Current Good Manufacturing Practice for Medical Gases

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2017
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Revision 1

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Contains Nonbinding Recommendations

Draft — Not for Implementation

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Current Good Manufacturing Practice for Medical Gases Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 of medical gases in complying with applicable current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211).[2] Medical gases are generally regulated as finished pharmaceuticals and are subject to CGMP requirements regardless of the processing stage. Compliance with applicable CGMP requirements helps to ensure the safety, identity, strength, quality, and purity of medical gases. Medical gases that are not manufactured, processed, packed, or held according to applicable CGMP requirements can cause serious injury or death.[3]

Pursuant to its review of Federal drug regulations under the Food and Drug Administration Safety and Innovation Act (FDASIA),[4] FDA determined, in part, that additional guidance regarding the application of certain regulations to medical gases would be useful.[5] This document provides such additional guidance regarding CGMP regulations. This guidance is expected to reduce the regulatory compliance burden for the medical gas industry by providing

[1] This guidance has been prepared by the Office of Pharmaceutical Quality and the Office of Compliance in the Center for Drug Evaluation and Research in cooperation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] In this guidance, the term *manufacturer* includes any person or firm that manufactures a medical gas, which includes producing, cascading, distributing, filling, mixing, purifying, separating, transferring, and transfilling medical gases. See section XIV, Glossary, for definitions of different types of manufacturers.

[3] A number of injuries and deaths have resulted from medical gases not being produced or handled properly. For example, there have been a number of incidents in which a medical gas container holding a gas other than oxygen was erroneously connected to a health care facility's oxygen supply system. For further details regarding several of these incidents, see proposed rule "Medical Gas Containers and Closures; Current Good Manufacturing Practice Requirements" (71 FR 18039, April 10, 2006).

[4] Public Law 112-144, 126 Stat. 993 (July 9, 2012); see section 1112(a)(2).

[5] See FDA, 2015, Report to Congress: Review of Federal Drug Regulations With Regard to Medical Gases, available at http://www.fda.gov/downloads/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/UCM453727.pdf.

clear, up-to-date, detailed recommendations regarding CGMP issues that have been the subject of industry questions.

This guidance supersedes the draft guidance for industry *Current Good Manufacturing Practice for Medical Gases* issued in May 2003.[6]

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. STATUTORY AND REGULATORY REQUIREMENTS

This guidance applies to medical gases that meet the definition of a drug under section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act),[7] including those that are recognized in the United States Pharmacopeia-National Formulary (USP-NF). Gases that do not meet the definition of a drug, including gases intended for industrial applications or nondrug medical applications (e.g., a calibration gas used as a standard), are outside the scope of this guidance. Medical gases—including those that are marketed pursuant to a new drug application (NDA) submitted under section 505 of the FD&C Act or the certification process described in section 576 of the FD&C Act[8]—are generally considered finished drug products.

A medical gas that meets the definition of a drug (referred to in this guidance as simply a *medical gas*) is deemed to be adulterated under section 501(a)(2)(B) of the FD&C Act if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice."[9] 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."

Medical gases that are subject to applicable CGMP requirements at 21 CFR parts 210 and 211, and manufacturers of such medical gases, must meet these requirements to comply with section 501(a)(2)(B) of the FD&C Act (see 21 CFR 210.1(b)). Manufacturers that solely produce gases for industrial or nondrug medical applications are not subject to these CGMP requirements.

[6] See 68 FR 24005 (May 6, 2003).

[7] See 21 U.S.C. 321(g)(1) for the definition of *drug* under the FD&C Act. See 21 U.S.C. 360ddd(2) for the definition of *medical gas* and 21 U.S.C. 360ddd(a) for the definition of *designated medical gas.*

[8] 21 U.S.C. 360ddd-1.

[9] 21 U.S.C. 351(a)(2)(B).

Manufacturers of medical gases need only comply with those CGMP requirements applicable to the operations in which they are engaged (see § 210.2(b)).

III. ORGANIZATION AND PERSONNEL

A. Quality Unit

The establishment of an effective quality system reflects the principle that quality should be built into the product; testing alone cannot ensure product quality. 21 CFR 211.22 provides that the quality control unit (hereinafter *quality unit*) has the authority needed to create, monitor, and implement a quality system.[10] The quality unit's responsibilities and procedures must be in writing and its procedures must be followed (§ 211.22(d)).

Manufacturers must have a quality unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products 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. The quality unit is also responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company (§ 211.22(a)).

1. Responsibilities

A quality unit's size and complexity can vary with the size of the operation. For example, a manufacturer that fills only oxygen and has very few employees might only have one person as the quality unit, whereas a larger manufacturer with several locations might have a corporate quality unit responsible for multiple locations. Either arrangement can satisfy the requirements of § 211.22. Staff at each manufacturing facility must follow procedures and specifications that are approved by the appropriate quality unit (§ 211.22(c)).

