CHAPTER 56 - DRUG QUALITY ASSURANCE

SUBJECT:	IMPLEMENTATION DATE
COMPRESSED MEDICAL GASES	*Upon Receipt*
	COMPLETION DATE
	Continuing

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Industry codes: 64J	56002E

FIELD REPORTING REQUIREMENTS

As soon as the district becomes aware of any significant adverse inspectional, analytical, or other information which could or should affect the agency's new product approval decisions with respect to a firm, the district should immediately notify HFC-240, Division of Medical Products Quality Assurance, via EMS or fax, and they will, in turn, convey the information by fax or equivalent expeditious means to the appropriate Center regulatory units.

Forward a copy of each Warning Letter issued under CPG 7132a.16 to the Division of Manufacturing and Product Quality, HFD-320. *A copy of the accompanying documentation such as the FDA483, establishment inspection report, etc., should not be sent.*

Current Change

PART I - BACKGROUND

Compressed medical gases (CMG) are prescription drugs that are administered to patients who are often unconscious or unstable. The methods of filling CMGs into refillable *high pressure* cylinders *or cryogenic vessels* are unique in the drug industry, and the container/closure systems are unlike other drug products. *Therefore, a set of strict prefill inspections is essential to give assurance that the container/closure systems are acceptable.*

Compressed medical gases must be manufactured, processed, filled and packaged using current good manufacturing practices (GMP), as set forth in 21 CFR Parts 210 and 211 and in conformance with current industry practice. All sections of Part 211 are applicable to the medical gases industry unless specifically exempted by regulation.

The inspectional guidance in this program is structured to reduce field resources devoted to routine surveillance of firms with a high compliance rate because such firms may not warrant in-depth inspectional coverage of all systems and processes on a biennial basis.

Current Change

PART II - IMPLEMENTATION

OBJECTIVES

A. To assess the operations of the CMG industry to determine if they conform with the CGMP Regulations.

B. To assure the quality of CMG through inspections, voluntary corrective action, and appropriate enforcement actions to achieve compliance with the CGMP Regulations.

C. To identify practices which need correction or improvement, and to assess the need for specific GMPs *or revisions to the guidelines* for the regulation of these operations.

PROGRAM MANAGEMENT INSTRUCTIONS

Inspections under this program are to be conducted as part of the regular statutory inspection cycle. Reports of mixups, injuries *or deaths,* or contamination are to be followed up on a priority basis with a comprehensive investigation. **Any incident involving injuries or deaths should be reported immediately to HFD-322, Duane Sylvia, and a copy of the final report should be submitted as well.**

SURVEILLANCE

The following manufacturing operations, i.e., filling liquid to gas, filling liquid to liquid, and filling gas to gas, are required to register and list with the agency.

Many firms which fill medical gases may not be registered with the FDA, particularly welding supply companies, *durable medical equipment suppliers,* and firms which may fill oxygen from large to small cylinders. Districts should develop a plan to identify such firms and inform them of their obligation to comply with the requirements of the FD&C Act, particularly registration, drug product listing, and current good manufacturing practices.

Current Change

TRAINING

The Center for Drug Evaluation and Research has produced a videotape "Compressed Medical Gases - The CGMP Inspection" which describes the production of compressed medical gases *filled into high pressure cylinders only* and the equipment and techniques used by the CMG industry.

Copies of the videotape should be available at each district.

This videotape is also available for the industry to purchase. It may be acquired in VHS format from the National Technical Information Service, (703)487-4660, by requesting PB93-781359.

Current Change

PART III - INSPECTIONAL

The Compressed Medical Gases (CMGG) guideline (revised February 1989) describes medical gas practices which FDA considers acceptable to comply with **certain sections** of the CGMP regulations and serves as a guide for the inspection of these firms.

It is acceptable to use equipment and/or procedures other than those listed in the CMGG, provided the firm can demonstrate that the equipment/procedures are equivalent or superior to those suggested in the guideline. For example, it is acceptable to use a non-official method to determine an official drug's conformance with established specifications and standards for batch release purposes.

However, analytical records must contain documentation which verifies that the accuracy and sensitivity of the non-official method is equivalent to or better than the official method. *For paramagnetic analyzers that have the required accuracy, we would consider the manufacturer's instruction manual as sufficient documentation of equivalency.*

Attachment D, provides inspectional guidance, *i.e., testing requirements* for firms who supply liquid oxygen for the filling of *cryogenic home vessels* or who fill "E" or "D" size cylinders. This guidance is included to aid the investigator's assessment of GMP compliance status at a firm.

