Medical Gases — Current Good Manufacturing Practice

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Inspections and Investigations (OII)
Office of Combination Products (OCP) in the Office of the Commissioner

November 2025
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Revision 2

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist ***manufacturers***[2] of ***medical gases*** in complying with current good manufacturing practice (CGMP) requirements. CGMP requirements, when adequately put into practice, help to ensure that medical gases meet appropriate quality standards, and prevent mix-ups, deviations, failures, and errors.[3]

On June 18, 2024, FDA established new and revised regulations tailored to medical gases,[4] including CGMP requirements codified in part 213 (21 CFR part 213). Before these requirements were implemented, medical gas manufacturers were subject to the CGMP regulations for finished pharmaceuticals in parts 210 and 211 (21 CFR parts 210 and 211). The draft guidance for industry *Current Good Manufacturing Practice for Medical Gases* (June 2017) described how to comply with those requirements. This guidance revises and replaces the 2017 draft and describes how to comply with the CGMP requirements for medical gases in part 213. This revision includes among its recommendations clarification on ensuring the reliability of a supplier's capabilities; protection against container closure leaks; appropriate cleaning and maintenance of buildings, facilities, and equipment used in medical gas manufacture; prevention of labeling and product mix-ups; circumstances requiring stability testing, expiration testing, or both; and handling of returned and salvaged medical gases.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research, in cooperation with the Center for Veterinary Medicine, the Office of Inspections and Investigations, and the Office of Combination Products in the Office of the Commissioner at the Food and Drug Administration.

[2] The Glossary defines many of the terms for purposes of this guidance. Words or phrases found in the Glossary appear in bold italics at first mention.

[3] For more information about CGMP regulations, see FDA's Facts About Current Good Manufacturing Practice (CGMP) web page at https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practice-cgmp.

[4] See 89 FR 51738.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Definition of Medical Gas and Designated Medical Gas

This guidance applies to medical gases as defined in section 575(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360ddd(2)). In this section, the term medical gas means a drug that is manufactured or stored in a liquefied, nonliquefied, or cryogenic state and administered as a gas. Medical gases include ***designated medical gases (DMGs)*** as defined in section 575(1) of the FD&C Act; medically appropriate combinations of DMGs; medical gases that are approved under an application submitted to FDA under section 505 of the FD&C Act (21 U.S.C. 355) for administration to humans or under section 512 of the FD&C Act (21 U.S.C. 360b) for administration to animals; and any marketed unapproved drugs that are medical gases. Additionally, some medical gases are marketed as part of a combination product, such as a medical gas marketed with a device constituent part.[5]

Section 575(1) of the FD&C Act defines a DMG as any of the following gases that meet the standards in an official compendium:[6] oxygen, nitrogen, nitrous oxide, carbon dioxide, helium, carbon monoxide, and medical air. The United States Pharmacopeia and National Formulary (USP-NF) is the applicable compendium for DMGs. Section 575(1)(H) of the FD&C Act authorizes FDA to add to the list of DMGs any other medical gas it deems appropriate.

The term medical gas does not include gases that are used as excipients in drug products that are not medical gases (e.g., a propellant for an inhalation drug); gases that serve as processing aids in drug manufacturing (e.g., a nitrogen overlay to prevent oxidation of an active pharmaceutical ingredient during manufacturing); or gases that do not meet the definition of a drug under section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)) (e.g., gases for food or industrial applications, gases used for device testing and verification activities, or gases used to clean or purge medical gas containers or medical gas pipelines). Gases that are not medical gases are outside the scope of this guidance.

B. CGMP Statutory and Regulatory Requirements

Under section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)), a drug, including a medical gas, is deemed to be adulterated if "the methods used in, or the facilities or controls used

[5] A *combination product* is a product comprised of two or more different types of products (i.e., a combination of a drug, device, and/or biological product with one another), as described in 21 CFR Part 3. A *constituent part* is a drug, device, or biological product that is part of a combination product (see 21 CFR 4.2).

[6] See section 201(j) of the FD&C Act.

for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice." Section 501 of the FD&C Act states that "the term *current good manufacturing practice* includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products." To implement oversight and controls, FDA strongly encourages medical gas manufacturers to establish an effective pharmaceutical quality system (PQS).[7] An effective PQS enables the manufacturer's ***quality unit*** to use information obtained about the product and the process to assess risks to manufacturing performance and drug quality and to identify opportunities to address those risks through changes to manufacturing practices.[8] This approach reflects the principle that quality should be built into the product; testing alone cannot ensure product quality.

The regulations implementing the statutory requirements for medical gas are located in part 213. They cover the same categories as the general CGMP drug regulations in parts 210 and 211 for finished pharmaceuticals but reflect differences in how medical gases are manufactured, processed, packed, and held. Differences include the fact that generally, medical gases are manufactured, stored, combined, and distributed under pressure in closed systems, which reduce the risk of contamination (e.g., dust, dirt, moisture, and unacceptable levels of impurities); are not expected to expire or chemically degrade under ordinary storage conditions; and are marketed in containers and closures that are typically reused many times.

CGMP requirements for combination products are addressed in 21 CFR part 4, subpart A. The combination product CGMP requirements that apply to each constituent part apply to the combination product they constitute. Because of the different CGMP requirements, a streamlined approach to demonstrate CGMP compliance while avoiding unnecessary redundancies is available to combination products, as described in part 4A. The medical gas final rule (see footnote 4) amended certain requirements in part 4A to reflect the new CGMP requirements for medical gases under part 213. The amendments to part 4A include the CGMP requirements applicable to a combination product that includes a drug constituent part that is a medical gas (see 21 CFR 4.3(e)) and how certain combination products that include a drug constituent part that is a medical gas can comply with the CGMP requirements, including use of a streamlined approach (see 21 CFR 4.4).

III. ORGANIZATION AND PERSONNEL

A. Quality Unit Responsibilities

The quality unit is responsible for quality oversight throughout manufacturing. Specifically, the quality unit has the responsibility and authority to approve or reject all ***components***, medical gas

[7] See the International Council for Harmonisation (ICH) guidance for industry *Q10 Pharmaceutical Quality System* (April 2009). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[8] See the ICH guidance for industry *Q9(R1) Quality Risk Management* (May 2023).

containers and closures, ***in-process materials***, packaging material, labeling, and medical gases, and the authority to review production records to ensure that no errors have occurred or, if errors have occurred, that they have been fully investigated (§ 213.22(a)). Quality unit responsibilities also include approving or rejecting medical gases manufactured, processed, packed, or held under contract by another company (§ 213.22(a)). To fulfill its responsibilities, the quality unit must have available to them adequate laboratory facilities for the testing and approval or rejection of components, medical gas containers and closures, packaging materials, in-process materials, and medical gases (§ 213.22(b)). The quality unit is also responsible for approving or rejecting all procedures or specifications impacting on the identity, ***strength,*** quality, and purity of the medical gas (§ 213.22(c)). The quality unit's responsibilities and procedures must be in writing, and its procedures must be followed (§ 213.22(d)).

A quality unit's size and complexity can vary with the size and number of operations for which the quality unit is responsible. For example, a manufacturer that fills only oxygen and has very few employees might have only one person as the quality unit. However, larger manufacturers with establishments at several locations might employ a corporate quality structure to oversee their staff at multiple locations or opt for a separate quality unit at each establishment. Either arrangement may satisfy the requirements of § 213.22 as long as all responsibilities of the quality unit are fulfilled.

Production personnel and the quality unit should remain independent. Some medical gas manufacturing establishments, however, have limited personnel, and in such cases, the individuals assigned quality unit responsibilities can also perform other functions (§ 213.22(e)). These individuals, regardless of their production functions or other roles, implement the controls and review the results of manufacture to ensure that product quality standards established by the manufacturer are met. Appropriate written controls must be in place to ensure any other functions are performed separately from quality unit responsibilities and that such other functions do not interfere with the quality unit's responsibilities or subordinate the quality unit's responsibilities to any other unit (§ 213.22(e)). For example, in instances where there are limited personnel, it would not be appropriate for personnel to check their own work.

Each person who performs quality unit functions must be adequately trained and experienced in all quality unit tasks assigned (§ 213.25(a)). For additional information see section III.C., Personnel Qualifications and Responsibilities. In addition, FDA recommends that each person who is part of the quality unit be identified by function and title in written procedures to ensure that quality unit responsibilities are fulfilled.