As described in FDA's guidance on maintaining a quality system,[11] production personnel and the quality unit typically remain independent. Some medical gas manufacturing sites, however, have limited personnel, and the individuals assigned to the quality unit also perform production functions. These individuals implement all the controls and review the results of manufacture to ensure that product quality standards established by the manufacturer have been met, regardless of their production functions or other roles. FDA considers this approach to comply with CGMP requirements provided that each individual who performs quality unit functions is adequately trained and experienced in all quality unit tasks assigned (§ 211.25). FDA recommends that all

[10] For purposes of this guidance, the term *quality unit* is synonymous with the term *quality control unit.* For the definition of *quality control unit,* see § 210.3(b)(15). We note that FDA also takes this approach in its guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[11] See the ICH guidance for industry *Q10 Pharmaceutical Quality System* and the guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations.*

individuals who are part of the quality unit be identified by function and title in written procedures to ensure that the appropriate quality unit responsibilities are fulfilled.[12]

2. Quality Agreements With Suppliers

The quality unit's procedures should call for written quality agreements with suppliers of goods and services that clearly describe the goods or services to be provided, quality specifications, and communication mechanisms between the contracting parties; this assists in ensuring drug quality and safety.[13] Timely communication about process changes that could affect the composition of the gas supplied or about changes in tank cleaning services, for example, can prevent contamination. Therefore, FDA recommends that written quality agreements with suppliers define CGMP responsibilities and the communication processes for reporting complaints and changes that could be critical to drug quality.

3. Supplier Qualifications

Written procedures should explain how manufacturers qualify and approve suppliers.[14] Manufacturers should determine supplier qualifications to ensure that quality standards are met and that purchased gases, including feeder gases, have an accurate and complete certificate of analysis (COA). If using a supplier's COA, manufacturers must conduct at least one specific identity test and establish the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (see § 211.84(d)). Such periodic testing may be performed by the manufacturer, a third party, or a contract-testing laboratory. Manufacturers can begin the supplier qualification process, for example, by fully testing several batches and examining the gas, containers, and closures provided.[15] Manufacturers should periodically verify the qualification of approved suppliers by conducting audits (on-site or remote), analyzing trends in the quality of received goods, testing, and evaluating the timeliness of supplier responses to complaints.

B. Personnel Qualifications

All personnel, including those working on the manufacturing floor or driving to customer sites to distribute medical gas, must have the education, training, and experience necessary to perform their assigned functions (§§ 211.25(a) and (b)). Inadequately trained personnel could inadvertently fill the wrong gas into a storage tank or connect the wrong gas to a gas supply system, which can result in serious injury or death.[16]

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[12] For quality unit requirements, see § 211.22.

[13] For more information on quality agreements, see the guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements.*

[14] Designated medical gases must be certified (see sections 575 and 576 of the FD&C Act). For more information on certification of designated medical gases, see the draft guidance for industry *Certification Process for Designated Medical Gases.* When final, this guidance will represent FDA's current thinking on this topic.

[15] In this guidance, the terms *batch* and *lot* are interchangeable.

[16] See footnote 3.

Personnel, including drivers, who connect portable cryogenic containers to gas supply systems must be trained appropriately in the specifics of those supply systems. Drivers who deliver multiple gases (including multiple medical gases or both medical and industrial gases) must be trained to accurately identify each gas and distinguish among them. Personnel must be trained in CGMP requirements on a continuing basis and with sufficient frequency to provide assurance that they remain familiar with the applicable requirements (§ 211.25(a)). FDA recommends that CGMP training be provided annually and that manufacturers keep training records that include time and attendance entries.

IV. BUILDINGS AND FACILITIES

The standard industry practice of refilling labeled medical gas containers underscores the importance of building and facility design as a control method for proper operation. For example, because facilities reuse labeled medical gas containers, filled and unfilled cylinders with identical labeling may only be distinguishable if they are quarantined in well-defined areas. Buildings must have a sufficient number of adequately sized areas for organized sequential operations, including well-defined areas for incoming medical gases, containers, manufacturing equipment, rejected containers and container closure systems, filling, and quarantine, as well as finished product that is ready for distribution (§§ 211.42, 211.89). Outdoor spaces and delivery truck beds may 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 separated physically in the warehouse or in the delivery truck. To separate these areas from other spaces (§ 211.42(c)), manufacturers should use identifiers such as signage, floor demarcation, or tagging.

V. EQUIPMENT

A. Filling Equipment Qualification

Automatic, mechanical, and electronic equipment, or other types of equipment, must be checked according to a written program designed to ensure proper performance (§ 211.68(a)). Equipment qualification helps ensure proper performance. FDA recommends the following:

- Equipment should be qualified at the temperature and pressures used during filling.
- Manifold valves should be qualified for use (e.g., appropriately designed to prevent mix-ups during medical gas filling operations and shown to prevent contamination of medical gas).
- Other valves that are critical to the prevention of drug contamination, such as check valves used in filling systems, should be qualified for use.

B. Equipment Cleaning and Maintenance

21 CFR § 211.67 requires that equipment be adequately cleaned and maintained. FDA recommends that medical gas manufacturers:

- Ensure that equipment used in the manufacture of medical gases (e.g., manifolds, pigtails, valve assemblies, hoses, gauges) is cleaned before initial use and after exposure to a contaminant (e.g., industrial gas impurities).

- Tailor their equipment cleaning and maintenance procedures to match the type and complexity of the particular operation, as appropriate.

Closed pressurized systems used for filling medical gases (e.g., manifolds) need not be cleaned between batches, unless exposed to a contaminant. To prevent contamination (§ 211.80(b)), manufacturers should ensure that open ends are appropriately covered (e.g., with physical caps).

Components and drug product containers and closures must at all times be handled and stored in a manner to prevent contamination (§ 211.80(b)). Accordingly, high-pressure cylinders exposed to the elements and hoses used to fill cryogenic containers must have caps or other protective means to prevent contamination (§ 211.80(b)).

Valves that are critical to the prevention of drug contamination, such as manifold or check valves used in supply systems, must be properly maintained (§ 211.67).

