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| SUBJECT: | | IMPLEMENTATION DATE |
| COMPRESSED MEDICAL GASES | | March 15, 2015 |
| Cross-reference: 7356.002 (version 02/01/2002) | | COMPLETION DATE |
| DATA REPORTING | | |
| PRODUCT CODES | PRODUCT/ASSIGNMENT CODES | |
| Medical Gases Industry codes: 64J Profile Class Code: GAS Establishment Type Code: MG | 56002E DPI/Medical Gas Manufacturers (CPGM: Compressed Medical Gases) | |

FIELD REPORTING REQUIREMENTS

Establishment Inspection Reports (EIRs) are to be created and filed electronically employing a medical gas specific module (e.g., TurboEIR) that is accessible to CDER, as well as to ORA, staff.

Prior to starting an inspection, please refer to the appropriate Subchapters of the Investigations Operations Manual (IOM) for direction on completing establishment inspections (i.e., Subchapter 5.2 Inspectional Procedures).

For inspections of routine commercial manufacturing classified as Official Action Indicated (OAI) due to failure to comply with 21 CFR Part 211 Current Good Manufacturing Practice (CGMP) as they apply to medical gases, submit advisory, administrative, or judicial action recommendations via MARCS-CMS in accordance with the Regulatory Procedures Manual (RPM).

Districts should immediately report significant issues according to current FACTS and EES procedures (see also IOM Investigations). Districts should additionally notify CDER via CMS.

During an inspection, if you obtain information pertaining to inadequate adverse drug experience (ADE) reporting, unapproved drug issues, or post-approval reporting violations (application supplements, Field Alert Reports, etc.), report in accordance with directions provided in the applicable compliance programs and under separate captions in the EIR. Data system information about these inspectional activities should be reported using applicable separate Program Assignment Codes (PACs). Expansion of coverage under these programs into a CGMP inspection should be reported under this compliance program.

If the intended use of the medical gas is as a medical device, including calibration gases and lung diffusion mixtures, please see 21 CFR Part 800.

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PART I - BACKGROUND

Compressed medical gases (CMG or medical gases) include gaseous and liquid (cryogenic) forms stored in high-pressure cylinders that are administered as a gas. Types of compressed medical gases include, but are not limited to, oxygen, carbon dioxide, helium, nitrogen, nitrous oxide, medical air, and combinations of these gases.

Medical gases are drugs within the meaning of section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(g)(1)) and, pursuant to section 503(b)(1)(A) of the FD&C Act (21 U.S.C. 353(b)(1)(A)), are required to be dispensed by prescription.

Medical gases are regulated as finished pharmaceuticals regardless of the stage of processing. Medical gases must be manufactured (e.g., processed, filled, transfilled, mixed, purified, separated, cascaded, transferred, packaged, and distributed) using CGMP, as set forth in 21 CFR Parts 210 and 211 and in conformance with current industry practice. The FD&C Act requires that a drug, including the finished dosage form and its components, meet CGMPs to assure drug safety, identity, strength, quality, and purity.

Medical gases are considered adulterated under section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) if the manufacturing methods, facilities, processing, packing, or holding do not conform to CGMP. Medical gases not manufactured and handled in accordance with CGMP regulations can cause serious injury or death to the patients who use them. Medical gas may also be deemed adulterated under 501 parts including 501(b) and (c) of the FD&C Act.

Beginning January 5, 2013, manufacturers of designated medical gases were subject to a new certification process created by Title XI, Subtitle B of the Food and Drug Administration Safety and Innovation Act (FDASIA).^[1] The term “designated medical gas” is defined to include oxygen, nitrogen, nitrous oxide, carbon dioxide, helium, carbon monoxide and medical air that meet the standards set forth in an official compendium.^[2] Under section 576, the designated medical gases are certified (i.e., deemed to have in effect an approved new drug application) only for the following indications:

- Oxygen: for treatment or prevention of hypoxemia or hypoxia.
- Nitrogen: for use in hypoxic challenge testing.
- Nitrous Oxide: for analgesia.
- Carbon Dioxide: for use in extracorporeal membrane oxygenation therapy or respiratory stimulation.
- Helium: for treatment of upper airway obstruction or increased airway resistance.
- Medical Air: to reduce the risk of hyperoxia.
- Carbon Monoxide: for use in lung diffusion testing.

¹ Public Law 112-144, 126 Stat. 993 (July 9, 2012).

² There is currently no monograph in the USP or the NF for Carbon Monoxide (CO). FDA does not plan to grant certification requests for CO until such monograph is available. The Homeopathic Pharmacopoeia of the U.S. (HPUS) monograph for CO is inapplicable unless the designated medical gas is labeled as a homeopathic.

Only the person or entity that introduces, or delivers for introduction, a designated medical gas into interstate commerce should have or request a certificate. In most cases, this will be the initial manufacturer of a designated medical gas or gases (for example, an air separation unit producing oxygen and nitrogen). However, if a person or entity downstream is the first to market that gas as a medical gas (for example, after re-processing an industrial gas into a medical gas for human or animal use) then that person or entity must obtain certification.

The methods of filling CMGs into refillable high-pressure cylinders or cryogenic vessels are unique to the drug industry, and the container/closure systems are unlike those used for other drug products. A set of strict prefill inspections is essential to give assurance that the container/closure systems are acceptable.^[3]

Medical Gas Establishment Types:

Compressed medical gas establishments can be classified as being in one of three broad categories:

1) Transfillers

A firm that manufactures medical gas by transferring the gas, either in a liquid or gaseous state, from a larger container into smaller containers is customarily referred to as a “transfiller.” These smaller containers, either high-pressure cylinders or cryogenic vessels, are filled from larger containers (in a process known as “cascading”) or from permanently mounted tanks. These firms may fill single or multiple types of gases. The vast majority of medical gas establishments are transfillers. Manufacturers who mix different gases that were obtained in bulk are also considered transfillers for the purpose of this program.

2) Air separation units (ASUs)^[4]

ASUs separate atmospheric air into its constituent gases of oxygen, nitrogen, and argon through a process of pre-cleaning, compression, cooling, and fractional distillation of liquefied air. Most of the bulk liquid oxygen and nitrogen, for both medical and industrial purposes, is produced at these establishments. The argon is produced for industrial use. ASUs are generally highly automated continuous production systems and have very few employees in attendance during operations, which usually take place 24 hours a day, seven days a week. Because of the limited number of on-site personnel, some Quality Unit functions, such as product release and batch record review, are typically handled electronically from central offices that are not registered or generally inspected, remote from the site. The CGMP regulations pertaining to in-process controls and testing, and validation of automated control systems and equipment, have greater direct applicability at these sites than at transfilling sites.

³ The term “prefill” refers to steps completed at a firm that manufactures by transfilling, prior to the actual fill.