B. Quality Agreements With Suppliers

The quality unit's procedures should provide for written quality agreements with suppliers of goods and services to ensure compliance with CGMP. The quality agreement should clearly describe the provided goods or services, quality specifications, and communication mechanisms between the contracting parties.[9] FDA recommends that CGMP responsibilities and the

[9] For more information on quality agreements, see the guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016). The term *quality specifications* refers to any quality controls (e.g., drug specifications, process parameters, responsibilities) established to ensure quality during manufacturing.

communication processes for reporting complaints and changes that could be critical to drug quality be defined in written quality agreements with suppliers. For example, timely communications about process changes are important because such changes could affect the composition of the gas supplied.

C. Personnel Qualifications and Responsibilities

Under § 213.25(a), all personnel engaged in the manufacture, processing, packing, or holding of a medical gas, including production personnel, repackers, ***transfillers***, and those driving to customer sites to distribute medical gas, must have sufficient education, training, and experience, or any combination thereof, necessary to perform their assigned functions. Section 213.25(a) specifies the following:

- Such training must be in both the particular operations that the employee performs and in CGMP requirements related to their assigned functions.

- The CGMP training must be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to their job functions. To comply with this requirement, FDA recommends that CGMP training be provided at least annually.

- Manufacturers must maintain written documentation, for each employee, of the completion of employee training, including the date of the training, the type of training, and the results of any completion criteria, such as test results.

Similarly, any consultants hired to advise on medical gas manufacturing must have the necessary education, training, and experience, or any combination thereof, to advise on the subject for which they are retained (§ 213.34).

Manufacturers must have an adequate number of qualified personnel to perform the manufacture, processing, packing, or holding of each medical gas (§ 213.25(b)). What would constitute *adequate* personnel would depend in part on the size and complexity of the performed operations. Additionally, any personnel entering limited-access areas of a manufacturing facility (e.g., certain storage areas) must be authorized to avoid improper manufacture or mishandling of medical gas (§ 213.25(c)).

IV. BUILDINGS AND FACILITIES

The standard industry practice of manufacturing multiple gases at the same facility and refilling labeled medical gas containers underscores the importance of building and facility design as a control method for proper operation. Buildings and facilities must be of adequate design, including adequate space, for the orderly placement of equipment and materials to prevent mix-ups between components, ***incoming DMGs***, medical gas containers and closures, labeling, in-process materials, and medical gases (§ 213.42(a)(1)). For example, the design should include

sufficient lighting for personnel to read labels. The design and construction must also allow for adequate cleaning, maintenance, and proper operations (§ 213.42(a)(2)).

Manufacturers must perform operations within specifically defined areas of adequate size to prevent contamination or mix-ups during manufacturing (§ 213.42(b)(1)). For example, because facilities may reuse labeled medical gas containers, filled and unfilled containers with identical labeling may only be distinguishable if they are in well-defined areas. Manufacturers must design the flow of components, incoming DMGs, medical gas containers and closures, labeling, in-process, materials, and medical gases through the buildings and facilities in a manner to prevent contamination and mix-ups (§ 213.42(b)(2)). Manufacturers must maintain establishments in a clean condition, as specified in written procedures, so as to assure the safety, identity, strength, quality, and purity of the medical gas (§ 213.42(c)).

Outdoor spaces and delivery truck beds can be appropriate areas to conduct certain operations (e.g., storage and handling) for medical gases in pressurized containers. For example, industrial and medical gases could be physically separated in the warehouse or in the delivery truck. To separate these areas from other spaces as required under § 213.42(b)(1), manufacturers should use identifiers such as signage, floor demarcation, physical dividers, or tagging.

V. EQUIPMENT

Equipment used in the manufacture, processing, packing, or holding of a medical gas must be of appropriate design and adequate size and be suitably located to facilitate operations for its intended use and any necessary cleaning and maintenance (§ 213.63). In addition, equipment must be constructed so that surfaces that contact components, in-process materials, or medical gases are not reactive, additive, or absorptive (§ 213.65(a)), and any substances required for manufacturing operations, such as lubricants or coolants, do not come into contact with components, containers, closures, in-process materials, or medical gases (§ 213.65(b)).

A. Equipment Maintenance and Cleaning

Under § 213.67 manufacturers are required to establish, maintain, and follow written procedures for adequate cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of medical gases. These procedures must include, but are not limited to the following:

- Assignment of responsibility for cleaning and maintaining equipment
- Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules
- A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance
- Removal or obliteration of previous ***batch*** identification

- Protection of clean equipment from contamination before use

- Inspection of equipment for cleanliness immediately before use

FDA recommends that medical gas manufacturers ensure that personnel can access all equipment that must be cleaned, and tailor their equipment maintenance, cleaning, and inspection procedures to match the type and complexity of the particular operation and to prevent malfunctions or contamination.

Manufacturers should ensure equipment used in the manufacture of medical gases (e.g., manifolds, pigtails, valve assemblies, hoses, gauges) is cleaned or verified as clean (e.g., ensuring no residual cleaning agents are present) before initial use and after potential exposure to a contaminant. Closed pressurized systems used for filling medical gases (e.g., manifolds) can be considered acceptable without cleaning between batches, unless exposed to a contaminant. To prevent contamination, manufacturers should ensure that open ends are appropriately covered (e.g., with physical caps) and that valves that are critical for preventing contamination are properly maintained and cleaned. Because industrial and medical gases can be filled on the same manifold rack, there should be procedures in place and followed to prevent cross-contamination.

B. Automatic, Mechanical, and Electronic Equipment

Automatic, mechanical, and electronic equipment must be routinely calibrated, inspected, and checked according to a written program designed to ensure proper performance (§ 213.68(a)).

1. Equipment Qualification

Manufacturers should perform equipment qualification to verify that equipment used in medical gas manufacturing is installed, operates, and performs as intended. FDA recommends that equipment be qualified for the anticipated temperatures and pressures used during filling. Manufacturers should also qualify manifold valves to ensure they are appropriately designed to prevent mix-ups during filling operations and shown to prevent contamination of the medical gas. Similarly, other valves that are critical to the prevention of drug contamination, such as check valves used in filling systems, should be qualified for the particular use.

2. Equipment Calibration

Manufacturers can calibrate equipment by either following the equipment manufacturer's recommended calibration schedule or a schedule based on the medical gas manufacturer's experience using the equipment (e.g., the manufacturer's frequency of use). Medical gas manufacturers can reference the equipment manufacturer's instruction manual in their written procedures if the manual is available for on-site use.

FDA recommends that manufacturers do the following:

- Check the performance of vacuum gauges daily to ensure that the needle on the gauge returns to zero when there is no vacuum or pressure (above atmospheric pressure).

- Calibrate vacuum and pressure gauges at least annually against an established standard (e.g., a standard from the National Institute of Standards and Technology). Low-pressure gauges and flow meters used in filling ***portable cryogenic medical gas containers*** do not require calibration, but manufacturers should ensure that they function properly for their intended use.

- Calibrate thermometers according to the equipment manufacturer's instructions. If the instructions do not specify frequency, calibration should be conducted at least annually.

3. Computerized Systems

Manufacturers must appropriately validate computerized systems that record, store, or use data in the manufacturing, processing, and holding of medical gases (e.g., computerized systems used in test analyses) (e.g., § 213.68(b)). The validation should address the intended use of the computerized system, and the extent of validation studies should be commensurate with the risk posed by the automated system.[10] In addition, manufacturers must maintain a backup file of any data entered into the computer system unless certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or automated processes (§ 213.68(c)).

Manufacturers must use appropriate change controls whenever modifications are made to computer systems so that changes do not adversely affect data integrity[11] or product quality, and records of such modifications must be maintained (§ 213.68(d)).[12] Appropriate personnel with expertise should assess the potential impact these changes could have on quality both before the change is approved and after the change is implemented, as well as any need for revalidation.

Manufacturers should enable audit trail functions for computerized systems to capture changes and maintain complete data about CGMP activities. This information is important for the manufacturer to trace CGMP activities throughout the supply chain when retrospective review or investigation is warranted.

[10] To comply with the requirement in § 213.68(b) when using commercially available software (e.g., off-the-shelf software), the medical gas manufacturer, as the party with regulatory responsibility, should assess the adequacy of the off-the-shelf software and must ensure it is validated, so that the software specifications conform to user needs and intended uses. See sections 6.1 through 6.3 of the guidance for industry and FDA staff *General Principles of Software Validation* (January 2002). Although the guidance focuses on the validation of medical device software, it states that "this document is based on generally recognized software validation principles and, therefore, can be applied to any software."