Industrial and medical gases can sometimes be filled at different times on the same manifold rack. This practice is acceptable as long as processes and procedures are in place and followed to prevent any possible contamination caused by backflow from the industrial cylinders into the medical cylinders or from residual industrial gas in the manifold.

For reporting requirements and recommendations, see section XI.B, Equipment Cleaning and Use Logs.

C. Equipment Calibration

Manufacturers must establish an appropriate schedule or frequency for equipment calibration (§ 211.68). This can be done using either the equipment manufacturer's recommended calibration schedule or a schedule based on the medical gas manufacturer's own historical data. Medical gas manufacturers can reference the equipment manufacturer's instruction manual in their written procedures if the manual is available for use on-site. Medical gas manufacturers that use automated, mechanical, or electronic equipment such as computer systems must ensure these systems are routinely calibrated, inspected, or checked according to a written program designed to ensure proper performance (§ 211.68(a)).

FDA recommends that manufacturers:

- 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 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 cryogenic home 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 at least annually.

- Calibrate handheld oxygen analyzers based on the equipment manufacturer's instructions or a schedule based on the gas manufacturer's own historical data.

See section XI.A.3 for records requirements related to equipment calibration, checks, and inspections.

D. Computerized Systems

Computerized systems, including hardware and software, used in the manufacturing, processing, and holding of medical gases must be validated for their intended use (e.g., §§ 211.63, 211.68(a) and (b)).[17] The depth and scope of the validation depend on the complexity and significance of the computerized system.

Automated filling systems must be validated to provide assurance that the filling is done properly (§§ 211.68, 211.100).

Computerized or automated systems must have sufficient controls to prevent unauthorized access or changes to master production control records or other records and to ensure records or data are accurate (§ 211.68(b)). In addition, any change to a computerized or automated system should be made according to approved procedures, and any changes should be documented.[18] A risk assessment should be performed to determine the potential of the computerized system to affect product quality, safety, and record integrity. Manufacturers can use an audit trail as part of these systems to address risk.

For examples of the validation of medical gas air separation unit (ASU) automated and computer controls, see the Compressed Gas Association's *Guideline for Validation of Air Separation Unit and Cargo Tank Filling for Oxygen USP and Nitrogen NF* (CGA P-8.2, 5th ed., 2013).

[17] For more information about validation, see the guidance for industry *Process Validation: General Principles and Practices*.

[18] 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.*

VI. COMPONENTS, CONTAINERS, AND CONTAINER CLOSURE SYSTEMS

A. Components

Manufacturers must control and assess the quality of components (i.e., any ingredient intended for use in the manufacture of a drug product) as specified in §§ 211.80, 211.82, 211.84, and 211.110. Recommendations for control of incoming components include the following:

- ASUs should assess the air quality when validating the manufacturing process to determine when it should be reassessed and to determine which air quality conditions could require additional testing.

- Original manufacturers that use a feeder gas as their raw material should perform an initial and periodic characterization of the feeder gas (e.g., fingerprinting) for any impurities that could affect the finished product safety and quality. They should also assess levels of impurities in the feeder gas to ensure that the manufacturing process is capable of adequate purification (i.e., remains valid under normal processing conditions). Furthermore, original manufacturers should maintain written agreements with suppliers of feeder gas so that they are informed of any changes that suppliers make that might affect the composition of the feeder gas. (See also section III.A.2, Quality Agreements With Suppliers.)

B. Containers and Container Closure Systems

1. General

The quality unit must examine, reexamine as appropriate, and approve or reject containers and container closure systems (§§ 211.22, 211.84, 211.87). A manufacturer should reexamine a container or container closure system when, for example, it is stored for an extended period or exposed to adverse environmental conditions. Rejected containers and container closure systems must be identified and quarantined (§ 211.89). After customers use containers and container closure systems and send them back for refilling, manufacturers must store them under quarantine until they have been tested or examined, as appropriate (§ 211.82(b)).

Containers and container closure systems must be clean and 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 (§ 211.94(a) and (c)). Thus, containers and container closure systems should be cleaned before initial use and after exposure to a contaminant. In addition, if converting a container's use from industrial grade gas to medical gas, or if there is reason to believe there was previous industrial use, manufacturers must implement appropriate cleaning and retesting procedures (§§ 211.84, 211.94(c)).

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 (§ 211.94(e)(1)). If the gas-specific use outlet connection can be readily removed and replaced, a container holding a gas other than oxygen could be inadvertently connected to an oxygen supply system, causing serious injury or death.

Manufacturers should not use vapor recovery systems during carbon dioxide delivery. It is possible that toxic contaminants or impurities 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

Manufacturers should conduct prefill inspections to provide assurance that containers and container closure systems are acceptable for use before filling begins. This section addresses prefill inspections that evaluate containers and container closure systems used to hold incoming medical gases and store medical gases and finished product containers and container closure systems. Any prefill inspections performed must be properly documented (§ 211.184(b)). Containers and container closure systems that fail prefill inspections must be quarantined until the container, container closure system, or valve has been repaired, cleaned, or replaced, as appropriate, and determined to pass reinspection (§§ 211.84, 211.89).

a. External inspection

i. Container

Manufacturers should carefully 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. Any container found to have any of these conditions must be quarantined until its suitability has been determined (§§ 211.82, 211.84, 211.89).

ii. Valves, inlets, outlets, and connectors

Manufacturers should carefully inspect each container's valve assembly, connectors, and fittings to ensure that they are appropriate for the medical gas. The valves, inlets, outlets, gauges, and connectors should be examined carefully for signs of damage (including fire damage), unusual wear, corrosion, or the presence of debris, oil, or grease. This inspection should cover any connections that are brazed, welded, or equipped with a locking device.

b. Label inspection

Manufacturers should examine the labeling on each container for legibility and accuracy and should remove and replace damaged labels. Product labels on medical gas containers can be reused. Labels that are obsolete or outdated must be removed (§ 211.122(e)).