⁴ Oxygen Concentrators are medical devices intended to provide a continuous flow of concentrated oxygen meeting the requirements of the “Oxygen 93 Percent” USP monograph directly to patients or to supply hospital systems. They are not ASUs. See [PART V - REGULATORY/ADMINISTRATIVE STRATEGY](#)

3) **Chemical synthesizers or processors**

Chemical synthesizers or processors include sites that produce bulk nitrous oxide or carbon dioxide. Nitrous oxide can be produced by chemical reaction (thermal degradation of ammonium nitrate) or by reprocessing waste streams from adipic acid manufacture. Carbon dioxide can also be processed from waste streams of other industrial manufacturing operations. Only a small number of sites fall into this category. The CGMP regulations pertaining to handling, documentation, quality control, and testing of components and in-process materials have greater direct applicability at these sites compared to the two other categories of establishments.

PART II- IMPLEMENTATION

A. Objectives

The goal of this program is to minimize consumers' exposure to adulterated and/or misbranded medical gas products. Under this program, inspection and investigations, sample collections and analyses, and regulatory or administrative follow-up are made to:

- 1) assess the operations of CMG manufacturing establishments to determine if they conform to the CGMP regulations in 21 CFR Parts 210 and 211 and applicable sections of the FD&C Act. For operations that fail to conform:
 - a. determine if there is evidence for actions to be taken by FDA to prevent adulterated products from entering the market or, as appropriate:
 - b. remove adulterated products from the market by compliance actions such as requesting a recall, seizure, or injunction and take action against responsible persons;
- 2) determine, for an initial manufacturer of a designated medical gas or gases, if the firm has a certificate for the gas(es) being marketed (if needed, see [PART I - BACKGROUND](#)) or certification pending and provide a 21 CFR Part 211 CGMP assessment of the acceptability of a firm named in a pending drug certification,^[5]
- 3) identify practices that need correction or improvement and provide input to firms during inspections in order to improve their compliance with regulations;
- 4) assess the need for changes to FDA statutes, regulations, guidance, and policy pertinent to medical gases.

B. Scope

All commercial medical gas manufacturing and repacking operations, including all transfilling operations, are required to register and list in accordance with requirements set forth in 21 CFR Part 207 and guidances on listing. Medical gas facilities that produce only medical gases for research purposes under an investigational new drug application (IND) or Drug Research Committee (DRC) application are not required to register or list. Medical gas facilities that only remotely review batch records for batch release and do not manufacture medical gas (e.g., central offices associated with ASUs), are not required to be inspected under this program.

C. Inspection Strategy

1. Routine Surveillance Inspections:

Routine surveillance inspections document and evaluate medical gas manufacturing establishment compliance with the drug CGMP requirements. The routine surveillance of

⁵ If the firm does not have certification or pending certification for a designated medical gas, consult with the product center. The gas would be considered an unapproved new drug and should be documented in the EIR (See IOM 5.2.3.3).

medical gas manufacturing establishments also facilitates timely decisions on the medical gas certification process and in awarding of government contracts.

2. Compliance Inspections:

Compliance inspections evaluate or verify firms' corrective actions after implementation of regulatory action, including warning letters and other actions. Compliance inspectional coverage should relate to previous deficiencies and the evaluation or verification of corrective actions.

The firm is expected to evaluate *all* of its operations and implement global and systemic corrective actions after a previous, violative inspection, rather than limiting its actions to address only those deficiencies noted in the Form FDA 483.

3. For-Cause Inspections:

FDA conducts For-Cause Inspections to investigate specific problems or to evaluate specific aspects of a manufacturing operation. For-Cause Inspections may be initiated when adverse event information is reported in FARs, Drug Quality Reporting System (DQRS), consumer complaints, recall notices, etc.

D. Program Management Instructions

Inspections under this program are to be conducted according to the risk profile, including previous inspections results, AEs, FARs, and **Medical Gas Firm Categories and Risk Factors** of the firm as well as the time since inspection (see [PART III - INSPECTIONAL](#)). Reports of mix-ups, injuries, 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 the "CDER OMQ Compliance Policy" mailbox; a copy of the final report should be submitted as well (see IOM Investigations).

1. State of Control

A medical gas manufacturer is considered to be operating in a state of control when it employs conditions and practices that assure compliance with the intent of Section 501(a)(2)(B) of the FD&C Act and CGMP regulations. A firm in a state of control produces finished medical gas drug products for which there is an adequate level of assurance of quality, strength, identity, and purity.

A firm is considered to be operating out of control if any **one system (or more)** is out of control. See [PART V - REGULATORY/ADMINISTRATIVE STRATEGY](#), for a discussion of compliance actions based on inspection findings demonstrating out of control systems or firm.

2. Inspection Planning

District Offices conduct medical gas inspections and maintain drug profiles. District Offices are responsible for determining the depth of coverage given to each drug firm in accordance with this program.

3. Inspection Teams

An inspection team (See IOM 5.1.2.5) may be composed of experts from within the District, other Districts, or Headquarters (CDER or ORA). Contact ORO/Division of Field Investigations if technical assistance or additional expertise is needed (see also [FMD 142 - Technical Inspection Assistance](#)).^[6] Participation on the inspection team by an analytical chemist with knowledge of medical gas drugs is also encouraged.

4. Profile Reporting

Update all applicable profile classes in the profile screen of the FACTS coversheet based on inspection findings. There is only one Profile Class for medical gas drug products and all medical gas drug inspections should use Industry code **64J** and Profile Class code **“GAS.”**

⁶ <https://www.fda.gov/media/89745/download>

PART III - INSPECTIONAL**A. General**

The Guidance for Industry: Current Good Manufacturing Practice for Medical Gases,^[7] (Medical Gas Guidance) describes medical gas practices that FDA considers to be in agreement with the CGMP regulations. However, deviations from the practices and procedures described in the Medical Gas Guidance 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 Parts 210 or 211.

Firms may use equipment and/or procedures other than those listed in the Medical Gas Guidance provided the firm can demonstrate that the equipment or procedures meet the intent of the relevant requirement. For example, it is acceptable to use a non-official (non-compendial, or alternative) method to determine an official (compendial) drug's conformance with established official compendial specifications and standards for batch release purposes so long as the firm has validated that the alternative, non-official method is equivalent to, or better than, the official method.

Review and apply the CGMP regulations for finished pharmaceuticals in 21 CFR Part 211 to evaluate production processes. Conduct inspections according to this compliance program. In addition, review [PART V - REGULATORY/ADMINISTRATIVE STRATEGY](#) section for guidance on inspections.

The Form FDA 483, if issued, should be specific and contain only significant items. The investigation team will prepare a narrative EIR per instructions in the IOM Chapter 5 on Establishment Investigations. The Medical Gas Guidance provides additional inspectional guidance, (e.g., testing requirements for firms who supply liquid oxygen for the filling of cryogenic home vessels).

B. Inspectional Approaches

Inspections of medical gas manufactures are to be performed under PAC 56002E as either Full or Abbreviated Inspections using the systems strategy outlined below. Full Inspections include coverage of at least four systems and Abbreviated Inspections include coverage of two systems plus a set of questions that cover key aspects of medical gas manufacturing, drawn from all of the systems. Abbreviated Inspections are recommended for oxygen-only transfillers with a satisfactory record of CGMP compliance and for other medical gas firms as described in this program.