[11] See the guidance for industry *Data Integrity and Compliance With Drug CGMP: Questions and Answers* (December 2018).

[12] For FDA's current thinking on the use of computerized systems for maintaining electronic records, see the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003).

VI. CONTROL OF INCOMING DMG, COMPONENTS, AND MEDICAL GAS CONTAINERS AND CLOSURES

Manufacturers must control and assess the quality of incoming DMGs, components, containers, and closures as specified in §§ 213.80, 213.82, and 213.84 because materials of poor quality can adversely affect the quality and safety of the medical gas. Materials can contain impurities (e.g., caused by poor air quality conditions in ***air separation units*** or inadequate purification during manufacturing), or a change to the manufacturing process could affect quality (e.g., an adjustment in a manufacturing step could alter the composition of a supplied gas). Any rejected incoming DMGs, components, and medical gas containers and closures must be handled in accordance with § 213.89, which requires rejected items to be identified and quarantined to prevent their use in manufacturing or processing operations for which they are unsuitable. In addition, manufacturers must document and assess the data on rejected material and take appropriate corrective action (§ 213.192(a)).

A. Receipt of Incoming DMGs and Components

Upon receipt of each shipment of each incoming DMG, the manufacturer must perform an identity test (§ 213.82(b)). The manufacturer must also perform either full compendial testing on the gas and record the results, or verify and record that a signed certificate of analysis (COA) from the supplier accompanied the shipment (§ 213.82(a)(1)). For incoming DMGs, if the supplier is not the ***original manufacturer***, the supplier must include complete information from the original manufacturer's COA (§ 213.82(a)(2)). Manufacturers must sample, test, and approve or reject each component, as appropriate, prior to use either by performing testing for conformance with written specifications or by an identity test on the component accompanied by an acceptable COA from the supplier (§ 213.84(c)).

1. Certificate of Analysis

For incoming DMGs, if a manufacturer relies on the supplier's COA, the COA must include (i) the supplier's name; (ii) the name of the incoming DMG; (iii) the ***lot number*** (also referred to as ***control number*** or ***batch number***) or other unique identification number; (iv) the actual analytical result obtained for strength, as well as the results of other performed tests; (v) identification of the test method(s) used for analysis; (vi) the incoming DMG's new drug application (NDA) and/or new animal drug application (NADA) number; and (vii) the supplier representative's signature and the date of signature (§ 213.82(a)(1)).

For a component, if a manufacturer relies on the supplier's COA, it should include the following data: (i) the supplier's name; (ii) the name of the component; (iii) the lot number or other unique identification number; (iv) the type of test or examination to evaluate conformance with written procedures and specifications; (v) the method(s) used; (vi) specification limits; (vii) all test results; and (viii) the supplier representative's signature and the date of signature.

2. Supplier Qualification

Reliance on information provided in a COA requires a high degree of confidence in the supplier. For both incoming DMGs and components, when the manufacturer is relying on a supplier's COA to verify that the incoming DMG or components meet specifications beyond identity testing, the manufacturer must establish and maintain a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures (§§ 213.82(a)(2), 213.84(a), and 213.84(c)). To establish the reliability of the supplier's analyses, the manufacturer, a contract-testing laboratory, or another third party can perform testing at appropriate intervals. Manufacturers can begin the supplier qualification process, for example, by fully testing several batches and examining the provided gas, containers, and closures. Written procedures should address how to qualify and approve suppliers and to periodically verify the qualifications of approved suppliers. This can be done by conducting audits (e.g., on-site for the initial audit and, as needed, remotely for subsequent audits), analyzing trends in the quality of received goods, testing, and evaluating the timeliness of the supplier's responses to complaints.

B. Medical Gas Containers and Closures

1. General Requirements

The quality unit must examine medical gas containers and closures, including valves, for conformance with appropriate written procedures and specifications, and approve or reject them, before manufacturing or filling (§§ 213.22(a), 213.84(a) and (c) and 213.89). A manufacturer should reexamine a medical gas container or closure when it is exposed to adverse storage conditions that could cause deterioration or contamination of the medical gas. Manufacturers must also protect against container and closure leaks (§ 213.84(b)). This includes performing leak tests on containers and closures and investigating any container closure defects identified either during production or upon receipt of a leak complaint (§ 213.198(a)). Valve replacements (e.g., due to a valve defect) should be performed as part of a planned program, with mitigation strategies, and investigated as a deviation. See section VIII.D.2., Valve Assembly Leak Testing for a discussion of leak testing.

Medical gas containers and closures must at all times be handled and stored in a manner to prevent contamination and mix-ups (§ 213.80(b)). Accordingly, high-pressure cylinders exposed to the elements and hoses used to fill cryogenic containers should have caps or other protective means to prevent contamination. Medical gas containers and closures must not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of a medical gas beyond the official or established requirements and must provide adequate protection against foreseeable external factors and use that can cause deterioration or contamination (§ 213.94(a) and (b)). Medical gas containers and closures must also be clean for their intended use (§ 213.94(c)). Thus, medical gas containers and closures should be cleaned before initial use and after exposure to a contaminant. To comply with the requirements in §§ 213.84 and 213.94(c), manufacturers should implement appropriate cleaning and retesting procedures when converting a container's use from industrial grade gas to medical gas, or if there is reason to believe there was previous industrial use.

Portable cryogenic containers that are not manufactured with permanent gas-specific use outlet connections (e.g., those that have been silver-brazed) must have gas-specific use outlet connections that are attached to the valve body so that they cannot be readily removed or replaced (without making the valve inoperable and preventing the container's use) except by the manufacturer (§ 213.94(e)(1)). If a gas-specific use outlet connection can be readily removed and replaced, a container holding one gas could be inadvertently connected to the supply system for another type of gas, which could cause serious injury or death because of the gas mix-up.

Manufacturers should not use vapor recovery systems during carbon dioxide delivery unless the manufacturer has adequately addressed potential contamination in a risk management program. Contaminants present in the gaseous head space of the storage tank or container could be drawn into the tank or container, thereby contaminating the carbon dioxide.

2. Prefill Inspections

Prefill inspections ensure that containers and closures are acceptable for use before filling begins. This section addresses prefill inspections that evaluate containers and closures used to hold incoming medical gases and store medical gases. Prefill inspections, like filling and postfilling inspections, are a significant step in the manufacturing, processing, packing, or holding of the medical gas produced and, therefore, must be properly documented (§ 213.189(b)). Medical gas containers and closures that are rejected must be quarantined and assessed (§§ 213.84 and 213.89). Manufacturers should address the problem by repairing, cleaning, or replacing unsuitable parts and then reinspecting.

a. External inspection of the container

Manufacturers should examine each container for dents, burns, dings, oil, grease, and other signs of damage or contamination that can cause a container to be unsafe for use.

b. External inspection of valves, inlets, outlets, gauges, and connectors

Manufacturers should inspect each container's valve assembly, connectors, and fittings to ensure that they are appropriate for the medical gas. Manufacturers should examine valves, inlets, outlets, gauges, and connectors for signs of damage (including fire damage), unusual wear, corrosion, or the presence of debris, oil, or grease. This inspection should cover connections that are brazed, welded, or equipped with a locking device. Manufacturers must ensure that portable cryogenic medical gas containers and small cryogenic gas containers for use by individual patients have a working gauge sufficient to assist the user in determining whether the container contains an adequate supply of medical gas for continued use (§ 213.94(e)(2)).

c. Label inspection

Product labels on medical gas containers may be reused if they are legible, properly affixed to the container, and otherwise meet all applicable requirements (§ 213.122(h)). Labels that are obsolete, outdated, or that do not meet applicable requirements must be destroyed (§ 213.122(e)).

Manufacturers must ensure that the labeling specified for portable cryogenic medical gas containers in § 201.328(a) (21 CFR 201.328(a)) is affixed to the container in a manner that does not interfere with (e.g., obscure) other labeling and that each label, as well as materials used for coloring medical gas containers, are reasonably resistant to fading, durable when exposed to atmospheric conditions, and not readily soluble in water (§ 213.94(e)(3)).