Each portable cryogenic container must be conspicuously marked with a 360° wraparound label identifying its 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 (e.g., lettering in the designated color against a white background, or white lettering on a background of the designated color) (§ 201.328(a)(1)(i)).[19]

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)).

The 360° wraparound label and, if separate, the *For Medical Use* label required for portable cryogenic medical gas containers must be affixed to the container in a manner that does not interfere with other labeling and such that it is not susceptible to becoming worn or inadvertently detached during normal use (§ 211.94(e)(2)). Each label, as well as materials used for coloring medical gas containers, must be reasonably resistant to fading, durable when exposed to atmospheric conditions, and not readily soluble in water (§ 211.94(e)(2)).

Although permanently mounted cryogenic containers are not required to have a 360° label, such containers should include content labeling that is easily readable from all sides.

c. 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)):

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

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

**For example, green and gray for a blend of oxygen and carbon dioxide.

[19] There are no specific color requirements for the 360° wraparound label for portable cryogenic medical gas containers containing a mixture of gases. As stated above, however, there are requirements addressing the color of the cryogenic container itself.

Unlike high-pressure cylinders, portable cryogenic medical gas containers are not required to be colored in whole or in part (see below for a discussion of the label requirements for portable cryogenic medical gas containers). However, a portable cryogenic container may only be colored, in whole or in part, in the FDA-designated colors in the chart above if the gas or gases held in the container correspond to those colors (§ 201.328(a)(1)(v)). Alternatively, these containers can be colored in a light-reflective color (e.g., white) that is not one of the FDA-designated colors in the chart above.

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 product. Color coding provides an additional safeguard to facilitate accurate identification and detection of potential errors.

d. Prefill inspection of high-pressure cylinders

When inspecting high-pressure cylinders, manufacturers should conduct the following prefill inspections (in addition to the previously mentioned prefill inspections).

i. Inspection of high-pressure cylinders for the DOT requalification date

Manufacturers should examine each high-pressure cylinder for the U.S. Department of Transportation (DOT) date stamped on the cylinder before use to verify that each cylinder conforms with DOT requirements for requalification and marking of cylinders (see, e.g., 49 CFR 180.209). If the DOT requalification date has been exceeded, the cylinder should be quarantined until either DOT requirements have been satisfied or the cylinder is removed from inventory.

ii. Hammer or dead-ring test

Manufacturers should conduct a hammer or dead-ring test to provide information about internal corrosion of steel cylinders. The test consists of lightly tapping the cylinder sidewall with a hammer-like instrument. The hammer or dead-ring test should not be performed on aluminum or composite cylinders because the test would not indicate internal corrosion and could damage the cylinder wall.

iii. Odor inspection

Manufacturers can use an odor test to detect the presence of any 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 finished product testing, for which an odor test 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 and perform an odor test on the resulting gas.

Residual pressure valves prevent the cylinder from emptying completely and also 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. For batch records and reporting requirements and recommendations, see section XI.E, Batch Production and Control Records.

iv. Venting or blow down of cylinders

High-pressure cylinders that are received for refilling should be vented or blown down appropriately to remove any 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.

C. Stock Rotation

Medical gas containers and container closure systems are typically reused over a period of years and undergo prefill testing. Accordingly, FDA does not intend to object if medical gas manufacturers do not comply with the containers and container closure systems requirements in § 211.86 for stock rotation and use of the oldest containers and container closure systems first. Manufacturers should address the continued suitability of containers and container closure systems after extended storage by having procedures in place to ensure that they (1) are not exposed to conditions that may render them unfit for use, and (2) have undergone prefill tests.

VII. PRODUCTION AND PROCESS CONTROLS

A. Sampling and Testing

Control procedures must be established to monitor output and to validate the performance of manufacturing processes that may cause variability in the quality of the medical gas (§ 211.110). For example, to address variation in the quality of feeder gas or atmospheric air, original manufacturers should validate the process to remove contaminants.

B. Vacuum Evacuation of High-Pressure Cylinders

For those cylinders that are not equipped with a residual pressure valve with backflow prevention, FDA recommends vacuum evacuation to remove residual gases when cylinders are being reused. FDA recommends manufacturers use 25 or more inches of mercury vacuum for high-pressure cylinders to vacuum evacuate the residual gases. If using less than 25 inches of vacuum, manufacturers should have data on file demonstrating that the amount of vacuum evacuation sufficiently removes all residual gases from high-pressure cylinders.

Manufacturers must maintain records of any problems that occur with container evacuation, such as the inability to adequately empty the cylinder of residual gases (§§ 211.84, 211.184). Data regarding changes to the amount of vacuum used must be available for inspection (§§ 211.84, 211.94, 211.100, 211.184), and such changes should be scientifically justified.

C. Filling Procedure Checks

Components must be weighed or measured as appropriate (§ 211.101(b)). When filling high-pressure cylinders, manufacturers should include the following checks to demonstrate the presence of gas in the container and to ensure net content is delivered.