FDASIA title XI allows initial manufacturers of designated medical gases to obtain certification in lieu of an NDA or ANDA (see [PART I - BACKGROUND](#)). Initial manufacturers of designated gases should be given priority for inspection, if they have not had an inspection in the past six years, to support their certification. Firms requesting certification represent a small portion of the medical gas inventory. They haven't been ranked in terms of risk in this document, though details

⁷ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs Guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> (accessed 12/2014).

are provided below on a few of the risk factors to be aware of as well as details of CGMP issues that have been previously observed. The main initial manufacturers of designated medical gases include Chemical Synthesizers or Processors (Carbon Dioxide, Nitrous Oxide, and Helium), Air Separation Units (Nitrogen and Oxygen), and Transfillers (Medical Air).

Initial manufacturers of Medical Air are normally transfillers of multiple medical gases. See Transfiller Relative Site Risk table, below, for more information on risk factors associated with these sites.

Medical Gas Firm Categories and Risk Factors

Initial Manufacturers

| Facility Type | Risk Factors |
|--|---|
| <p>Chemical Synthesizer or Processor May be original manufacturers of Carbon Dioxide, Nitrous Oxide, or Helium</p> | <p>Carbon Dioxide manufacturers are higher risk due to the use of varied sources of starting material, including waste streams from other industries.</p> <p>Nitrous Oxide manufacturers are uncommon, with only a few in the U.S. CGMP issues have included failure to establish specifications for, and control over, raw materials, and incomplete process validation.</p> <p>Helium manufacturers are uncommon. CGMP issues have included failure to test product for impurities that can be reasonably anticipated based on the origin of the source gas entering the process, in accordance with the USP General Notices.</p> |
| <p>Air Separation Units Original manufacturers of Oxygen and Nitrogen</p> | <p>Historically, the CGMP issues have been failure to validate automated control systems and failure to establish effective Quality Unit control over the release of product.</p> <p>There is an additional risk factor if the firm installs health care facility medical oxygen systems, which requires employee training to ensure that connections are done correctly.</p> |

Transfiller Relative Site Risk (from highest to lowest risk to patients)

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|---|
| 1. Medical and industrial gases, multiple gases |
| 2. Multiple medical gases |
| 3. Medical and industrial Oxygen only |
| 4. Medical Oxygen only |

Full Inspections are recommended when:

- The inspection is the initial inspection of the firm.
- The inspection is a compliance inspection, unless otherwise instructed.

- The inspection is the first to be done as a follow-up to a Warning Letter, other regulatory action or significant Form FDA 483 findings.^[8]
- Significant changes have occurred in the firm’s operations since the last inspection, such as:
 - New potential for mix-ups or contamination arising through change in process or product line
 - New technology requiring new expertise, such as new computer systems, significantly new equipment, or new facilities
 - Any significant change in processing method, technique, or personnel at the site
- The firm has a history of recurring violations or of fluctuating in and out of compliance (recidivist).
- Other information (samples, complaints, Field Alerts, recalls, DQRS, etc.) raises questions about the firm’s ability to manufacture quality drugs.

1. Full Inspection Option

Firms with higher levels of risk, as outlined above, should be considered for Full Inspection. Normally, a Full Inspection will include inspection of at least four systems. A Full Inspection must include the Quality System and should include the Laboratory System, due to the critical role these systems play in medical gas manufacturing, as well as two additional systems.

Full Inspection conversion to an Abbreviated Inspection:

A Full Inspection may convert to the Abbreviated Inspection Option, with District concurrence, if it is found during the inspection that the firm is in a lower risk category than indicated by information available before inspection and no significant deviations are being found.

2. Abbreviated Inspection Option

Abbreviated Inspections are recommended for oxygen-only transfillers with a satisfactory record of CGMP compliance and may be appropriate for firms that do not meet the criteria listed above for Full Inspections.

Abbreviated Inspections should cover the Quality System and one other system as well as address the questions below:

- Does the firm adequately test both incoming components and finished products? (Laboratory System; Materials System; Production System)
- Has the analytical equipment been appropriately calibrated? (Laboratory System)
- Have alternative test methods been validated against official compendial test procedures? (Laboratory System)

⁸See [PART V – REGULATORY ADMINISTRATIVE STRATEGY](#) for significant Form FDA 483 findings.

- Is equipment qualified prior to first use (for example, stainless steel hoses, large cryogenic containers)? (Facilities and Equipment System; Laboratory System; Materials System; Production System)
- Are personnel (including filling personnel and delivery staff) adequately trained to do their jobs, including training in CGMPs? (Quality System)
- Are there standard operating procedures for manufacturing, processing, and testing and are they followed? (Laboratory System; Production System)
- Do production records document all significant steps? (Quality System; Production System)
- Are prefill checks conducted (especially for new cylinders)? (Laboratory System; Materials System; Production System)
- Is equipment checked for continued suitability after cleaning, repairs, refurbishment, etc.? (Facilities and Equipment System)
- Are labels controlled (i.e., reconciliation of labels and no observed mislabeling)? (Quality System; Packaging and Labeling System)
- Are labels accurate and do they include adequate instructions for use? (Quality System; Packaging and Labeling System)
- Are control mechanisms used to prevent contamination or mix-ups (e.g., are operations performed in specifically defined areas)? (Facilities and Equipment System; Materials System; Production System)

Abbreviated Inspection conversion to a Full Inspection:

An Abbreviated Inspection may be converted to a Full Inspection, with District concurrence, if:

- significant changes have occurred since the previous inspection,
- violative or potentially violative conditions are noted, or
- information obtained during the Abbreviated Inspection reveals significant deficiencies with the firm’s practices and procedures in one or more system areas (see also questions above).

C. System Inspection Coverage

The section on each system contains a list of questions intended to be an aid in conducting inspections and obtaining information needed to assess a firm’s operations. Questions are to be used at the investigator’s discretion. The answers do not have to be reported in the EIR unless they are relevant. The questions provided are specific to medical gas operations.

1. Quality System⁹

Inspection of the quality system has two parts: review of quality records as guided by the

⁹ Ref. 21 CFR Parts 211.22, 211.25, 211.28, 211.34, 211.80, 211.82, 211.84, 211.86, 211.87, 211.89, 211.100, 211.101 211.122, 211.125, 211.130, 211.160, 211,165, 211.180, 211.186, 211.188, 211,192, and 211.198

list below and evaluation of the quality unit by observation of manufacturing operations in critical areas, as guided by the quality system specific questions.