Portable cryogenic medical gas containers must be conspicuously marked with a 360° wraparound label identifying their contents (§ 201.328(a)(1)). The wraparound label must be placed on the sidewall of the container as close to the top portion of the container as possible, but below the top weld seam (§ 201.328(a)(1)(iv)). The name of the gas must be printed continuously around the 360° wraparound label so that it can be read around the entire container (e.g., Oxygen USP, Oxygen USP, Oxygen USP) (§ 201.328(a)(1)(iii)), and the lettering for the name of the gas on the label must be at least 2 inches high (§ 201.328(a)(1)(ii)). For containers that hold a single gas, either the lettering or the label's background must be in the appropriate color (e.g., green for oxygen) with contrasting background or lettering (i.e., lettering in the designated color against a white background, or white lettering on a background of the designated color) (§ 201.328(a)(1)(i)).[13]

The 360° wraparound label or a separate label on the portable cryogenic medical gas container must include, in conspicuous lettering, the phrase *For Medical Use*, *Medical Gas*, or some similar phrase that indicates the gas is for medical use (§ 201.328(a)(2)).

Although permanently mounted cryogenic containers are not required to have a 360° label, any content labeling should be easily readable from all readily accessible viewing angles.

d. Color code inspection

The shoulder of each high-pressure medical gas cylinder must be colored in the color or colors that correspond to the gas held in the cylinder; furthermore, the shoulder's color or colors must be visible when viewed from the top of the cylinder (§ 201.328(b)). The FDA-designated colors identifying medical gases in high-pressure medical gas containers and portable cryogenic medical gas containers are (§ 201.328(c)):

[13] There are no specific color requirements for the 360° wraparound label for portable cryogenic medical gas containers containing a mixture of gases. As discussed in this guidance, however, there are requirements under § 201.328(a)(1)(v) addressing the color of the cryogenic container itself.

Labeling of Medical Gas Containers[1]

Medical Gas	Color
Medical Air	Yellow
Carbon Dioxide	Gray
Helium	Brown
Nitrogen	Black
Nitrous Oxide	Blue
Oxygen	Green
Mixture or Blend[2]	Colors corresponding to each component gas[3]

[1] Adapted from 21 CFR 201.328(c)

[2] The terms *mixture* and *blend* refer to combinations of medical gases.

[3] For example, green and gray for a blend of oxygen and carbon dioxide.

Unlike high-pressure cylinders, portable cryogenic medical gas containers are not required to be colored in whole or in part. Portable cryogenic medical gas containers can be colored in a light-reflective color (e.g., white), any color that is not an FDA-designated gas color, or no color. However, if a manufacturer chooses to color a portable cryogenic container in an FDA-designated color, it may only be colored, in whole or in part, with the color corresponding to the gas or gases held in the container (§ 201.328(a)(1)(v)).

Manufacturers should not rely solely or primarily on color coding to identify medical gases; the label should be used as the primary means of identifying the medical gas. Color coding provides an additional safeguard to facilitate accurate identification and detection of potential errors.

A container filled with a DMG or medically appropriate combination of DMGs can bear a statement identifying the name of the owner of the container or the address to which the container should be returned after use. If the owner of the medical gas container is not the manufacturer, packer, or distributor, it must be clearly stated on the container (§ 201.328(d)).

e. Inspection of high-pressure cylinders

For high-pressure cylinders, manufacturers should include the following as part of prefill inspections:

- Examination of the U.S. Department of Transportation (DOT) requalification date
- Hammer or dead-ring test
- Odor inspection
- Venting or blow-down of cylinders

Manufacturers should examine each high-pressure cylinder for the DOT date stamped on the cylinder before use to verify that each cylinder conforms with DOT requirements under 49 CFR 180.209 for the requalification and marking of cylinders. If the DOT requalification date has been exceeded, the manufacturer should quarantine the cylinder until either DOT requirements have been satisfied, or the cylinder is removed from inventory.

Manufacturers should also conduct a hammer or dead-ring test to provide information about internal corrosion of steel cylinders that could lead to cylinder failure. The test consists of lightly tapping the cylinder sidewall with a hammer-like instrument and listening to the sound produced. A clear bell tone indicates that the cylinder is clean and free of internal corrosion. A dull ring indicates the possibility of internal corrosion and warrants further investigation. Manufacturers should not perform a hammer or dead-ring test on aluminum or composite cylinders because the test would not indicate internal corrosion and could damage the cylinder wall.

Manufacturers can use an odor test to detect the presence of a foreign gas or odor remaining in the container. This test should *not* be performed on carbon dioxide, nitrous oxide, or toxic or corrosive gases for safety reasons. This test should *not* be confused with odor testing conducted as part of finished product testing, which may be included in a USP-NF monograph. If a cylinder is empty at atmospheric pressure, manufacturers can introduce Nitrogen NF into the cylinder at a predetermined pressure (i.e., a pressure that is high enough to introduce gas into the container) and perform an odor test on the resulting gas. Residual pressure valves prevent the cylinder from emptying completely and prevent backflow. A prefill odor test on a cylinder with a qualified residual pressure valve is not necessary if the cylinder has residual pressure. Manufacturers should document verification of residual pressure on the batch record.

High-pressure cylinders that manufacturers receive for refilling should be vented or blown down to remove gas remaining in the cylinders. Manufacturers can omit this step if the cylinder is equipped with a qualified residual pressure valve and has residual pressure. Manufacturers should address the continued suitability of medical gas containers and closures after extended storage by having procedures in place to ensure that they (1) are not exposed to conditions that render them unfit for use, and (2) have successfully completed prefill tests.

VII. PRODUCTION AND PROCESS CONTROLS

Under § 213.100(a) manufacturers are required to have written procedures for production and process controls designed to assure that medical gases have the identity, strength, quality, and purity they purport or are represented to have. This regulation requires manufacturers to design a process, including operations and controls, so that products meet these attributes, and is therefore the foundation for process validation.[14] For example, validation of automated filling systems provides assurance that filling will be done properly. This regulation also requires that the procedures, and any changes, be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit.

During production, if contamination is found, or it seems likely that contamination occurred, the manufacturer must quarantine the batch or lot of medical gas in which the contamination was found until an investigation has been completed (§§ 213.84, 213.89, 213.110(c)). Given that products with a USP monograph must meet the monograph standards if tested or be considered

[14] For more information on FDA recommendations regarding process validation generally, see the guidance for industry *Process Validation: General Principles and Practices* (January 2011).

adulterated under section 501(b) of the FD&C Act, any tests for detecting contaminants in medical gas should be equivalent to, or better than, USP compendial methods and suitable for their intended use.[15] For additional information, see section X.C., Test Method and Alternative Test Method Validation.

When monitoring medical gas production, adverse trends of errors or deviations can indicate a drift in the state of control, which warrants an appropriate investigation and an effective corrective and preventative action (CAPA).[16] Manufacturers should pay particular attention to critical defects (e.g., leaking units, contamination) and assess whether marketed units were potentially impacted.

A. Charge-In of Components and Incoming DMGs

Under § 213.101(a), a batch must be formulated with the intent to provide 100 percent of the labeled or established amount of each medical gas unless a monograph or formulary specifies a range. Where a monograph or formulary specifies a range for the contents of a medical gas, the medical gas must be formulated with the intent to provide an amount within that specified range.

Under § 213.101(b) components and incoming DMGs added to in-process supply or final product containers must be weighed or measured as appropriate. In-process and final product containers must identify (1) the name of the component or DMG, or if there are multiple, the name and percentage of each component or DMG; and (2) the unique lot number assigned.

B. Sampling and Testing of In-Process Materials

During production, in-process materials must be tested for identity, strength, quality, and purity as appropriate, and the quality unit must approve or reject the in-process materials (§ 213.110(a)). In-process control procedures and tests or examinations on appropriate samples of in-process materials of each batch must be established to monitor output and to validate the performance of manufacturing processes that can cause variability in the quality of the medical gas (§ 213.110(b)). For example, in-process controls could include validation of processes to remove contaminants. Manufacturers must identify and quarantine any rejected in-process materials to prevent their use in manufacturing or processing operations for which they are unsuitable (§ 213.110(c)).

C. Vacuum Evacuation of High-Pressure Cylinders

For cylinders that are not equipped with a residual pressure valve with backflow prevention, FDA recommends vacuum evacuation to remove residual gases if cylinders are reused. FDA recommends manufacturers use 25 or more inches of mercury vacuum to evacuate the residual gases. If using less than 25 inches of vacuum (e.g., when compensating for altitude),

[15] USP-NF General Notices, Section 5.60, *Impurities and Contaminants in Official Articles* is an example of an appropriate reference for a contaminant test method.

[16] To identify an adverse trend, we recommend that the quality unit establish appropriate alert and action limits to ensure investigation expansion to reassess process design and control.

manufacturers should maintain data demonstrating sufficient evacuation). Changes to the amount of vacuum used must be documented (§§ 213.184, 213.186, and 213.189) and available for inspection (§ 213.180(a)), and the changes should be scientifically justified.