1. Temperature and Pressure Readings

A medical gas in a high-pressure cylinder increases in pressure as the temperature of the gas rises. Overfilled cylinders can reach dangerously high pressures if exposed to elevated temperatures, even if the pressure at room temperature is safe. To ensure that high-pressure cylinders are filled correctly (i.e., contents as indicated on the label), the manufacturer can attach a thermometer to one cylinder per manifold-filling sequence, or to each cylinder if filling one at a time, and adjust the final filling pressure according to a temperature/pressure chart. Manufacturers should use temperature/pressure charts or temperature/pressure calculations (Boyle's Law) to adjust filling pressure, thereby achieving proper content. This is usually stated as the pressure at 70°F with appropriate tolerances.

The manufacturer must record the actual temperature and/or pressure readings on the batch production record (§ 211.188(b)). For batch records and reporting requirements and recommendations, see section XI.E, Batch Production and Control Records.

2. Valve Assembly Leak Testing

During filling operations, manufacturers should test each valve assembly for leaks by spraying or brushing an appropriate leak detection solution on and around the entire assembly.[20] The solution should be safe for use with oxygen, leave no residue that is flammable, and be noncorrosive to the valve assembly. That is, 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, there is a leak.

Once the cylinders are filled and disconnected, manufacturers should perform a second valve assembly leak test. If any leaks are detected, the cylinder must be removed from service and quarantined until repaired (§§ 211.82, 211.89).

Performing these two tests helps ensure that the contents of high-pressure cylinders will not leak during storage or shipment.

[20] See ASTM International, 2011, G188-05 (2011), Standard Specifications for Leak Detector Solutions Intended for Use on Brasses and Other Copper Alloys.

3. Heat-of-Compression Check

During or immediately after filling high-pressure cylinders, manufacturers should perform a heat-of-compression check by lightly touching the exterior of each cylinder or by following 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 may not be filling properly. Manufacturers should investigate cool or cold cylinders.

D. Calculation of Yield

Medical gas loss is expected during manufacturing and can be variable even under normal operating conditions. Accordingly, FDA does not intend to object if medical gas manufacturers do not comply with the requirements in § 211.103 for calculation of actual yield and percentages of theoretical yield. Filling to a predetermined and acceptable temperature or pressure limit, along with finished product testing, is sufficient to determine that the medical gas or medical gas mixture in the container is the amount and type indicated by the label and required by the final product specifications (see §§ 211.134, 211.165).

VIII. PACKAGING AND LABELING CONTROLS

A. Materials Examination and Usage

According to §§ 211.122(a), (d), and (e) and 211.125(b), manufacturers must:

- Representatively sample new labels and other labeling materials and compare them for accuracy to the master label before use in labeling of a medical gas.
- Secure labeling by limiting access to authorized personnel.
- Destroy obsolete and outdated labeling.

Different medical gas labels should be stored separately. They can be stored in the same cabinet provided they are adequately separated to prevent mix-ups (see § 211.130). Industrial gas labels should be stored in a separate area.

Only labeling that meets appropriate written specifications may be approved and released for use (§ 211.122(b)). Previous lot numbers on any labeling must be removed or obliterated (§ 211.67(b)(4)).

See section VI.B.2.c for more information about prefill label inspections.

B. Labeling Control

Manufacturers must strictly control labeling issued for use in medical gas operations (§ 211.125(a)). To prevent mix-ups, manufacturers should compare the number of labels issued with the number of labels applied.

For cut labeling that does not use a dedicated product labeling and packaging operation, manufacturers must use appropriate electronic or electromechanical equipment or visual inspection to conduct a 100-percent examination for correct labeling or any automated technique that physically prevents incorrect labeling from being processed by labeling and packaging equipment (§ 211.122(g)).

Label reconciliation is waived for 360° wraparound labels on portable cryogenic medical gas containers (§ 211.125(c)).

FDA recommends that all labeling be issued for use in medical gas labeling operations by authorized personnel only.

C. Packaging and Labeling Operations

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.[21] For continuous manufacturing operations (including ASUs), manufacturers should designate a batch as the amount of medical gas produced in 24 hours or less. Each batch must be assigned a lot or control number from which the history of the manufacture and control of the batch may be determined (§§ 210.3(b)(11), 211.130(c)).

Transfillers receiving shipments of medical gas into a storage tank should assign a new lot number to the contents of the storage tank each time it is refilled, regardless of whether it contains previously received medical gas.

Manufacturers should ensure that for each container, the labeling accurately identifies the contents of the container and that any other required or included information in labeling is accurate. This is particularly important given that medical gas containers and labels are typically reused many times. Labels should be affixed to the container in a manner that does not interfere with other labeling and will not be susceptible to wear or inadvertent detachment during normal use. For portable cryogenic container labeling requirements, see § 211.94(e)(2).

A separate sticker or decal may be used to identify the lot number for a batch of medical gas, as long as the sticker remains adhered to the container and is legible. The sticker should be readily visible and should not obscure required drug information. A separate sticker can also be used for the container's net content information.

For information about prefill label inspections, see section VI.B.2.c and for labeling records, see sections XI.C and XI.E.

[21] Under § 210.3, "*batch* means a specific quantity of a drug 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."

D. Expiration Dating

Medical gases have unique stability characteristics. Accordingly, FDA does not intend to object if manufacturers of designated medical gases do not comply with the expiration dating requirements in § 211.137(a) for those gases (see also section X.E, Stability Testing). The containers and closures should, however, be verified as capable of holding gas at the appropriate pressure before release for distribution (see section VII). If a manufacturer labels a medical gas with an expiration date, it must be supported by stability studies (§ 211.137(b)).