The information gained here can be used to select other system(s) to be covered during the inspection.

a. Significant Deficiencies Include:

- Inadequate label control
- False or misleading label, label contains an inaccurate statement of the contents, or label contains inadequate directions for use (however, do not cite on FDA 483 as per IOM instructions 5.2.3.3 - Non-Reportable Observations).

b. Records to Review:

1) General documents to review

- a) periodic product evaluations
- b) complaints
- c) salvaging^[10]
- d) ADEs
- e) FARs
- f) rejected lots
- g) stability data (if product bears an expiration date on the label)^[11]
- h) returned goods that indicate possible product contamination or risks to patients (e.g., incorrect labeling of medical gas, complaints of odors, or ADEs).

2) Discrepancy and failure investigations, such as:

- Out-of-Specification (OOS) results for assay impurities or any test result that is outside of the established limits
- Unexpected results or trends
- Unusual loss of pressure or contents from finished medical gas products during or after filling, or customer complaints about loss of contents (See Medical Gas Guidance). Valves occasionally wear out and need to be replaced, sometimes due to conditions outside the control of the gas manufacturer. Infrequent instances of valve replacement, or when replaced on an established cycle, are not considered failures or problems requiring an investigation under 211.192 or 211.198 .
- All investigations involving raw materials, containers/closures, stability (if product bears an expiration date on the label), and labeling
- Process deviations or equipment malfunctions that involve critical equipment, such as stainless steel hoses, pump, manifolds, pigtailed, valve assemblies,

¹⁰ This is uncommon with medical gases.

¹¹ For labels that do not bear an expiration date, see [PART V – REGULATORY ADMINISTRATIVE STRATEGY](#).

hoses, gauges, large cryogenic containers, or computerized systems used either in production processes or for records

- Product rejects (rejects determined during manufacturing and quality testing)

3) Trend reports or summaries of quality indicators.

- a) For transfillers, do batch records indicate large numbers of cylinders rejected because of:
- Failing prefill or in-process checks (e.g., odor test, hammer test (on steel cylinders), or valve leak test?
 - Failing finished product odor tests?
 - Failing post-fill valve leak tests?
- b) For transfillers, were any manifold fills of high-pressure cylinders aborted because of:
- Some cylinders failing heat of compression?
 - Incorrect temperature readings at end of fill leading to incorrect fill pressure?
 - Pressure loss from manifold at end of fill or inability of manifold to hold vacuum prior to fill (back flow)?

4) Changes to critical utilities and equipment since the last inspection, for example:

- Changes to placement of equipment and materials to prevent mix-ups and contamination
- Changes in test methods?
- New, replaced, or refurbished storage tanks?
- For air separation units, changes in computerized operating systems or other automated controls, as well as major maintenance or replacement of equipment

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| Quality System Specific Questions: | |
| All questions apply to all medical gas establishment types. | |
| 1. | Are quality unit (QU) functions performed? |
| 2. | Does QU examine and approve or reject components, containers, closures, and process materials, packaging materials, label, and finished medical gas to ensure compliance with procedures and specifications that affect the identity, strength, quality, or purity of the medical gas? |
| 3. | Does the QU control the receipt, storage, reconciliation, and issuance of labeling? |
| 4. | Does the firm establish and meet appropriate specifications for the finished medical gas product (does the firm meet or exceed USP, if applicable)? |
| 5. | Does QU adequately review production records for errors? |

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| 6. | Does QU conduct an investigation of non-conforming medical gas products, including review of the process, operations, records and complaints? |
| 7. | Were the investigations of non-conforming products adequate? |
| 8. | Does the firm take action to correct any identified problems to prevent recurrence of a nonconforming product or other quality problem? |
| 9. | Does the firm adequately handle complaints concerning the quality, purity, or possible adverse reactions of their medical gas products? |
| 10. | Does the firm have procedures in place to handle recalls? |
| 11. | Does the firm train and qualify its employees, including delivery personnel, to perform their assigned functions adequately? |
| 12. | Is CGMP training conducted on an annual basis? |

2. Facilities and Equipment System:

The inspectional evaluation of the Facilities and Equipment System is two-part, as follows:

- Facilities - Review and document the firm’s rationale for, and adequacy of, its facility design and evaluate the state of control of the facility (see Section IV of Medical Gas Guidance). Gas manufacturing facilities often include open areas where unfilled tanks are stored or where large bulk vessels are stored for safety and other practical purposes; such conditions are generally acceptable practices.
- Equipment - Review and document the firm’s rationale for and adequacy of its equipment design and evaluate the data relevant to the state of control of the equipment (see Section V of Medical Gas Guidance).

a. Investigators should look for:

- Visible deficiencies in the facility and equipment, such as cleanliness, equipment deterioration (e.g., warping, corrosion), inaccessible and/or difficult to clean surfaces, and changes to critical equipment or systems that have not been qualified and which may impact product quality.
- Aberrant events due to facility deterioration, a pattern of recurring and uncorrected maintenance issues, and increase or changes in production output that exceed the capacity of the facility and equipment.

b. Significant Deficiencies Include:

- Failure to conduct tests to confirm continued suitability of filling equipment or containers for medical use after repairs, cleaning, refurbishment, long periods in storage or exposure to condition that adversely affect the containers or equipment
- In firms filling multiple gases, failure to perform operations within specifically defined areas or to use other control mechanisms to prevent contamination and mix-ups.

FACILITIES

Evaluate the design and layout of the facility (e.g., personnel and material flow, storage, and delivery). The design of facilities should be based on the risk of product contamination or mix-ups (see Section IV of Medical Gas Guidance).

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| Facilities Specific Questions: | |
| All questions apply to all medical gas establishment types. | |
| 1. | Is there adequate space in the building for an orderly placement of equipment and materials to prevent mix-ups and contamination? |
| 2. | Are industrial gases and medical gases stored separately? |
| 3. | Is the manufacturing facility maintained in good physical condition, kept clean, and does it have sufficient areas for organized operations, such as a well-defined filling area and a well-defined quarantine area? (Note: 21 CFR Part 211.42 allows for other control mechanisms, such as tagging) |
| 4. | Do the quarantine areas adequately separate incoming medical gases, high-pressure cylinders, cryogenic containers, manufacturing equipment, rejected containers and closures, and the finished product? |
| 5. | Do delivery vehicles have well-defined and separate areas for medical gases and industrial gases or other control systems in place to prevent mix-ups from occurring? |
| 6. | Are the facilities for medical gas distribution secure from unauthorized entry? |

EQUIPMENT (Reference: Section V of Medical Gas Guidance)

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| Equipment Specific Questions: | |
| All questions apply to all medical gas establishment types. | |
| 1. | Does the firm implement procedures to ensure that all production equipment is qualified, maintained, and clean and suitable for its intended purpose prior to use (e.g., manifolds, pigtails, valve assemblies, stainless steel hoses, gauges, and large cryogenic containers)? |
| 2. | Do hoses used to fill cryogenic containers have protective end caps to prevent contamination from insects, dirt, debris, and other materials? |
| 3. | Was the firm's equipment constructed and maintained in such a way that the surfaces of the equipment that contact the components, in-process material or medical gases, are not reactive, additive or absorptive, so as to alter the quality of the medical gas product? For example, are equipment surfaces kept free of dirt, oils, cleaning solvents, etc., that may ingress into or react with the gas so as to contaminate the drug product? |
| 4. | Are automatic, mechanical, and electronic equipment used in the manufacturing, processing, packing, and holding of medical gas products routinely calibrated, inspected, or checked (e.g., vacuum gauges, thermometers, check valves, and computerized systems)? |
| 5. | Are the activities for qualification and maintenance of the medical gas equipment documented? |

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| 6. | If the firm’s employees are using gloves, are the gloves maintained and used in such a manner as to reduce potential contamination of the drug product by industrial residues? |
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3. Materials System ^[12]

CGMP requirements for testing ingredients and other raw materials are more applicable to firms that manufacture by chemical synthesis than to transfillers. For transfillers, the regulations apply mainly to the examination and testing of new containers and returned empty containers (See section VI of Medical Gas Guidance).