Manufacturers must maintain records of their testing or examination of any problems that occur with container evacuation, such as the inability to adequately empty the cylinder of residual gases (§ 213.184).

D. Filling Procedure Checks

When filling medical gas containers, filling to a predetermined and acceptable temperature or pressure limit, along with the required finished product testing at § 213.165, indicates that the medical gas or medical gas mixture in the container is the amount[17] and type indicated by the label and required by the final product specifications. Manufacturers should include the following checks:

1. Temperature and Pressure Readings

A medical gas in a container will increase in pressure as the temperature of the gas rises. Overfilled containers can reach dangerously high pressures if exposed to elevated temperatures, even if the pressure at room temperature is at a safe level. To ensure that high-pressure containers filled with DMG(s) in a gaseous state are filled correctly (i.e., contents as indicated on the label), the manufacturer can attach a thermometer to one container per manifold-filling sequence, or to each container if filling one at a time, and adjust the final filling pressure according to a temperature/pressure chart or temperature/pressure calculations (Boyle's Law) to achieve proper content (expressed on the label in liters or cubic feet based on the filled pressure at 70°F as required under 21 CFR 201.51(b)(1)).

The manufacturer must record the temperature and/or pressure readings on the batch production record as part of the required documentation that each significant step in the manufacture, processing, packing, or holding of the medical gas produced was accomplished (§ 213.189(b)). See section XI.E., Batch Production and Control Records.

2. Valve Assembly Leak Testing

Manufacturers must take appropriate actions to identify and protect against container and closure leaks, which include leak testing at the time of fill and after fill but prior to release (§ 213.84(b)). Leak testing, performed at additional time points, may be warranted (e.g., if leaks are detected after leaving the manufacturer) to provide sufficient assurance of the durability and suitability of the container closure system throughout its period of use.

In the event the manufacturer receives a complaint involving a possible leak in a medical gas container or closure, that complaint must be reviewed, evaluated, and investigated in accordance with § 213.192 (§ 213.198(a)). An appropriate investigation includes a determination of the

[17] For requirements related to the measure of contents for DMGs, see 21 CFR 201.51(b), which explains how net quantity must be expressed on the label, depending on container type.

source of a leak. Based on the results of the investigation, additional leak testing, such as upon pickup, could be warranted as part of an appropriate corrective action to prevent recurrence.

During leak testing, manufacturers should test each valve assembly for leaks by spraying or brushing an appropriate leak detection solution on and around the entire assembly.[18] The solution should be safe for use with the particular medical gas, leave no residue that is flammable, and be noncorrosive to the valve assembly. Among other things, it should not contain hydrocarbons, ammonia, ethylene glycol, or halide ions. Solutions containing soap are not recommended because they can corrode the valve stem and leave a residue. Manufacturers should perform this test while the cylinder is under pressure with the cylinder valve open. If bubbles appear in the solution, there is a leak. If leaks are detected, the cylinder must be removed from service and quarantined until repaired (see §§ 213.84(a) and 213.89).

3. Heat-of-Compression Check

During or immediately after filling a high-pressure cylinder, manufacturers should perform a heat-of-compression check by lightly touching the exterior of the cylinder or an alternative method that verifies temperature change. A warm cylinder indicates that the cylinder is filling properly; a cool or cold cylinder indicates that the cylinder is not filling properly. Manufacturers should investigate, in accordance with § 213.192, any cool or cold cylinders.

VIII. PACKAGING AND LABELING CONTROL

A. Materials Examination and Usage

To ensure the quality and legibility of medical gas labels, in particular because labels may be reused (§ 213.122(h)), manufacturers must do the following:

- Representatively sample, and examine or test, labeling and packaging materials upon receipt and before use in packaging or labeling of a medical gas (§ 213.122(a)).

- Approve and release for use any labeling or packaging materials that meet appropriate written specifications and reject any labeling or packaging materials that do not meet specifications to prevent their use in operations for which they are unsuitable (§ 213.122(b)). We note that previous lot numbers on any labeling must be removed or obliterated as part of equipment maintenance and cleaning requirements (§ 213.67(a)(4)).

- Maintain records of each shipment of each different labeling and packaging material, indicating receipt, examination, and whether accepted or rejected (§ 213.122(c)).

- Store labels and other labeling materials for each different medical gas, strength, or quantity of contents with suitable identification to avoid mix-ups (§ 213.122(d)). Labels

[18] See ASTM International, 2021, G188-05 (Reapproved 2021), Standard Specification for Leak Detector Solutions Intended for Use on Brasses and Other Copper Alloys.

and labeling materials can be stored in the same cabinet provided they are adequately separated and identified. Labels for nonmedical purposes (e.g., industrial gas) should be stored in a separate area.

- Secure labeling by limiting access to authorized personnel (§ 213.122(d)).

- Destroy obsolete and outdated labeling (§ 213.122(e)).

- Include one of the following special control procedures:

  - Dedicate labeling and packaging lines to each different strength of each different medical gas (§ 213.122(f)(1))

  - Use appropriate electronic or electromechanical equipment to conduct a 100 percent examination for correct labeling during or after completion of finishing operations (§ 213.122(f)(2))

  - Use visual inspection to conduct a 100-percent examination for correct labeling during or after completion of labeling operations for hand-applied labeling, which must be independently verified by a second person (§ 213.122(f)(3))

- Monitor any printing devices on, or associated with, manufacturing lines used to imprint labeling on the unit label or case for conformance with the print specified in the batch production record (§ 213.122(g)).

B. Labeling Issuance

Manufacturers must strictly control labeling issued for use in medical gas operations to prevent labeling and product mix-ups (§ 213.125(a) (21 CFR 125(a)). Appropriate controls include labeling reconciliation (§ 213.125(b)) and the discarding of all excess lot number stickers or decals that are unused (§ 213.125(c)). FDA recommends that labeling be issued for use in medical gas labeling operations by authorized personnel only.

Manufacturers must reconcile the number of labels issued, used, and returned and evaluate any discrepancies outside narrow preset limits based on historical operating data (§ 213.125(b)) and investigate those discrepancies (§ 213.192).

Labeling reconciliation is waived for cut or roll labeling if manufacturers perform a 100 percent examination for correct labeling in accordance with § 213.122(f)(2) and is also waived for 360° wraparound labels on portable cryogenic medical gas containers (§ 213.125(b)).

C. Packaging and Labeling Operations

Manufacturers must handle packaging and labeling operations in a manner that assures that correct labels, labeling, and packaging materials are used for medical gases (§ 213.130). Measures include the following:

- Physically or spatially separating labeling and packaging operations for medical gas from operations on other products (e.g., gases for industrial use) (§ 213.130(a)).

- Identifying any filled, unlabeled containers that have been set aside for future labeling operations to prevent mislabeling (§ 213.130(b)). Each container does not need to be individually identified. This requirement can be met by having signage for an area designated to store these containers.

- Identification of a batch medical gas with a lot or control number (§ 213.130(c)). A separate sticker or decal can be used to meet the requirement as long as the sticker or decal remains adhered to the container and is legible. The sticker or decal should be readily visible and should not obscure required drug information. Manufacturers should consider as a batch each (1) manifold filling sequence, (2***) uninterrupted filling sequence***, and (3) filled rail tank car, trailer, and cryogenic container. For continuous manufacturing operations, a batch is the amount of medical gas produced in a unit of time (e.g., in 24 hours) or quantity in a manner that assures its having uniform character and quality within specified limits (§ 213.3(b)(9)), with the unit of time or quantity defined by the manufacturer.

- Inspection of packaging and labeling facilities immediately before use to assure that all medical gases have been removed from previous operations and any packaging or labeling materials unsuitable for subsequent operations have been identified and removed (§ 213.130(d) and (e)).

If a manufacturer includes an expiration date on the medical gas product labeling, it must appear on the labeling in accordance with 21 CFR 201.17. The date must be supported by a stability testing program as described in § 213.166. See section X.D., Stability Testing and Expiration Dating for additional information and requirements.

IX. HOLDING AND DISTRIBUTION

Manufacturers must establish and follow written procedures describing medical gas distribution (§ 213.150(a)). These procedures must include a system by which the distribution of each ***lot*** can be readily determined to facilitate its recall if necessary (§ 213.150(a)). The procedures should explain (1) who would evaluate distribution information, (2) how a recall would be initiated, (3) who would be informed about the recall, (4) what would be done with the recalled product, and (5) how these steps would be accomplished.