IX. HOLDING AND DISTRIBUTION

Manufacturers must establish and follow written procedures describing medical gas distribution (§ 211.150). These procedures must include a system by which the distribution of each batch can be readily determined to facilitate its recall if necessary (§ 211.150(b)).

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, and (4) what would be done with the recalled product.

Because of the nature of medical gas manufacturing and the stability characteristics of the gases, FDA does not intend to object if medical gas manufacturers do not establish and follow written procedures to distribute their oldest stock first (as required by § 211.150(a)), provided that manufacturers establish a system to manage and handle medical gas stock in an orderly manner and have procedures in place. These procedures should ensure that the components, containers, and container closure systems (1) are used in a timely manner, (2) are not exposed to conditions that may render them unfit for use, and (3) have undergone prefill and other testing as required before distribution.

X. LABORATORY CONTROLS

A. General Requirements and Recommendations

Manufacturers must follow the laboratory control requirements in subpart I of part 211, follow and document the laboratory controls at the time of performance, and record and justify any deviations from the written specifications, standards, sampling plans, test procedures, and other laboratory control mechanisms (§ 211.160(a)). For example, manufacturers must record and justify changes made to the analytical method, such as a different column length or a different carrier gas.

Designated medical gases that have been certified must meet the standards set forth in an applicable compendium.

The manufacturing processes used for industrial grade gas could result in a gas with higher levels of impurities than permitted in gas for medical use or impurities not specified in the relevant USP-NF monograph. Accordingly, FDA does not recommend converting industrial grade gas to medical gas. However, if a manufacturer chooses to convert industrial grade gas to medical gas,

such conversion requires testing in addition to testing for conformance to the applicable USP-NF monograph (see section VI.A, Components, for discussion of characterizing a feeder gas).

When the likelihood of contamination has been identified during prefill inspections or filling operations, the manufacturer must quarantine the medical gas until an investigation has been completed (§§ 211.84, 211.89, 211.110(d), 211.192). The medical gas may not be released unless the investigation shows that the medical gas is not contaminated and that it meets product specifications (§ 211.84). Manufacturers should use tests suitable for detecting such contaminants as well as the tests provided in the approved application or USP-NF monograph.[22]

B. Calibration of Instruments

Laboratory controls must include a written program for calibration of instruments, apparatus, gauges, and recording devices at suitable intervals (§ 211.160(b)(4)).

Manufacturers should verify that the calibration gas 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.

See section V.C. for additional information about equipment calibration.

C. Medical Gas Sampling and Testing

For each batch of medical gas, there must be an appropriate laboratory determination of satisfactory conformance to final specifications for the medical gas, including testing for identity and strength, before release (§ 211.165(a)). Written procedures must describe (1) sampling and testing plans that include the number of units per batch that will be sampled and tested, (2) the acceptance criteria for sampling and testing, and (3) actions to be taken if test results are outside of specifications (§ 211.165).

FDA recommends that manufacturers document conformance to specification(s) in a COA for each batch of medical gas filled. See section XI.J for more information about COAs. When test

[22] Refer to USP-NF General Notices, Section 5.60, Impurities and Foreign Substances, available at http://www.usp.org/usp-nf/development-process/policies-guidelines/usp-nf-general-notices.

results do not meet specifications, retesting is not recommended until a thorough investigation has been performed according to established written procedures.[23]

1. 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.

2. Cylinders Filled Individually

One high-pressure cylinder per uninterrupted filling sequence should be tested for identity and strength.

3. Mixtures

For mixtures containing two gases, each high-pressure cylinder 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 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.

Note: For mixtures containing oxygen, each cylinder should be tested for the identity and strength of the oxygen.

4. Medical Gas From Suppliers

Manufacturers receiving a batch of medical gas from suppliers should test for conformance to established specifications after receipt or before the manufactured lot is released (e.g., for further processing or transfilling). This can be done either by sampling directly from the storage tank or by testing one container from the first batch of medical product filled.

If manufacturers receive and maintain supplier COAs, the manufacturers must conduct specific identity testing (§ 211.84(d)(2)) and should conduct purity testing. FDA does not intend to object if Oxygen USP transfillers delivering to sites that only receive Oxygen USP do not conduct at least one specific identity test, as long as they witness the identity testing that their oxygen suppliers conduct. Employees who witness oxygen testing must have appropriate training (§ 211.25) and should record that they have witnessed the testing and document the method used and identity of the person who performed the test.

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

D. Test Method and Alternative Test Method Validation

When a test is approved as part of an NDA or an abbreviated new drug application, it becomes the approved analytical test method or manufacturing method for the medical gas.

Manufacturers must use approved analytical test methods for the medical gas they manufacture (§ 211.22(d)). USP-NF monograph drug products must meet USP-NF monograph standards (section 501(b) of the FD&C Act; 21 U.S.C. 351(b)), and manufacturers should use the test methods in the appropriate USP-NF monograph. For USP-NF test methods, a full test method validation study is unnecessary (§ 211.194). Data that verify that the USP-NF test method is accurate and reliable should be generated on the appropriate equipment and maintained at the manufacturing site. If a medical gas manufacturer relies on the equipment manufacturer's study, the medical gas manufacturer should retain a copy of the actual 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 (§ 211.165).

For USP-NF monograph drug products, 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 (§§ 211.160(b), 211.165(e)). 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.[24]

FDA recommends that methods be validated under the same conditions in which they will be used. If the testing environment is considerably different, manufacturers should conduct additional on-site tests, such as with a small number of standard gases, to demonstrate that method performance has not been affected by local conditions. For example, paramagnetic oxygen analyzers can give inaccurate readings when used at high altitudes unless special adjustments are made. The results of these tests should be fully documented.