Significant Deficiencies Include:

- Inadequate cylinder prefill and post-fill inspections and procedures,
 - failure to test new cylinders
 - failure to test cylinders after being used for industrial gas ^[13]
 - failure to perform procedures intended to remove or detect residual gases or other contaminants in the cylinders (e.g., vacuum evacuation, prefill and post-fill odor tests, etc.)
- Failure to test either bulk gases or finished product lots

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| Materials System Specific Questions: | |
| Questions may be applicable to different establishment types | |
| 1. | Did the firm establish and follow procedures for the receipt, login, identification, storage, handling, testing, and acceptance or rejection of drug product components, containers, and closures? |
| 2. | Are prefill inspections conducted, particularly on new cylinders, after a cylinder has been used for industrial purposes, or whenever there is a potential for residual gases or other contaminants in a container? |
| 3. | Are the suppliers qualified? Was a reliable supplier used as a source of each lot of components, containers or closures? For example: Are suppliers of bulk gases FDA- registered and certified? If so, did their most recent FDA inspection disclose any issues of concern? Are suppliers’ certificates of analysis (COAs) for bulk gases periodically verified? |
| 4. | Does the firm designate incoming lot(s) of components, containers, closures, or other materials as quarantined and then test or examine them before accepting or rejecting for use? |

¹² Ref. 21 CFR Parts 211.80, 211.82, 211.84, 211.86, 211.87, 211.89, 211.94, 211.142, 211.150

¹³ In rare instances, a firm may relabel and market a gas as industrial grade. FDA recommends that containers that previously held medical-grade gas that were then converted to use with industrial-grade gas, not be subsequently used for medical-grade product. If they are subsequently reused, they should undergo a defined re-qualification validation procedure.

| | |
|---|---|
| 5. | Did the firm handle and store components, containers, and closures in a manner that prevents contamination, mix-ups, and deterioration and ensures that they are suitable for intended use? |
| 6. | Do the records for the receipt of components, containers, or closures include the identity and quality of each shipment, the supplier's name, lot number, date of receipt, results of any testing performed, disposition of rejected material, and expiration date (if applicable)? |
| * Additional questions for Transfillers | |
| 7. | For each shipment received, was a record kept of each lot of components, containers and closures? |
| 8. | Does the firm perform a visual identification and examination or any applicable testing of representative samples from each lot of new medical gas containers or closures to verify conformance to established specifications? |
| 9. | Does the finished product testing of medical gas ensure that the correct components were used? Applicable to transfillers who produce gas mixtures |
| 10. | When finished product testing conducted by the firm does not ensure that the correct components have been used, did the firm conduct an identity test on each lot of each component of an active ingredient and each lot of inactive ingredient used in that medical gas product? Applicable to transfillers who produce gas mixtures |
| * Additional questions for Chemical Synthesizers and Processors: | |
| 11. | Do the lot(s) of component(s) used for production meet the established specification, and are they used before expiry? |
| 12. | For representative samples of components, does the firm perform a visual identification and examination of the COA against established specifications? Are COAs periodically verified? |
| 13. | Does the finished product testing of medical gas ensure that the correct components were used? |
| 14. | When finished product testing conducted by the firm does not ensure that the correct components have been used, did the firm conduct an identity test on each lot of each component of an active ingredient and each lot of inactive ingredient used in that medical gas product? |
| 15. | Was a record kept for each shipment received of each lot of components? |
| * Additional questions for ASUs | |
| 16. | Is air quality checked? Does the firm obtain local air quality reports and does it confirm the efficacy of their process in removing the known impurities in the ambient air by periodically performing impurity profile analyses of the finished drugs? |

4. Production System ^[14]

The CGMP regulations pertinent to in-process controls and process validation are more directly applicable to ASUs and manufacturers by chemical synthesis than to transfillers.

Production records for compressed medical gases are often a single page containing the

¹⁴ (Ref. 21 CFR Parts 211.100, 211.101, 211.105, 211.110, 211.111, 211.113, 211.115, 211.186, 211,188)

results of prefill inspections, manufacturing operations, post-fill inspections, deviations, and evidence of quality review.

Significant Deficiencies Include:

- Failure to perform operations within specifically defined areas or to use other control mechanisms to prevent contamination and mix-ups.
- Inadequate cylinder prefill inspections and procedures, particularly failure to perform those intended to remove or detect residual gases or other contaminants in the cylinders (most important **before first use or after industrial use**).
- No written specifications of test procedures, or procedures not followed by individual(s) performing the test.
- Failure to test either bulk gases or finished product lots

| Production System Specific Questions: | |
|---|---|
| Questions for all medical gas establishment types: | |
| 1. | Is finished product testing performed? |
| 2. | Does the firm have written production and process control procedures to ensure and document that key process parameters are controlled and that deviations from the procedures are justified? |
| 3. | Does the firm have master production and control records that document all steps in the production process? |
| 4. | Do the master production and control records contain complete production and control instructions, complete sampling and testing procedures, complete specifications, and special notations or precautions to be followed? |
| 5. | Do the master production and control records contain a description of the medical gas product containers, closures, and packaging materials, or a specimen or copy of each label and all other labeling? |
| 6. | Do the master production and control records contain all of the names and strengths of the medical gas products? <i>Note: Applies to all facility types but for transfillers, only applies to gas mixtures.</i> |
| 7. | Does the firm create a unique batch production record for each batch? <i>Note: For transfillers, there should be a review of batch production and control records (usually in the form of a pumper's or filler's log) for a representative number of batches manufactured by the firm.</i> |
| 8. | Do the batch production records include each major production step obtained from the approved master production and control record? (Section XI of Guidance Document) |
| 9. | Do the batch production records include the dates of production steps or times of critical production steps? <i>Note: For transfillers, all steps will usually take place within the same day.</i> |