Deviations from the practices and procedures described in the CMGG should not be considered violations of the CGMP Regulations unless appropriate documentation demonstrates that such deviations are in direct violation of a specific section of 21 CFR 211.

Inspection

This program circular provides two inspectional options: Abbreviated Inspectional Option and Full Inspectional Option. To determine which option should be used an evaluation of the following is appropriate:

Current Change

1. Review and Evaluation

A full inspection should be conducted for initial inspections and may also be conducted on a surveillance basis at the District's discretion. Also, whenever information becomes known which would question the firm's ability to produce quality products an appropriate in-depth inspection should be performed.

An abbreviated inspection should not be conducted for the initial inspection of a facility, nor when the firm has a past history of fluctuating in and out of compliance. The District should utilize all information at their disposal such as past history, results of sample analysis, complaints, recalls, etc., to determine if coverage under the abbreviated inspectional option is appropriate for the specific firm.

a. Determine if changes have occurred by comparing current operations against the EIR for the previous full inspection. The following changes are typical of those that would warrant the full inspectional option:

   1. New potential for mix-ups or contamination arising through change in process or product line.

   2. Use of new technology requiring new expertise, *such as computer systems,* significantly new equipment, or new facilities.

b. Review the firm's complaint file and determine if the pattern of complaints (or other information available to the District) as well as the firm's records of internal rejection warrant expanding the inspection to the full inspectional option to look for weaknesses in the firm's processes, systems or controls.

Current Change

c. If no significant changes have occurred and no violative conditions are observed, the abbreviated inspectional option may be adequate.

d. If significant changes have occurred or if violative or potentially violative conditions are noted, the inspection should be expanded to the full inspectional option to provide appropriate coverage.

e. If an inspection needs to be expanded to the full inspectional option, it need be expanded only for the applicable general product or process area in question.

2. Abbreviated Inspectional Option

This option involves a brief inspection of the manufacturer to maintain surveillance over the firm's activities. An abbreviated inspection as described below is adequate for routine coverage and will satisfy the biennial inspection requirement.

a. Perform a brief inspection of the firm's facility including review of batch production and control records (usually in the form of a pumper's or filler's log) for a representative number of products manufactured by the firm. *(See Attachment E for a sample batch production record.)* Products with a history of previous problems should be included. Include a spot-check of a limited number of analytical test records to assure that batches are being subjected to adequate testing for conformance to specifications.

Special note should be taken of the firm's filling and labeling controls, *especially the calibration of the analytical equipment.* Any observations of inadequate controls *or calibration* will indicate that the full

Current Change

inspectional option should be utilized. In the event a firm fills only one gas and has only one label, the lack of labeling accountability controls would not be a significant GMP deviation. If the brief inspection reveals no significant objectionable conditions, then the use of the abbreviated inspection is adequate.

b. The minimum reporting required for an abbreviated inspection is a brief summary describing the scope of the inspection, the persons interviewed and a description of any changes which may have occurred since previous inspections. Report any adverse findings as described in the IOM.

3. Full Inspectional Option

This option may involve a complete inspection of all systems and processes or a particular product or process as noted in 1.d. and e. above,

Be particularly alert to the following areas where significant deviations from CGMPs have been frequently encountered:

- ∃Failure to test incoming component and/or the finished product
- ∃*Inadequate calibration of the analytical equipment*
- ∃*Inadequate training both on-the-job and/or CGMP*
- ∃*Inadequate* written procedures (SOPs)
- ∃*Inadequate* batch production records, i.e., not all of the significant steps are documented
- ∃Inadequate cylinder prefill inspections
- ∃Inadequate labeling control and reconciliation

Current Change

In addition to the information contained in the CMGG, pay particular attention to the following:

a. Determine if the firm has written procedures covering production and process control, analytical procedures, quarantine of filled cylinders prior to final release, label issuance procedures, calibration and maintenance of equipment, *especially the oxygen analyzer, batch production records*, and complaint files.

b. Determine that analytical methodology is equal in accuracy and sensitivity to the methodology described in the USP monograph for the *product,* and that electronic analytical equipment is calibrated using *certified reference* standards.

c. Compare the Compressed Gas Association standard color markings (Attachment A) for cylinders intended for use with medical gases against the firm's color coding practices. There are no standard colors for industrial, diagnostic, or calibration gases.

SAMPLE COLLECTION

Routine physical samples should not be collected.

Documentary samples should be collected to document labeling and significant CGMP deviations. Physical samples should be collected only in the case of injuries *or deaths,* mix-ups, potency or contamination problems. Consult your home district or the testing laboratory, if different, for guidance concerning sample size and shipment.

