable to aluminum cylinders).

6. Home Respiratory Company (HRC)--Any firm that fills, transfills, or distributes compressed medical gases intended for use by patients at their residence.

7. Manifold--Equipment or apparatus designed to fill one or more CMG containers at a time.

8. Odor test--A test performed by opening a CMG cylinder valve to allow the CMG to flow into a cupped hand. The gas is then organoleptically examined by smelling for foreign gases. This test is not done on cylinders containing anesthetic gases or carbon dioxide.

# APPENDIX

## CURRENT GOOD MANUFACTURING PRACTICE

## QUESTIONS AND ANSWERS ON COMPRESSED MEDICAL GASES

1. QUESTION: Why are compressed medical gases for medical use considered prescription drugs?

   ANSWER: Because their use as drugs, without the supervision of a licensed practitioner or by properly instructed emergency personnel, is not safe.

2. QUESTION: Are CMG liquefaction plants and container filling facilities required to register with FDA as drug manufacturers?

   ANSWER: Yes, a drug registration form must be submitted to FDA for every liquefaction plant and for every container filling facility. Furthermore, a drug listing form must be submitted to FDA listing each compressed medical gas filled or relabeled at that facility. Drug registration and drug listing forms can be obtained from any FDA District Office (see attached list).

3. QUESTION: How often are such plants inspected by FDA?

ANSWER: The Act requires FDA to inspect each liquefaction plant and each container filling facility at least once every two years. However, more frequent inspections may be made for several reasons; such as to investigate an industry or consumer complaint, product recall, or as a follow-up to a Warning Letter.

4. QUESTION: What are FDA investigators authorized to inspect?

ANSWER: FDA investigators are authorized to enter a drug manufacturer's place of business to inspect the buildings, equipment, finished and unfinished materials, containers, and labeling. In the case of prescription drugs such as compressed medical gases, the inspection authority includes access to all records (including shipping and receiving records), but not including financial records.

5. QUESTION: What do FDA investigators routinely look for during an inspection?

ANSWER: They look to see whether compressed medical gases are being manufactured according to FDA's current good manufacturing practice (CGMP) regulations. FDA investigators will also look at labeling to determine compliance with FDA's labeling regulations (21 CFR Part 201).

6. QUESTION: What are the CGMP regulations?

ANSWER: Section 501(a)(2)(B) of the Act requires that the methods used in the manufacture, processing, packing, or holding and the facilities used must conform to current good manufacturing practice. The CGMP regulations explain to drug manufacturers what controls they must have in order to comply with the Act and, thereby, assure that the drug products they produce meet the quality and purity characteristics that they are represented to have. These regulations are published in Title 21, Parts 210 and 211 of the Code of Federal Regulations, and are included in the volume containing Parts 200 to 299. Copies of that volume may be ordered from:

Superintendent of Documents
Government Printing Office
Washington, D. C. 20402

7. QUESTION: What are the most common violations that FDA investigators look for?

ANSWER: The most common violations are:

a) Failure to establish written operating procedures [21 CFR 211.100(a)];

b) Failure to follow the written operating procedures [21 CFR 211.100(b)];

c) Failure to test the final product for identity and strength (21 CFR 211.165);

d) Failure to keep adequate batch production and laboratory records (21 CFR 211.188 & 211.194); and

e) Failure to register as a drug manufacturer.

8. QUESTION: What must a batch record contain?

ANSWER: A batch record (pumper's log) must include documentation that each significant step in the manufacture, processing, packing, or holding of the batch has been accomplished. It must also include the identity of the person(s) performing and directly supervising each significant step. (21 CFR 211.188)

9. QUESTION: Must a firm produce a batch record for each batch of CMG filled and how long must it be retained?

ANSWER: The firm must produce a batch record (pumper's log) for every batch of CMG filled. This batch record and all other production and control records must be retained on file by the firm for at least one year after the expiration date of the batch. (21 CFR 211.180)

10. QUESTION: What if the person performing the significant step, such as vacuum evacuation of the cylinders, fails to indicate that the step was accomplished?

ANSWER: The supervisor or person checking the batch record should determine if the step was accomplished and, if it was, require completion

of the batch record. If the record review by FDA reveals that the batch record is incomplete, FDA assumes that the step was not accomplished.

11. QUESTION: What should a firm do if a mix-up is discovered?

ANSWER: The batch should be rejected, blown down, and evacuated per written procedures. An investigation should be initiated to determine the cause of the mix-up. If the lot has been distributed the firm should initiate an immediate recall and notify the nearest FDA district office (see attached list).

12. QUESTION: How soon will the firm be notified of the FDA investigator's inspectional findings?

ANSWER: Prior to finishing the inspection, the FDA investigator will discuss the findings of the inspection with the most responsible person present. A Notice of Observations (Form FDA-483) will be prepared by the investigator listing the conditions which the investigator considers to be objectionable. If the items listed are serious deficiencies, the firm may also receive a Warning Letter from FDA's District Office.

13. QUESTION: What court-enforced actions can be taken against a firm that violates the Act?

ANSWER: The court-enforced actions include seizure of finished product, bulk product, ingredients, and equipment; temporary or permanent injunction from manufacturing or filling CMG's; and criminal prosecution.

14. QUESTION: What are the penalties for violating the Act?

ANSWER: If found guilty of violating a provision of the Act, an officer or employee of the firm may be imprisoned for up to one year and/or fined up to $100,000 ($250,000 if death occurs) for each violation. If the prohibited act was committed with intent to defraud or mislead or if an officer or employee is convicted a second time under the Act, the offense is punishable by a fine of $250,000 to $500,000 and imprisonment of up to three years for each violation. The firm can also be fined the same amounts. (Note: The limits of the amount of fine that can be imposed were raised by the Comprehensive Crime Control Act of 1984, for all criminal violations for which the basic Federal law imposes a prison sentence of six months or more.)

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