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| 10. | Do the batch production records include labeling? |
| 11. | Does the firm perform and check each significant step of the operation to verify its adherence to written procedures through observation whenever possible? |
| 12. | Does the firm have records for the sampling and testing of medical gas products? |
| 13. | Does the firm perform an investigation of any out-of- specification test results obtained? |
| 14. | Do the batch production records include the results of any investigations conducted? |
| 15. | Does the firm have a production area and equipment that is clean and suitable for use (e.g., have manifolds and piping used for O ₂ transfilling been “oxygen cleaned”)? |
| 16. | Does the firm perform installation and operational qualification for each type of equipment used in production? <i>Note:</i> For transfillers, this includes calibration records for manifold gauges, thermometers, scales, etc. For ASUs, this includes qualification of computer-controlled or other automated systems. |
| 17. | Does the finished product testing ensure their conformance to all specifications? |
| 18. | Are alternative test procedures validated against the official USP methods? |
| 19. | Does the firm refer to the specific compendial test procedure in a specification for final release? |
| 20. | Did the firm first verify and document that the compendial test procedure or alternate procedure works under the conditions of actual use? |
| 21. | Are procedures established and followed to ensure that each batch of a medical gas product was given final release only after laboratory test data and documentation were reviewed by the QU? |
| 22. | Does the firm have the production records reviewed by the person responsible for quality to determine if errors have occurred? |
| 23. | Does the firm have procedures for the rejection of a non-conforming batch? |
| 24. | Did the firm follow its written procedures to reject a batch of medical gas product that did not conform to specification? |
| 25. | Does the firm follow written procedures to identify and segregate rejected products to avoid mix-up? |
| 26. | Does the firm investigate nonconforming products, including review of the process, operation, records, and complaints? |
| 27. | Does the firm correct identified problems to prevent recurrence of a nonconforming product or other quality problem? |
| 28. | Does the batch production record include the name, lot number, and (if applicable) measurement of each active or inactive ingredient, per batch or per unit of measurement of the medical gas product? |
| 29. | Do the master production and control records contain all names and, if applicable, an accurate statement of the volume or weight of each component, using the same volume or weight system for each component? |
| * Additional questions for Transfillers: | |
| 30. | Are the lot numbers of the bulk gas lots recorded? |

| | |
|---|---|
| * Additional questions for Chemical Synthesizers and Processors: | |
| 31. | Does the batch production record include the weights or other measure of quantity for components, or identification codes of components? |
| 32. | Do the process controls include control of in-process materials until the required tests or other verification activities have been completed or necessary approvals are received and documented? |

5. Packaging and Labeling System ^[15]

Refer to Sections VI and VIII Medical Gas Guidance.

Special note should be taken of the firm's filling and labeling controls. 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 CGMP deviation.

Compare the standard color markings ([Attachment A, CMG Cylinder Colors](#)) 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. ^[16]

Significant Deficiencies Include:

- Inadequate label control in firms filling multiple gases
- Inadequate label control in firms filling both industrial and medical gases

| | |
|---|--|
| Packaging And Labeling System Specific Questions: | |
| All questions apply to all medical gas establishment types. | |
| 1. | Does the firm control packaging and labeling operations to prevent mix-ups (i.e., examination and reconciliation of labels issued, used, and returned, in accordance with written procedures)? |
| 2. | Does the firm apply the labels so they remain legible and affixed during processing, storage, handling, distribution, and use? |
| 3. | Are medical gas containers correctly labeled (e.g., is there only one label on the container)? |
| 4. | Does each batch record include a specimen copy of the label? |

6. Laboratory System ^[17]

Refer to Section X of Medical Gas Guidance.

Products with a history of previous problems should be included. Spot-check a limited number of analytical test records to assure that batches are being adequately tested for conformance to specifications.

¹⁵ Ref. 21 CFR Parts 211.122, 211.125, 211.130, 211.134, 211.184.

¹⁶ No specific regulation requires the use of this color-coding system, but FDA recommends its use (Section VI of Draft Medical Gas Guidance).

¹⁷ Ref. 21 CFR Parts 211.160, 211.165, 211.167, 211.170, 211.173, 211.192, 211.194.

Special note should be taken of the firm's calibration of the analytical equipment. Any observations of inadequate controls or calibration will indicate that the full inspectional option should be utilized.

Significant Deviations:

- Failure to test bulk gases or finished product lots
- Non-compendial test methods used not validated and shown to be equivalent to USP methodology
- Inadequate cylinder prefill and postfill inspections, particularly failure to perform procedures intended to remove or detect residual gases or other contaminants in the cylinders (e.g., odor tests).

| Laboratory System Specific Questions: | |
|---|--|
| All questions apply to all medical gas establishment types. | |
| 1. | Does the firm have and follow procedures for the sampling and testing of medical gas products and components for assay, identification, odor, and other appropriate tests? |
| 2. | Are analytical methods suitable for their intended use, and sufficiently sensitive, specific, accurate, and reproducible? Is there documentation to support this? |
| 3. | Have release test procedures been validated, (including documenting accuracy, sensitivity, specificity, and reproducibility, etc.)? |
| 4. | Does the analytical methodology document its equivalency to USP or NF official methods, if applicable? |
| 5. | For electronic analytical instruments, is there documentation of the validation protocols demonstrating USP or NF equivalency, including a copy of the actual validation study with data generated for each analyzer by model number? |
| 6. | For analytical equipment, is the manufacturer's instruction manual on file or referenced in the firm's own written procedures to assure proper calibration? |
| 7. | Is the analytical equipment calibrated using certified reference standards? |
| 8. | Is there testing for potential contaminants, if there is reason to believe that contamination might be present? |
| 9. | Are samples tested representative of the lot or batch being tested? <i>Note:</i> Lengths of piping or tubing may separate testing equipment from the bulk tank or finished product lot being tested. Firms should be able to demonstrate that the product reaching the analyzer is representative of the lot or batch being tested. |
| 10. | Were the reagents, solutions, or supplies used in the testing procedures adequately controlled (applies, for example, if the Orsat method is used for O ₂ or CO ₂ and to other wet chemistry assays)? |
| 11. | Has the firm established and followed procedures to ensure that the lab equipment is routinely calibrated, inspected, checked, and maintained, and is this documented? |

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|-----|--|
| 12. | Do the laboratory records contain all data obtained in the course of each test? |
| 13. | Do the lab test records contain a description of each method used, a statement of the sampling method, a record of all calculations performed in connection with each test, and if applicable, a statement of the weight or measurement of the sample used for each test? (Note: Statements of weight or measurement of sample size do not apply for paramagnetic analyzers or indicator tubes since these rely on continuous flow at a particular rate.) |
| 14. | Does the firm’s analyst, prior to each day of use, perform a system suitability test on the gas chromatographs (GCs), if used for analysis? |
| 15. | Do the laboratory records contain the signature or initials of the person performing the test? |
| * | Items 16-18, below apply if the firm’s container label includes an expiration date: <i>If the labels do not bear an expiration date, we are currently applying enforcement discretion. See PART V – REGULATORY/ADMINISTRATIVE STRATEGY.</i> |
| 16. | Were the test methods for stability testing of the medical gas products reliable, meaningful, stability indicating, and specific? |
| 17. | Were the samples tested for stability under suitable storage conditions? |
| 18. | Does the firm have a written stability program? |

D. Sample Collection

Routine physical samples should not be collected.