Manufacturers must also establish and follow written procedures describing the warehousing of medical gas, including quarantine before release by the quality unit (§ 213.150(b)).

X. LABORATORY CONTROLS

Laboratory control requirements in § 213.160 include establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, medical gas containers and closures, in-process materials, labeling, and medical gases conform to appropriate standards of identity, strength, quality, and purity (§ 213.160(b)). These laboratory control mechanisms must be drafted by the appropriate organizational unit, reviewed and approved by the quality unit, followed, documented at the time of performance, and any deviations from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms recorded and justified (§ 213.160(a)). For example, to comply with this requirement, manufacturers must record and justify changes made to the analytical method, such as a different column length or a different carrier gas (§ 213.160(a)).

A. Instrument Calibration

Laboratory controls must include a written program for the calibration, or verification of calibration, for instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met (§ 213.160(b)(4)). Under this requirement, any downstream entities[19] that do not perform their own calibration must verify calibration. It is of particular importance that instruments measuring a quality characteristic are calibrated to ensure proper performance.

If using a calibration gas, manufacturers should verify that it is traceable to a nationally recognized standard and that it ensures the appropriate level of precision and accuracy. The COA for the calibration gas should be specific to the cylinder of calibration gas received and should contain the following:

- Name and address of the supplier
- Name of the calibration gas
- Lot number or unique identification number
- Description of the analytical method used to assay the calibration gas
- Analytical results expressed quantitatively (e.g., 99.9 percent nitrogen)
- Statement that the calibration gas is traceable to a nationally recognized standard
- Responsible person's signature and the date signed

B. Testing and Release for Distribution

For each batch of medical gas, there must be an appropriate laboratory determination of satisfactory conformance to final specifications for the medical gas, including the identity and strength, before release (§ 213.165(a)). An appropriate laboratory determination would include

[19] *Downstream entities* are entities that manufacture, process, pack, or hold medical gases, including firms that combine, commingle, refill, or distribute DMGs and medically appropriate combinations of DMGs but are downstream from the manufacturer that initially manufactures the medical gas.

meeting the standards listed in an applicable compendium (e.g., a USP-NF monograph for certified DMGs,[20] relevant general USP NF chapters[21]) or the specifications established in an application approved under section 505 or section 512 of the FD&C Act.

Written procedures must describe the method of sampling and testing, including the number of units per batch that will be sampled and tested and the acceptance criteria (§ 213.165(b)). The method of sampling must be suitable and verified under actual conditions of use (§ 213.165(c)). Test results that fail to meet specifications must be rejected (§ 213.165(d)). Samples can be retested, but retesting is not recommended until the manufacturer has conducted a thorough investigation according to established written procedures.[22]

For cylinders filled on a multiple-outlet manifold, at least one high-pressure cylinder from each manifold filling sequence should be tested for identity and strength.

For cylinders filled individually, one high-pressure cylinder per uninterrupted filling sequence should be tested for identity and strength.

For mixtures containing two gases, each high-pressure cylinder in a batch should be tested for both the identity and strength of one of the gases, and one cylinder from each batch should be tested for the identity of the second gas. For mixtures containing three gases, each high-pressure cylinder in a batch should be tested for both the identity and strength of two of the gases, and one cylinder from each batch should be tested for the identity of the third gas. If mixtures contain oxygen, each cylinder in the batch should be tested for the identity and strength of the oxygen.

C. Test Method and Alternative Test Method Validation

The manufacturer must demonstrate that test methods are accurate, sensitive, specific, and reproducible under actual conditions of use (§ 213.165(c)) and must be approved by the quality unit (§ 213.22(c)). Validation and documentation must be accomplished as described in § 213.194(a)(2).

Because USP-NF monograph drug products must meet USP-NF monograph standards (section 501(b) of the FD&C Act), FDA recommends that manufacturers use the test methods in the appropriate USP-NF monograph for the medical gas. For USP-NF test methods, a full test method validation study is unnecessary, as long as the referenced method is not modified. Data that verify that the USP-NF test method is accurate and reliable for testing the particular product (i.e., suitable for its intended purpose) should be generated on the appropriate equipment and

[20] See section 576(a)(2)(A) and (B) of the FD&C Act (21 U.S.C. 360ddd-1(a)(2)(A) and (B)) (a certification will not be granted if the Secretary finds that the medical gas is not a DMG, or if the request does not contain required information or otherwise lacks sufficient information to permit the Secretary to determine that the medical gas is a DMG); section 575(1) of the FD&C Act (defining each DMG as a gas that "meets the standards set forth in an official compendium").

[21] See footnote 15.

[22] See the guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* (May 2022).

readily available. If a medical gas manufacturer relies on the equipment manufacturer's study, the medical gas manufacturer should retain a copy of the study, including the protocol and data.

Manufacturers that use approved test methods that are not USP-NF monograph methods must maintain a copy of the full and complete test method validation (§ 213.165(c)). When a test is approved as part of an NDA submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act, an abbreviated new drug application (ANDA) submitted and approved under section 505(j) of the FD&C Act, a NADA submitted under section 512(b)(1) and approved under section 512(c)(1) of the FD&C Act, or an abbreviated new animal drug application (ANADA) submitted under section 512(b)(2) and approved under section 512(c)(2) of the FD&C Act, it becomes the approved analytical test method for the medical gas.

For drug products with a USP-NF monograph, a manufacturer can establish alternative test methods, as long as the USP-NF monograph standards are met or exceeded. Alternative test methods must be validated (§§ 213.160(b) and 213.165(c)). The validation can be performed in accordance with USP-NF General Chapter <1225> *Validation of Compendial Procedures,* and the validation study should include data comparing it to the official test method.[23]

The suitability of all testing methods must be verified under the actual conditions of use (§ 213.165(c)). For example, paramagnetic oxygen analyzers can give inaccurate readings when used at high altitudes unless special adjustments are made. The results of these tests must be fully documented (§ 213.165(c)).

Certain changes made to instrumentation can be substantive enough to be considered changes to the test method itself; these changes would require additional documentation of the accuracy and reliability of the method or a new validation study (see § 213.194(b)).

D. Stability Testing and Expiration Dating

For medical gases marketed under applications submitted under section 505 or section 512 of the FD&C Act, any stability testing performed and any expiration dating established must be in accordance with § 213.166(b), subject to the conditions established in their approved applications, if any. For example, if an approved application states that both stability testing and expiration dating are conditions for the safe and effective use of the medical gas, the manufacturer must have a stability program to assess the stability characteristics of the medical gas and the integrity of its container closure (§ 213.166(b)(1)). The stability program must include the appropriate sample size, test intervals, container closure systems, and storage conditions for samples retained for testing, and the results of the stability testing would be the basis for determining appropriate storage conditions and any expiration date included on the label (§ 213.166(b)(1)).

If an approved application does not require stability testing or expiration dating for the safe and effective use of a medical gas, but the manufacturer nonetheless chooses to include an expiration date on the labeling, the expiration date must be based on the results of a stability program as described in § 213.166(b)(1). Similarly, stability testing and expiration dating are not required

[23] See the guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015).

for DMGs, but if a manufacturer of a DMG chooses to include an expiration date on the label, the date should be determined by stability testing.

Manufacturers must evaluate stability periodically to ensure that the medical gas continues to meet the standards for identity, strength, quality, and purity stated on the labeling to support the expiration date (§ 213.166(b)(3)).

XI. RECORDS

This section discusses general records requirements and requirements related to records maintenance for equipment cleaning and use; components, containers and closures, and labeling; master production and control; batch production and control; laboratory records; distribution records; record review; and complaint files.

A. General Requirements

1. Record Retention and Availability

Manufacturers must maintain all records required under part 213 for at least 3 years after the distribution of the batch of medical gas, except as otherwise provided in this part (§ 213.180(c)).

All records must be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred (§ 213.180(a)). Records must be originals or accurate copies of original records that are legible and stored to prevent deterioration or loss (§ 213.180(b)). Electronic records that can be immediately retrieved satisfy this requirement.[24]

2. Maintenance of Written Records

Manufacturers must maintain written records so that data therein can be used for evaluating, at least annually, the quality standards of each medical gas to determine the need for changes in specifications or manufacturing or control procedures (§ 213.180(d)). There must be written procedures for the review of the following:

- A representative number of batches, whether approved or rejected, and where applicable, records associated with the batch (§ 213.180(d)(1))

- Complaints, recalls, returned or salvaged medical gases, and investigations conducted under § 213.192 for each medical gas (§ 213.180(d)(2))

Also, under § 213.180(e), the manufacturer must have written procedures to notify responsible officials of the firm, in writing, of any recalls, reports of inspectional observations by FDA, regulatory actions related to good manufacturing practices brought by FDA, or investigations

[24] Electronic records are subject to the requirements of 21 CFR part 11. See the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application*.

resulting from adverse event complaints. Manufacturers should use these records to identify potential product quality issues and opportunities for continuous process improvement. This can be done on a company-wide or site-by-site basis.