Certain changes made to instrumentation may 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 § 211.194(b)).

E. Stability Testing

If an expiration date is assigned to a batch, manufacturers must establish, document, and follow a stability testing program (§§ 211.137, 211.166). If an expiration date is not assigned to a designated medical gas, supporting stability studies are not needed (see section VIII.D, Expiration Dating).

[24] See the guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics.*

F. Reserve Samples

Per § 211.170, reserve samples for compressed medical gases need not be retained.

XI. RECORDS AND REPORTS

Manufacturers must maintain a number of records, including but not limited to those described by § 211.68 and subpart J of part 211. This section reviews some of these requirements and also provides recommendations regarding records and reports.

A. General Requirements and Recommendations

1. Record Retention

For products with an expiration date, any required production, control, or distribution record must be retained for 1 year after the expiration date of the batch (§ 211.180(a)). If the batch of medical gas is not labeled with an expiration date, the aforementioned records should be maintained for at least 3 years after the batch distribution date. FDA also recommends that manufacturers retain training records and COAs for at least 3 years.

All records required under part 211, or copies of such records, must be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred (§ 211.180(c)). Records can be kept on paper or electronically.[25]

2. Record Review

Manufacturers must review a representative number of batch records, complaint files, investigations, recalls, and returned products annually to determine the need for changes in drug product specifications for manufacturing or control procedures (§ 211.180(e)). In addition, manufacturers should use these records to identify potential product quality issues and opportunities for continuous process improvement. This can be done on a companywide or site-by-site basis.

3. Equipment Calibration, Checks, and Inspections

Manufacturers must keep records of calibration, checks, and inspections of electronic equipment used in the manufacture, processing, and holding of medical gas (§ 211.68(a)). See section V.C. for more information about equipment calibration.

[25] 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*).

4. Computer Validation Data

Manufacturers (including ASUs) must have documentation that their automated, mechanical, and electronic equipment—including computers used in the manufacturing or holding of a gas—demonstrates proper performance (§ 211.68(a)).

5. Process Validation Data

Manufacturers must have process validation records showing that their operational and process control procedures ensure that medical gases have the identity, strength, quality, and purity that they purport or are represented to possess (§ 211.100). (For more information on FDA recommendations regarding process validation, see the guidance for industry *Process Validation: General Principles and Practices.*)

B. Equipment Cleaning and Use Logs

For medical gases that are manufactured using closed pressurized systems and equipment, the system and equipment generally does not need to be cleaned between batches, unless exposed to a contaminant. See section V.B, Equipment Cleaning and Maintenance.

Manufacturers should retain records of cleaning pressurized systems and equipment before commissioning for production use.

When cleaning or maintenance is required, manufacturers should document the work on separate cleaning or maintenance records that are not associated with specific batch records. The people who perform cleaning and maintenance and those who verify it must date and sign or initial the log indicating that the work was performed (§ 211.182). If automated equipment is used in cleaning and maintenance in accordance with § 211.68(c), only the person verifying the cleaning and maintenance needs to date and sign or initial the log.

If using equipment dedicated to a single medical gas, manufacturers may keep control records for cleaning, maintaining, and using the equipment as a part of the batch records, provided that batches of the medical gas follow in numerical order and are manufactured in numerical sequence (§ 211.182).

Equipment logs, including maintenance records, are critical for original manufacturers (including ASUs) because of the complex nature of the manufacturing equipment and associated maintenance requirements (e.g., carbon beds, dryer beds, distillation units).

Manufacturers should maintain cleaning and use logs for their filling equipment used on- or off-site.

See also section V.B. Equipment Cleaning and Maintenance.

C. Component, Container, Container Closure System, and Labeling Records

Records must include the following (§ 211.184):

- The identity and quantity of each shipment or each batch of newly purchased components, containers, or container closure systems. The records must contain the supplier's name, lot number if known, and date of receipt. Manufacturers should also maintain records of the serial numbers of newly purchased containers or container closure systems. Original manufacturers (including ASUs) that use a feeder gas or atmospheric air as a component should maintain records of the periodic testing they conduct. (See section VI.A for testing recommendations.)

- The results of any test or examination performed on components, containers, and container closure systems. (See section VI for testing requirements and recommendations.)

- Documentation of the examination of labels and labeling for conformity with established specifications. (See section VIII for labeling requirements and recommendations.)

- The disposition of rejected medical gas components, containers, container closure systems, and labeling.

Medical gas loss is expected during storage and manufacturing, and medical gas is subject to release testing (see section X.C, Medical Gas Sampling and Testing). Therefore, because of the expected loss, FDA does not intend to object if the requirement at § 211.184(c) regarding reconciliation of individual inventory records is not met with respect to medical gases that are components of the finished drug product.

Quality agreement records should be maintained with the other required records and available for FDA review. See section III.A.2 for more information about quality agreements.

D. Master Production and Control Records

Master production and control records are necessary to ensure uniformity from batch to batch. These required records must be prepared, dated, and signed by one person and independently checked, dated, and signed by a second person (§ 211.186(a)). These records must include (§§ 211.186(a) and (b)):

- A description of the medical gas containers, container closure systems, and packaging materials, including a specimen or copy (e.g., electronic copy) of each label and labeling.