Physical samples should be collected only in the case of injuries or deaths, mix-ups, potency problems or contamination problems. Contact ORA-HQ/ORS for sample collection guidance at such time as a physical sample collection decision is made. Consult your home district or the testing laboratory, if different, for guidance concerning sample size and shipment.

Documentary samples should be collected to document labeling and significant CGMP deviations.

If no interstate documentation of the incoming or outgoing product is possible, then document the following (as applicable):

- The manufacturer of the storage tank.
- The manufacturer of high-pressure cylinders (each cylinder manufacturer has a unique logo that should be documented by photos, tracings, or pencil rubbing).
- The manufacturer of high-pressure cylinder valves.
- The manufacturer of the vehicle-mounted vessels.
- 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.

For a seizure recommendation, document the interstate commerce of the liquid or gaseous state, whichever is appropriate.

E. Reporting

Refer to Compliance Program 7356.002, Drug Manufacturing Inspections for additional guidance.

PART IV - ANALYTICAL

Routine physical samples should not be collected.

If the decision to collect samples is made, see instructions on sample collection under Part III Section D. SAMPLE COLLECTION, above.

A. Analyzing Laboratories

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

Chemical analysis by USP procedures using the Orsat apparatus (for CO₂, O₂) if needed, should be performed by the Northeast Regional Laboratory (HFR-NE500).

Samples collected in connection with illness, injury, or ADE reports are to be sent to the FDA Forensic Chemistry Center for analysis.^[18]

B. Analysis:

Samples are to be examined for compliance using the methods found in the Medical Gas Analytical Manual (Orsat O₂ analysis) or other equivalent methods. Check analysis will be by the official method, or when no official method, by other suitable validated procedure.

¹⁸ Contact information: FDA Forensic Chemistry Center, 6751 Steger Drive, Cincinnati, Ohio, 45237; Tel: 513-679-2700 Fax: 513-679-2761

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

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

A recommendation for regulatory action should be submitted by the District Office when a judgment is made that the firm is not operating in a state of control, displays significant deviations per the list below, and management of the firm is unwilling or unable to make adequate corrective actions in an appropriate time frame.

A. Significant deviations that may result in regulatory and/or administrative action:

1. False or misleading label, label contains an inaccurate statement of the contents, or label contains inadequate directions for use. (Quality System; Packaging and Labeling System)
2. Failure to perform operations within specifically defined areas or to use other control mechanisms to prevent contamination and mix-ups. (Facilities and Equipment System; Production System)
3. Inadequate cylinder prefill inspections and procedures, particularly failure to perform those intended to remove or detect residual gases or other contaminants in the cylinders (most important **before first use or after industrial use**). (Laboratory System; Materials System; Production System)
4. No written specifications of test procedures, or procedures not followed by individual(s) performing the test. (Laboratory System; Production System)
5. Use of test methodology that has not been validated against official test procedure. (Laboratory System)
6. Testing instrument not adequately calibrated per the instrument manufacturer's directions. (Laboratory System)
7. Failure to conduct tests to confirm continued suitability of filling equipment or containers for medical use after repairs, cleaning, refurbishment, long periods in storage or exposure to condition that adversely affect the containers or equipment. (Facilities and Equipment System)
8. Inadequate label control. (Quality System; Packaging and Labeling System)
9. Failure to test commingled lots of a single compressed medical gas for identity and strength or failure to examine at least one cylinder per uninterrupted filling sequence for both identity and strength, provided the same equipment, personnel, and lot of bulk is used. (Laboratory System)

10. Failure to test bulk gases or finished product lots. (Laboratory System; Materials System; Production System)

B. Warning Letters For Medical Oxygen (Oxygen, USP) Only Firms:

Warning letters should be considered for Oxygen, USP-only firms under the following circumstances:

- 1) Violation of #1 alone, or
- 2) Violation of #2, plus at least one other violation (of #3-7) from the preceding list.

C. Policy on Medical Gas CGMPs:

1. Periodic Reports

The Agency at the present time does not require firms manufacturing designated medical gases to submit the periodic reports required under 21 CFR Parts 314.80(c)(2), *Periodic adverse drug experience reports* and 314.81(b)(2), *Annual report*. Please note that firms manufacturing a designated medical gas are still required to comply with all other regulatory requirements for ADE and FARs reporting (please see also CPGM 7353.001 "Post-Marketing Adverse Drug Experience Inspections" and CPGM 7356.021 "Drug Quality Reporting System Reports and Field Alert Reports").

2. Yield Determination, Component Reconciliation, Expiry Dating, and Stability Studies:

Yield determinations (21 CFR Part 211.103) are generally not well-suited for the manufacture of medical gas, and should not be cited as a possible violation without prior CDER concurrence.

Component reconciliation (21 CFR Part 211.184(c)) is also generally not well-suited for medical gases, and should not be cited as a possible violation without prior CDER concurrence.

If a firm chooses not to include expiration dating (21 CFR Part 211.137) on the label, no action will be taken. If a firm labels a gas with an expiration date it must be supported by data (stability studies), which is subject to review during a site inspection. Lack of an expiration date should not be included on a Form FDA 483 unless prior concurrence has been given by CDER.

Stability studies (21 CFR Part 211.166) are not required unless a firm labels a gas with an expiration date.

3. Air Separation Unit Validation:

CDER regards "current industry standards" for the validation of medical gas ASU automated and computer controls as substantially compliant with CGMP requirements. The relevant current industry standards are best represented by CGA guide P-8.2. "Guideline for Validation of Air Separation Unit and Cargo Tank Filling for Oxygen USP and Nitrogen NF." Investigators should review this document before conducting an ASU inspection.

4. Oxygen Concentrators:

Oxygen Concentrators are medical devices intended to provide a continuous flow of concentrated oxygen directly to hospital supply systems and are generally regulated as devices by 21 CFR Part 820. They are not ASUs. Oxygen concentrators may be used to fill cylinders for later use. If a firm uses oxygen concentrators to fill standard cylinders for later sale, then the oxygen concentrator(s) is (are) considered medical gas manufacturing equipment subject to all drug manufacturing CGMPs.

5. Labeling:

For any possible misbranding violations, follow IOM instructions including 5.2.3.3 - Non-Reportable Observations, and contact CDER's Office of Unapproved Drugs and Labeling Compliance (see Part VI) for instructions.