3. Equipment Calibration, Checks, and Inspections

Manufacturers must keep records of calibration, checks, and inspections of automatic, mechanical, and electronic equipment used in the manufacture, processing, packing, and holding of medical gas (§ 213.68(a)). See section V.B.2., Equipment Calibration for more information about equipment calibration.

4. Computer Validation Data

Manufacturers must have documentation that their automated, mechanical, and electronic equipment—including computers used in the manufacturing or holding of a gas—demonstrates proper performance as required under § 213.68(a) through (d), including data after modifications are made to computer systems.

5. Process Validation Data

Records required under part 213 include process validation records. Such data must show that the manufacturer has production and process controls designed to assure that medical gases have the identity, strength, quality, and purity that they purport or are represented to possess as required under § 213.100.

B. Equipment Cleaning and Use Log

Under § 213.182, manufacturers must retain cleaning records for major equipment cleaning, nonroutine maintenance, and equipment use, including the date, time, product, and lot number of each batch processed.

Manufacturers must document the work on individual equipment logs, which are separate cleaning or maintenance records that are not associated with specific batch records. The people who perform and double-check cleaning and maintenance must date and either sign or initial the log indicating that the work was performed, with entries made in chronological order (§ 213.182). If using equipment dedicated to the manufacture of a single medical gas, and lots or batches follow in numerical order and are manufactured in numerical sequence, individual equipment logs are not required. However, records for cleaning, maintenance, and use would be required as a part of the batch record (§ 213.182). If automated equipment is used in cleaning and maintenance in accordance with § 213.68, only the person verifying the cleaning and maintenance needs to date and sign or initial the use log.

C. Records for Components, Medical Gas Containers and Closures, and Labeling

Records associated with component, container and closure systems, and labeling requirements covered in §§ 213.84, 213.122, and 213.130 must include the following (§ 213.184):

- Results of any test or examination performed on components, containers, and container closure systems, including those performed as required by §§ 213.84 or 213.122, and the conclusions derived from the results

- Documentation of the examination and review of labels and labeling for conformity with established specifications in accordance with §§ 213.122 and 213.130

- Disposition of rejected medical gas components, containers and closures, and labeling

D. Master Production and Control Records

Master production and control records for each medical gas must be prepared, dated, and signed to assure uniformity from batch to batch. The manufacturer must have written procedures for the preparation of these records that must include the following (§ 213.186):

- The name and strength of the medical gas

- A complete list of components and any incoming DMGs used in manufacturing designated by names or codes sufficiently specific to indicate any special quality characteristic

- A description of the medical gas containers and closures, packaging materials, and labels

- Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed

E. Batch Production and Control Records

Batch production and control records must be prepared for each batch of medical gas produced (§ 213.189(a)).

The records must contain documentation that each significant step in batch manufacture, processing, packing, or holding was accomplished, including:

- Dates of each significant step, including in-process and laboratory tests as applicable (§ 213.189(b)(1)). Manufacturers should not use a single entry to indicate that all significant manufacturing, processing, packing, and holding steps have been performed.

- Description of the container for the medical gas, including the number and size of the containers filled as applicable (§ 213.189(b)(2)).

- Specific identification of each component and its source or in-process material used as applicable (§ 213.189(b)(3)).

- Measures of components used in the course of processing, as applicable (§ 213.189(b)(4)).

- Testing results, including in-process test results and finished product test results (§ 213.189(b)(5)).

- Dated signature or initials of each person performing and directly supervising or checking each significant step in the operation (§ 213.189(b)(6)).

- Inspection of the packaging and labeling area before and after use (§ 213.189(b)(7)).

- Complete labeling control records, including specimens or copies of all labeling used and label application and reconciliation records as appropriate (§ 213.189(b)(8)). Considering that all written, printed, and graphic matter upon or accompanying an article is labeling,[25] any accompanying labeling (e.g., booklets, brochures) is to be part of the complete labeling control records. Manufacturers should consider the following:

    - A photocopy or printed digital image can be an alternative to a label specimen. Manufacturers should include a specimen of the specific lot number labeling (e.g., lot number sticker) in the batch record.

    - At the time a container is transferred from one entity to another, each entity is responsible for the labeling on or accompanying the container. This labeling should be part of the complete labeling control records. For example, § 201.328(d) states that a container filled with a DMG or medically appropriate combination of DMGs may bear a statement identifying the name of the owner of the container or the address to which the container should be returned after use and that this statement may appear on a separate sticker or decal. In addition, this regulation requires that if the owner of the medical gas container is not the manufacturer, packer, or distributor of the medical gas, this fact must be clearly stated on the container. The above information is considered labeling and therefore is expected to be part of complete labeling control records.

    - Labeling control records maintained by original manufacturers that fill bulk trailers may or may not include a finished product label. These manufacturers should maintain both product and lot-specific labeling.

- Any investigation made according to § 213.192 (§ 213.189(b)(9)).

[25] Section 201(m) of the FD&C Act defines the term *labeling* to mean "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."

Batch production records should reflect actual production practices and conditions at the time of manufacture. Transfiller pumper or filler logs can serve as batch production records if they contain the relevant information specified in § 213.189.

In addition, FDA recommends that batch records maintained by transfillers, including curbside vendors, document the following information:

- Findings from the transfiller's inspections conducted prefill, during fill, and postfill
- Number and size of the containers filled
- Final temperature and pressure results
- Other inspection results

All required batch record information should be easily located and traceable to each specific batch manufactured. Manufacturers need not maintain batch production records as one document. Each lot number should be traceable in records for batch manufacturing, labeling, testing, and release. Manufacturers that use computer-controlled equipment during manufacture should establish and follow procedures to maintain, review, and approve the manufacturing data.

A checkmark or other symbol should not be used in place of an actual value, such as for temperature and pressure readings, or results from purity and identity testing.

FDA recommends that records of nonconforming medical gas describe the rejection relative to the rest of the batch to ensure that the scope of the investigation is appropriate. For example, medical gases rejected for container or manifold leaks during filling must be documented (§§ 213.84, 213.165, and 213.189) and investigated (§ 213.192), and the scope of the investigation should extend to other batches of medical gas that could have been associated with the same failure.

F. Production Record Review

The quality unit must review and approve all manufacturing production and control records, including those for packaging and labeling, before a batch is released or distributed (§ 213.192(a)). Unexplained discrepancies or the failure of a batch to meet its specifications, including any test results falling outside of specifications, must be investigated (by the quality unit) and corrective actions taken (e.g., removing a faulty cylinder from circulation) (§ 213.192(a)).

Manufacturers must maintain written records of investigations that include conclusions and follow-up information (§ 213.192(a)). In the event that filling occurs when the quality unit official(s) is temporarily not on site, the quality unit may review and approve production and control records within one business day after fill (§ 213.192(b)).

G. Laboratory Records

Laboratory records related to the manufacturer of a medical gas must include complete data derived from all tests necessary to ensure compliance with established specifications and

standards, including examinations and assays (§ 213.194(a)). These records include the following:

- Description of the sample, batch or lot number to be tested; date the sample was taken; and date the sample was tested (§ 213.194(a)(1)).

- The test method, the test result, how the results compare with established standards of identity, strength, quality, and purity for the component, container, in-process materials (as applicable), and medical gas tested; a record of any calculations performed and any calculated results; and the unit of measurement of the result. It would not be necessary to provide the actual calculation where the result is evident through use of simple addition and subtraction (§ 213.194(a)(2)).

- Where applicable, any graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, in-process material, or medical gas for each lot tested (§ 213.194(a)(3)). If the analytical equipment only provides a direct reading, recording the result for each test would fulfill the requirement.

- Initials or signature of the person who performs each test and a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards (§ 213.194(a)(4)).

In addition, manufacturers must maintain complete records of the following:

- Any modification of an established test method, including the reason for the modification and the data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method (§ 213.194(b)).

- Any testing and standardization of laboratory reference standards, reagents, and standard solutions (e.g., a reference gas or calibration gas used as a standard) (§ 213.194(c)).