Current Change

If no interstate documentation of the *the incoming product* is possible, then document the following:

*∃the manufacturer of the storage tank, if applicable,

∃the high pressure cylinders. Each cylinder manufacturer has a unique logo, you should document the logo by photos, tracings or pencil rubbing. An abbreviated list of logos and the corresponding manufacturer is included as Attachment B,

∃the manufacturer of high pressure cylinder valves,

∃the manufacturer of the vehicle mounted vessels, or,

∃the manufacturer of the cryogenic home vessels. This would apply to vessels filled at the filling site only, not vessels filled at a patient's home.*

An example of a DOC C/R is included as Attachment C.

For a seizure recommendation, document the I/S of both the liquid and the gaseous states, whichever is appropriate.

REPORTING

Refer to the general Drug Process Inspection Compliance Program (7356.002) for guidance.

Current Change

PART IV - ANALYTICAL

Chemical analyses by gas chromatography are to be performed by the Districts' normal servicing pharmaceutical laboratories for PMS 56.

Chemical analysis of USP procedures using the Orsat apparatus (CO_2, 0_2) NRL.

Analysis

Samples are to be examined for compliance using the methods found in the Medical Gas Analytical Manual or other equivalent methods. Check analysis will be by the official method, or when no official method exists, by other validated procedures.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

See Part V - Regulatory/Administrative Strategy of the Drug Process Compliance Program 7356.002.

All sections of 21 CFR Part 211 are applicable to the compressed medical gas industry unless specifically exempted from the regulations (e.g., per 21 CFR 211.196, lot or control numbers are not required on CMG distribution records). Practices and procedures which differ from those described in the CMGG are not violations of CGMP Regulations unless the practice/procedure is in direct violation of a specific section of 21 CFR 211.

Compliance Policy Guide 7132a.16 provides District offices direct reference authority for issuing *warning* letters to the CMG industry for specific CGMP violations. This authority will expedite further regulatory follow-up (e.g., submission of a recommendation for seizure, etc.) in cases where firms fail to institute significant corrective action as a result of the District's *warning* letter. *This guide also provides certain labeling guidance for including specific misbranding charges into a warning letter without Center concurrence.*

Oxygen, USP, is regarded to be a prescription drug and its labeling should bear adequate directions for use in accordance with 21 CFR 201.100. *It would be misbranded if its label fails to indicate whether or not it has been produced by the air-liquefaction process as required by the United States Pharmacopeia (USP *XXIII*), and fails to bear the statement, "Caution: Federal law prohibits dispensing without a prescription.*

All other compressed medicinal gases should meet the requirements of 21 CFR 201.161.

Current Change

PART VI - REFERENCES, ATTACHMENTS AND CONTACTS

A. REFERENCES

1. *United States Pharmacopeia (USP) 23*
2. Medicinal Gas Analytical Manual (Finkelson, New York District, December 1971)
3. Handbook of Compressed Medical Gas (Compressed Gas Association)
4. Compressed Medical Gases Guideline (Revised February 1989)
5. "Compressed Gas Cylinder Valve Outlet and Inlet Connections" CGA Pamphlet V-1
6. "Transfilling of Legend Oxygen to be Used for Respiration" CGA Pamphlet P-2.6
7. "Characteristics and Safe Handling of Medical Gases" CGA Pamphlet P-2
8. "Compressed Air for Human Respiration" CGA Pamphlet G-7
9. "Oxygen" CGA Pamphlet G-4
10. "Commodity Specification for Oxygen" CGA Pamphlet G-4.3
11. "Commodity Specification for Oxygen Produced by Chemical Reaction" CGA Pamphlet G-4.5
12. "Carbon Dioxide" CGA Pamphlet G-6

Current Change

13. "Commodity Specification for Nitrous Oxide" CGA Pamphlet G-8.2

14. Videotape "Compressed Medical Gases - the CGMP Inspection"

15. Drug Process Inspection Program, CP 7356.002

16. Compliance Policy Guide 7132a.16 (*Compressed Medical Gases - Warning Letters for Specific Violations covering liquid and gaseous oxygen.*)

17. Regulatory Procedures Manual, Chapter 8

Current Change

B. ATTACHMENTS

A - Compressed medical gas cylinder colors as recommended by the Compressed Gas Association

B - Compressed medical gas cylinder *manufacturer's registered symbol or numeric I.D.*

C - Example of a DOC C/R

D - Inspectional guidance and the *testing requirements for the filling of liquid to liquid and high pressure cylinders*

E - *Batch Production Record Example*

F - Compliance Policy Guide 7132a.16 (*Compressed Medical Gases - Warning Letters for Specific Violations covering liquid and gaseous oxygen.*)