PART VI – REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

A. References

1. CGA Guide P-8.2, “Guideline for Validation of Air Separation Unit and Cargo Tank Filling for Oxygen USP and Nitrogen NF,” <http://www.cganet.com/>
2. CGA Pamphlet P-2.6, “Transfilling of Liquid Oxygen Used for Respiration,” <http://www.cganet.com/>
3. CGA, “Handbook of Compressed Gas,” <http://www.cganet.com/>
4. CGA Standards and Specifications, C-9, “Standard Color Marking of Compressed Gas Containers for Medical Use,” <http://www.cganet.com/>
5. Finkelson, M. J., 1971, Medicinal Gas Analytical Manual: New York District.
6. FDA Compliance Program 7356.002, “Drug Manufacturing Inspections,” <http://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/UCM125404.pdf>
7. FDA guidance for industry, *Current Good Manufacturing Practice for Medical Gases*; <https://www.fda.gov/media/70973/download>
8. FDA guidance for industry, *Certification of Designated Medical Gases; 2012 draft guidance*; <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/certification-process-designated-medical-gases>
9. FDA Investigations Operations Manual, <http://www.fda.gov/iceci/inspections/iom/default.htm>
10. FDA Regulatory Procedures Manual, <http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm>
11. United States Pharmacopeia and National Formulary (USP-NF), FDA Library electronic resources intranet page; <http://www.usp.org/usp-nf>

B. Attachments

Attachment A

CMG Cylinder Colors

Attachment B

Oxygen Transfiller Firm Testing Requirements

C. Contacts

Office of Regulatory Affairs (ORA)

For technical questions concerning inspections contact:

Office of Regulatory Affairs (ORA)

Office of Medical Products and Tobacco Operations (OMPTO)

Division of Medical Products and Tobacco Program Operations (DMPTPO)

Telephone number: 301-796-0358

FAX number: 301-827-6685

Center for Drug Evaluation and Research

CGMP or any Quality-Related Policy Questions

For CGMP or any quality-related policy question, technical or scientific questions or information needs, including questions about this program, please send an email to the following address and it will be handled as a top priority:

CDER-OPQ-Inquiries@fda.hhs.gov

Compliance and Enforcement-Related Guidance or Policy

For compliance and enforcement-related guidance or policy, including evidence need and sufficiency, citations, and case evaluation/recommendation advice, please send an email to the following address and it will be handled as a top priority:

CDER OMQ Compliance Policy: CDEROMQCompliance@fda.hhs.gov

Labeling Requirements and Policies

Office of Unapproved Drugs and Labeling Compliance, see intranet home page for contacts
[CDER | Office of Compliance | Office of Unapproved Drugs and Labeling Compliance]

Registration and Drug Listing Requirements

CDER Office of Compliance, see “CDER: Who’s the Lead” intranet page for contacts
[CDER | Office of Communications | CDER: Who’s the Lead]

PART VII- CENTER RESPONSIBILITIES

See Drug Process Inspection Compliance Program 7356.002, see “Drug Compliance Programs”
intranet master list

[Policies & Procedures | SOPs by Programs : Drug]

[2 Attachments]

CMG Cylinder Colors¹⁹

A. Single Gases

| COLOR | GAS |
|--------------|--------------------|
| Green | Oxygen USP |
| Gray | Carbon Dioxide USP |
| Blue | Nitrous Oxide USP |
| Brown | Helium USP |
| Black | Nitrogen NF |

B. Mixtures

| COLOR | GAS |
|-----------------|--|
| Gray and Green | Carbon Dioxide USP and Oxygen USP |
| Brown and Green | Helium USP and Oxygen USP |
| Yellow | Medical Air (Mixtures of NF Nitrogen and USP Oxygen containing 19.5% to 23.5% Oxygen) |
| Green and Black | NF Nitrogen/USP Oxygen mixtures other than those containing 19.5% to 23.5% Oxygen |

[End Attachment A]

¹⁹ “Standard Color Marking of Compressed Gas Containers for Medical Use Fifth Edition” CGA Standards and Specifications, C-9- 2013

Oxygen Transfiller Firm Testing Requirements

Many firms are in business to supply Oxygen, USP to patients in need of supplemental oxygen, either as cylinders of compressed oxygen or as liquid oxygen for the patient's home vessel. Our primary interest during an inspection of these firms is to establish that the oxygen provided to the patients meets the identity and strength specifications for Oxygen, USP. This may be accomplished by the firm testing the high-pressure cylinder contents and/or the liquid oxygen.

A. Testing Requirements for Cylinders of Compressed Oxygen USP

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

B. Testing Requirements for Cryogenic Home Vessels of Liquid Oxygen

Cryogenic home vessels are either filled on a periodic basis or are filled when the firm is notified that the oxygen has reached a predetermined level. The firm will 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.

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 oxygen, or (2) the contents of the cryogenic home vessel?

1. Testing of Incoming Liquid Oxygen in Firms that Fill Cryogenic Home Vessels

- a. If a firm dispenses liquid oxygen (LOX) from either a permanently-mounted vessel 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:
 - 1) 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.
 - 2) 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:

- i. witnessing the testing performed at the supplier. Again, the firm's employee who is responsible for witnessing the testing should receive training specific to the analytical methodology used, or
 - ii. if the firm's responsible employee 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.
- 3) 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 (e.g., produced via air liquefaction), then the USP requires two additional tests be performed for carbon dioxide and carbon monoxide impurities.
- b. 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:
- 1) there are no other storage tanks on the premises,
 - 2) the VMVs are dedicated to the delivery of oxygen, and
 - 3) the VMVs filled from the storage tank have not been completely emptied or out of service.

2. Testing of Cryogenic Home Vessels

The most important criteria in the filling of cryogenic home vessels is who maintains possession or 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 CGMPs require full 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.

- a. No testing is required as long as the following three criteria are met:
 - 1) Liquid oxygen is the only liquid being filled on the premises.
 - 2) Incoming liquid oxygen is adequately tested for identity and strength according to one of the above methods.
 - 3) Cryogenic home vessels are filled by the firm.
- b. If cryogenic home vessels are sent out for repair/maintenance then, at a minimum, each vessel returned should be retested for identification before redistribution (see 21 CFR Part 211.87).
- c. If any other gas drug product is being filled on the premises, then ALL cryogenic home vessels filled on the premises are required to be tested for identity and strength.

- d. 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 TESTING OF THE INCOMING LIQUID OXYGEN.

C. Testing Requirement for Commingled Bulk Oxygen:

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 commingling of the material. The new commingled bulk batch or lot is assigned a new lot number and the source of the new bulk shipment is considered the sole source of the new commingled batch or lot for CGMP recordkeeping purposes. The commingled lot cannot be used until approved for use.

1. Testing of Liquid Oxygen Filled into Large Cryogenic Vessels

A firm that fills large cryogenic vessels and supplies these to a separate 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 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.

2. Testing of the Liquid Oxygen to be Used for Filling High Pressure Cylinders

When high-pressure cylinders and other cryogenic vessels are filled from a storage tank then immediately after each delivery, the commingled liquid oxygen is to be tested for full USP specifications before it is used to fill any cryogenic vessels. This testing may be conducted on:

- a. a sample taken directly from the storage tank (i.e., the new commingled batch), or
- b. a cylinder from the first manifold filling sequence (this is the most commonly seen method).

This testing assures 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).

[End Attachment B]