- Periodic calibration or verification of calibration of laboratory instruments, apparatus, gauges, and recording devices required by § 213.160(b)(4) (§ 213.194(d)). For example, medical gas equipment calibrated by a supplier before it arrives at the laboratory can be verified rather than performed again.

- Stability testing performed in accordance with § 213.166 (§ 213.194(e)).

When a chromatographic method specified in the USP-NF (e.g., the assay method for Nitrogen NF) is used for testing, the chromatographic system must meet all system suitability requirements listed in the monograph (see section 501(b) of the FD&C Act). If the USP-NF monograph lacks specific suitability requirements, manufacturers should use USP-NF General Chapter <621> *Chromatography* as a reference.

H. Distribution Records

Distribution records must contain the product name, the lot or batch number, consignee's name and address, shipping date, and quantity shipped (§ 213.196). For medically appropriate combinations of DMGs, the distribution record must include the percentage of each gas in the combination (§ 213.196). Record maintenance according to written procedures is critical for batch traceability, particularly in the event a safety-related problem leads to a product recall.

I. Complaint Files

Under § 213.198(a), the quality unit must review all written and oral complaints involving the possible failure of a medical gas to meet any of its specifications. The quality unit must also determine the need for an investigation in accordance with § 213.192, as well as determine whether the complaint contains an event reportable under 21 CFR part 230. For example, any complaint involving a possible leak of a container or closure must be reviewed, evaluated, and investigated in accordance with § 213.192. Further, if multiple complaints indicate an adverse trend, it is important that the investigation extend to evaluating state of process control and ensure appropriate CAPAs to resolve any operational problems.

Manufacturers must maintain written records of each complaint concerning a medical gas. These records must include (§ 213.198(b)) the following:

- Name of the gas
- Lot or batch number
- Name of the complainant
- Date the complaint was received
- Nature of the complaint
- Response provided to the complainant
- Findings of any investigation and follow-up

In addition to the name of the complainant, FDA recommends that manufacturers list any known contact information and the date of the FDA response to the complainant. The description of the nature of the complaint should contain sufficient information to facilitate investigative follow-up and identify adverse trends or patterns (e.g., a higher-than-expected rate of valve replacement indicating a recurring container closure defect). If the manufacturer conducts an investigation, a record of the findings should include the following:

- Nature of the complaint and date the complaint was received
- Action initially taken, including dates and the identity of the person taking the action
- Follow-up action taken, which can include both corrective action and preventative measures to address the complaint
- Whether other batches of medical gas were potentially affected

- Outcome regarding the problem(s) raised by the complainant

If an investigation was not conducted, there must be a record of the reason an investigation was found to be unnecessary and the name of the responsible person making such a determination (§ 213.198(b)).

XII. RETURNED AND SALVAGED MEDICAL GASES

The requirements pertaining to the handling of returned medical gas are in 21 CFR 213.204. If the conditions under which a returned gas had been held, stored, or shipped before or during their return casts doubt (e.g., is unknown) on the safety, identity, strength, quality, or purity of the gas, or if the condition of the gas, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality, or purity of the gas, then the manufacturer must destroy the returned gas. However, the returned gas does not need to be destroyed if the manufacturer can prove through examination, testing, or other investigations that the gas meets appropriate standards. If the reason a medical gas was returned is because of a quality issue or implicates associated batches, the manufacturer must conduct an investigation as required under § 213.192. FDA recommends that manufacturers vent or completely evacuate the container holding returned gas.

FDA does not consider gas remaining in high-pressure cylinders or cryogenic containers that are returned for refilling in the normal course of business to be returned medical gas. In these cases, a small amount of gas is expected to remain in a returned container and can be reused if the medical gas meets specifications.

Manufacturers must have written procedures for the holding, testing, and use of returned medical gases and must maintain records of returned medical gases that include the following (§ 213.204):

- Name of the returned medical gas
- Lot number (or control number or batch number)
- Reason for the return
- Quantity returned
- Date of disposition
- Ultimate disposition of the returned gas

The requirements pertaining to the salvaging of medical gas are in 21 CFR 213.208. Manufacturers may salvage medical gases that have been improperly stored and return the medical gas to the marketplace unless the container was subjected to adverse conditions that impact the identity, strength, quality, and purity of the medical gas, or the integrity of the container closure. Examples of such adverse conditions include natural disasters, facility structural damage, and changes in external factors such as temperature. In these instances, manufacturers must demonstrate through laboratory tests that the gases continue to meet all applicable standards of identity, strength, quality, and purity, and that the adverse conditions did

not compromise the integrity of the container closure system. Manufactures must have written procedures for the holding, testing, and use of salvaged medical gases.

XIII. ADAPTERS

For safety reasons, FDA recommends avoiding the use of adapters of any kind to circumvent the specific medical gas valves and connections associated with a medical gas.

In limited circumstances, such as when filling medical gas mixtures, manufacturers can use adapters (e.g., to reduce or expand the connection size for a specific medical gas while still maintaining the connection system). Manufacturers should have written procedures detailing system checks and controls to prevent mix-ups or contamination when using adapters, and to promptly identify and quarantine compromised gases if a mix-up or contamination should occur.

GLOSSARY

The following terms are defined for the purposes of this guidance:

Air separation units: Air separation units separate atmospheric air into constituent gases of oxygen, nitrogen, and argon through a purification process of precleaning, compression, cooling, and fractional distillation of liquefied air.

Batch: A specific quantity of a medical gas or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.[1]

Component: Any ingredient intended for use in the manufacture of a medical gas, including those that may not appear in such gas. It does not include an incoming designated medical gas.[2]

Designated medical gas (DMG): A drug that is manufactured or stored in a liquefied, nonliquefied, or cryogenic state; is administered as a gas; and is defined in section 575(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360ddd(1)).[3]

In-process material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the medical gas.[4]

Incoming DMG: A DMG received from one source that, after receipt, is commingled with the same gas from another source, used in a medically appropriate combination of DMGs or in the production of another medical gas, or further distributed.[5]

Lot: A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a medical gas produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.[6]

Lot number, control number, or batch number: Any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of medical gas or other material can be determined.[7]

Manufacturer: Any person or firm that manufactures, processes, packs, or holds a medical gas, which includes packaging and labeling operations, testing, and quality control.[8]

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[1] See 21 CFR 213.3(b)(2).
[2] See 21 CFR 213.3(b)(4).
[3] See 21 CFR 213.3(b)(5).
[4] See 21 CFR 213.3(b)(7).
[5] See 21 CFR 213.3(b)(8).
[6] See 21 CFR 213.3(b)(9).
[7] See 21 CFR 213.3(b)(10).
[8] This definition is based on the definition of *manufacture, processing, packing, or holding of medical gases* in 21 CFR 213.3(b)(11).

Medical gas: A drug that is manufactured or stored in a liquefied, nonliquefied, or cryogenic state and administered as a gas.[9]

Original manufacturer: The person that initially produces a DMG by chemical reaction, physical separation, compression of atmospheric air, purification (e.g., reprocessing an industrial gas into a medical gas), or other means.[10]

Portable cryogenic medical gas containers: Containers that are capable of being transported and are intended to be attached to a medical gas supply system within a hospital, health care entity, nursing home, other facility, or home health care setting, or is used to fill small cryogenic gas containers for use by individual patients. The term excludes cryogenic containers that are not designed to be connected to a medical gas supply system, e.g., tank trucks, trailers, rail cars, or small cryogenic gas containers for use by individual patients (including portable liquid oxygen units, as defined in 21 CFR 868.5655).[11]

Quality unit: Any person or persons designated with the authority and responsibility for overall quality management and other responsibilities as defined in 21 CFR 213.22.[12]

Strength: The concentration of the medical gas (for example, weight/weight, weight/volume, or unit dose/volume basis); and/or the potency, that is, the therapeutic activity of the medical gas as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).[13]

Transfillers: Transfillers manufacture medical gas by transferring a finished medical gas, either in a liquid or gaseous state, from one container to another, including a container that contains the same medical gas. Manufacturers that combine different medical gases are considered both transfillers and original manufacturers.

Uninterrupted filling sequence: A single, continuous filling sequence with no breaks or shutdowns occurring during the filling operation. This sequence uses the same personnel, equipment, and batch of component(s).

[9] See section 575(2) of the FD&C Act; 21 CFR 213.3(b)(12).
[10] See 21 CFR 213.3(b)(13).
[11] See 21 CFR 213.94(e)(1); 21 CFR 201.328(a).
[12] See 21 CFR 213.3(b)(14).
[13] See 21 CFR 213.3(b)(15).