C. CONTACTS

ORA :

Inspectional

Division of Field Investigations
Investigations Branch, HFC-132
Jay S. Allen
Telephone: (301) 443-3340

Method Inquiries

Division of Field Science, HFC-141
Elise Murphy
Telephone: (301) 443-3007

Current Change

Center for Drug Evaluation and Research:

CGMPs, *Labeling, & Compliance Program Guidance*

Division of Drug Manufacturing and Product Quality
Sterile Drugs Branch, HFD-*322*
Duane Sylvia
Telephone: (301) 594-0095

*Registration and Drug Listing Requirements

Product Information Management Branch
Gary Anderson
Telephone: (301) 594-1086*

Current Change

PART VII - CENTER RESPONSIBILITIES

See Drug Process Inspection Compliance Program 7356.002

ATTACHMENT A

CMG CYLINDER COLORS*:

SINGLE GASES

Green	Oxygen
Gray	Carbon Dioxide
Blue	Nitrous Oxide
Orange	Cyclopropane
Brown	Helium
Black	Nitrogen

MIXTURES

Gray and Green	Carbon Dioxide and Oxygen
Brown and Green	Helium and Oxygen
Yellow	Air (Mixtures of Nitrogen and Oxygen containing 19.5% to 23.5% Oxygen)
Green and Black	Nitrogen/Oxygen mixtures other than those containing 19.5% to 23.5% Oxygen

*(as recommended by the Compressed Gas Association)

ATTACHMENT B

Five (5) pages not included.

Symbols of Cylinder Manufacturers

Company Name	Head Office	Manufacturers Symbol

ATTACHMENT C

Two (2) pages not included

Sample Collection Report (Form FDA 464)

ATTACHMENT D

*TESTING REQUIREMENTS

Many firms are in business to supply Oxygen, USP, to patients in need of supplemental oxygen. This may be liquid oxygen for the patient's cryogenic home vessel or high pressure cylinders.

Our primary interest during an inspection of these firms is to establish that the oxygen provided the patients meets the identity and strength specifications for Oxygen, USP. This may be accomplished by testing the high pressure cylinder contents and/or the liquid oxygen.

Cylinders of Compressed Oxygen, USP

If a firm receives finished, labeled drug product, i.e., liquid and/or high pressure cylinders and neither manipulates the product nor the labeling in anyway, they are considered a distributor and would not be required to register with the agency. However, distribution procedures capable of determining traceability should be established and followed. NOTE: This does not apply to cryogenic home vessels.

If the firm is following GMP in the filling of high pressure cylinders, then the requirements are easily met by testing one cylinder from each manifold filling sequence for identity and strength as each cylinder is representative of every other cylinder filled during the filling sequence.

If the firm is filling one cylinder at a time, then one cylinder from each uninterrupted filling sequence should be tested, provided the same personnel, equipment, and lot of bulk is used. An uninterrupted filling sequence is defined as a single, continuous filling sequence with no breaks or shut-downs occurring during the filling.*

Current Change

ATTACHMENT D

Cryogenic Home Vessels of Liquid Oxygen

*Cryogenic home vessels are either routinely filled on a periodic basis or when the firm is notified that the oxygen has reached a predetermined level. The firm will usually weigh the patient's vessel, credit them with the amount of residual liquid oxygen remaining, and then either exchange the vessel for a full one (Commonly referred to in the industry as milk canning) or fill the patient's vessel from a cryogenic vessel mounted on their delivery vehicle.

Knowing the above background information, the investigator must decide at what point the liquid oxygen must be tested and who is responsible for performing that testing. For example, is the firm required to perform a test for identity and strength on (1) the incoming liquid, or (2) the contents of the cryogenic home vessel, whether filled on site or at a patient's home, i.e., curbside?

TESTING OF THE INCOMING LIQUID OXYGEN

1) If a firm dispenses liquid oxygen (LOX) from either a permanent mounted vessel(s) or from a portable cryogenic vessel such as Vertical Gas Liquid (VGLs), Gas Pack (GPs), Portable Liquid Container (PLCs), etc., to fill cryogenic home vessels then:

   a) No testing is required, as long as the receiving firm witnesses the testing, i.e., identity and strength, for each vessel received or filled, receives a valid certificate of analysis (COA) for each vessel, and documents that the testing has been witnessed.

      Further, the person witnessing the testing is required to receive training specific to the analytical methodology being witnessed, and this training should be documented.*

Current Change

ATTACHMENT D

*b) If the testing is not witnessed, then the firm can rely on a valid COA for the strength determination, however, it should perform an identity test on **EACH** cryogenic vessel received or filled by the supplier.

In addition, the firm is required to periodically verify the reliability of the supplier's analysis. This should be performed at least once a year by:

1) witnessing the testing performed at the supplier. Again, the firm's employee who is responsible for the witnessing of the testing should receive training specific to the analytical methodology utilized, or

2) if the firm has not received training or is not knowledgeable of the supplier's analytical methodology, then a sample from a delivery should be taken to a third party for analysis for conformance with USP specifications.

c) If a firm neither witnesses the testing nor receives a valid COA, then full USP testing would be required. Please note that if a firm fails to receive a COA or a letter from the supplier indicating the method of manufacture for the product, i.e., produced via air liquefaction, then the USP requires two additional tests be performed for carbon dioxide and carbon monoxide impurities.

2) If the firm owns or leases a storage tank, then an identity and strength test taken directly from the storage tank after each oxygen delivery should be performed before any cryogenic vessels including any cryogenic home vessels are filled. Vehicle mounted vessels (VMVs) filled from this storage tank need not be tested if:

a) there are no other storage tanks on the premises,

b) the VMVs are dedicated to the delivery of oxygen, and*

Current Change

*c) the VMVs filled from the storage tank have not been completely emptied or out of service.

TESTING OF CRYOGENIC HOME VESSELS

The most important criteria in the filling of cryogenic home vessels is who maintains possession/control of the cryogenic home vessels. If the possibility exists that a contaminant or a foreign gas could be introduced into a cryogenic home vessel, then the GMPs require full USP testing of each vessel. Industry practice calls for the firm that owns the cryogenic home vessels to perform the filling and not allow any other firm to fill these vessels.

1) No testing is required as long as the following three criteria are met:

   a) Liquid oxygen is the only liquid being filled on the premises.

   b) Incoming liquid oxygen is adequately tested for identity and strength according to one of the above methods.

   c) Cryogenic home vessels are filled by the firm.

2) If cryogenic home vessels are sent out for repair/maintenance then each vessel returned should be retested for identification at the least, prior to redistribution. [This is in accordance with Section 211.87 of the regulations.]

3) If any other drug product, i.e., liquid is being filled, then ALL cryogenic home vessels filled on the premises are required to be tested for identity and strength.

4) If a firm owns cryogenic home vessels and allows these vessels to be filled by a third party, then each cryogenic home vessel should be tested according to one of the methods outlined under the TESTING OF THE INCOMING LIQUID OXYGEN.*

Current Change

ATTACHMENT D

*COMBINING A NEW BULK SHIPMENT OF A COMPONENT INTO A BULK STORAGE TANK WITH THE REMAINDER OF A PREVIOUSLY RECEIVED, TESTED, AND APPROVED COMPONENT LOT CAUSES THE COMMINGLING OF THE MATERIAL. THE RESULT IS THAT THE PREVIOUSLY APPROVED MATERIAL BECOMES AN INTEGRAL PART OF AN UNAPPROVED NEW LOT AND CANNOT BE USED UNTIL SUCH LOT IS APPROVED FOR USE.

TESTING OF LIQUID OXYGEN
FILLED INTO LARGE CRYOGENIC VESSELS
VGLs, GPs, PLCs, etc.

A firm that fills large cryogenic vessels, i.e., VGLs, GPs, PLCs, etc. and supplies these to a firm who then fills cryogenic home vessels either on site or at a patient's home, is required to test **EACH** large cryogenic vessel filled, prior to release. Since cryogenic vessels usually always contain a residual, whenever a new product is introduced into the vessel a commingling occurs. This commingling produces a new batch which is required to be analyzed and assigned a lot or batch number.

TESTING OF THE LIQUID OXYGEN
TO BE USED FOR FILLING HIGH PRESSURE CYLINDERS

A lot of confusion exists on the testing requirements for a storage tank where the product is used for the filling of high pressure cylinders and other cryogenic vessels. (This scenario is similar to that of a welding supply company.) The testing requirements are that immediately after each delivery, the commingled liquid oxygen is to be tested for full USP specifications, prior to the filling of any cryogenic vessels. This may be accomplished by testing:

1) a sample directly from the storage tank, i.e., the new commingled batch, or*

Current Change

ATTACHMENT D

*2) a cylinder from the first manifold filling sequence. This is the most commonly seen method.

This testing gives assurance that the commingled oxygen component is acceptable, however, finished product testing of the high pressure cylinders is still required, i.e., one cylinder per manifold filling sequence.*

Current Change

ATTACHMENT E

One (1) page not included
Sample (blank) batch production record

ATTACHMENT F

Nine (9) pages not included.
Copy of Compliance Policy Guide 7132a.16, 98/31/92