- 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 and must include complete information related to the production and control of each batch (§ 211.188). These records must include but are not limited to:

- A reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed.
- Documentation that each significant step in batch manufacture, processing, packing, or holding was accomplished, including:
  - Date of performance.
  - Lot number or other unique identification number.
  - In-process and batch test results.
  - Description of medical gas containers and container closure systems.
  - Any sampling performed.
  - Identification of the people performing and directly supervising or checking each significant step.
  - Any investigation made according to § 211.192.
  - Results of examinations made according to § 211.134.

Batch production records must clearly and accurately reflect actual production practices and conditions at the time of manufacture (§ 211.188). Transfiller pumper's or filler's logs can be used as batch production records if they contain all relevant information as specified in § 211.188 and in section XI.D, Master Production and Control Records.

In addition to the requirements listed above, FDA recommends that batch records maintained by transfillers, including curbside vendors, also document:

- Prefill inspections.
- Number and size of the cylinders or cryogenic containers filled.
- Filling inspections.
- Postfill inspections.
- Final temperature and pressure results or other inspection results.

Manufacturers need not store and maintain batch production records as one document; however, all the required batch record information should be easily located and traceable to each specific batch manufactured. Continuous processing logs can designate lot numbers and entries (e.g.,

initials, dates) demonstrating that each significant step in the operation has been checked. Manufacturers that use computer-controlled equipment during manufacture should establish and follow procedures to maintain, review, and approve the manufacturing data.

Manufacturers must not use a single entry to indicate that all of the significant manufacturing, processing, packing, and holding steps have been performed (§ 211.188(b)). A checkmark or other symbol should not be used in place of an actual value, such as for temperature and pressure readings, purity, and identity results.

FDA recommends that manufacturing records identifying nonconforming medical gas describe the rejection relative to the rest of the batch to ensure that the scope of the investigation is appropriate. Medical gases rejected for container leaks and medical gases rejected for manifold leaks during filling must be documented (§§ 211.165, 211.188) and investigated (§ 211.192). The scope of the investigation into a manifold leak must extend to other batches of medical gas that may have been associated with the same failure (§ 211.192).

Complete labeling control records, including specimens or copies of all labels used, and examination results must be included in the batch record (§ 211.188(b)(8)). A photocopy or printed digital image can be an appropriate alternative to a label specimen. A specimen of the specific lot number labeling (e.g., lot number sticker) should also be included in the batch record. Labeling control records maintained by original manufacturers (including ASUs) that fill bulk trailers may or may not include a finished product label; however, these manufacturers should maintain both product and lot-specific labeling.

Each lot number should be traceable in records for batch manufacturing, labeling, testing, and release.

F. Production Record Review and Investigations Records

The quality unit must review and approve all medical gas production and control records, including those for packaging and labeling, before a batch is released or distributed (§ 211.192). Unexplained discrepancies or the failure of a batch to meet its specifications, including any test results outside of established limits, must be thoroughly investigated, whether or not the batch has already been distributed (§ 211.192). Manufacturers must maintain records of investigations, which must include conclusions and follow-up information (§§ 211.180, 211.192).

For original manufacturers (including ASUs):

- FDA recommends that third-party consignees (e.g., trucking company staff) not perform the quality unit release of a medical gas.

- If filling occurs when the quality unit is not on site, the quality unit is responsible for review and approval before distribution (§ 211.192).

For curbside vendors of oxygen, the quality unit must review documentation associated with the off-site filling operation, including records of all inspections and maintenance procedures performed (§ 211.22(a)).

G. Laboratory Records

Laboratory records must include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays (§ 211.194). These records include the following:

- Description of the sample, lot number, location from which the sample was obtained, date the sample was taken, and date received for testing.
- Statement of each method used to test the sample.
- Complete record of all data created in the course of each test—including graphs, charts, and spectra from laboratory instrumentation—properly identified to show the specific medical gas and the batch tested. If the analytical equipment only provides a direct reading, visual observation and subsequent recording of the specific result for each test would fulfill the data requirements.
- Record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.
- Statement of the test results and how the results compare with established standards of identity, strength, quality, and purity for the component (e.g., feeder gas), in-process materials (as applicable), and finished product (see section XI.J, Certificate of Analysis).
- Initials or signature of the person who performs each test and the dates the tests were performed.
- Initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

In addition, manufacturers must maintain complete records of:

- Any modification of an established method employed in testing, including justification.
- Any testing and standardization of laboratory reference standards, reagents, and standard solutions (e.g., a reference gas or calibration gas used as a standard).
- The periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by § 211.160(b)(4).

When testing is done by a chromatographic method specified in the USP-NF (e.g., the assay method for Nitrogen NF), 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 and strength, dosage form description, consignee's name and address, shipping date, and quantity shipped (§ 211.196). For medical gases, distribution records do not need to contain lot numbers. Instead, manufacturers can use the name of the medical gas, consignee's name and address, shipping date, and quantity shipped to comply.

Record maintenance according to written procedures is critical for batch traceability, particularly during a product recall. See section IX of this guidance and § 211.150 for more information.

I. Complaint Files

Manufacturers must maintain written records of each complaint in a file designated for medical gas complaints (§ 211.198(b)). Manufacturer complaint records must include, if known (§§ 211.198(a) and (b)):

- Medical gas name and lot number.
- Complainant's name and contact information (and, if appropriate, title).
- Full description of the nature of the complaint.[26]
- Any evaluation to determine if the complaint is also an adverse event.
- Response provided to the complainant, which should include the date the response was sent.

The quality unit must review and, as needed, investigate all written and oral complaints involving the possible failure of a medical gas to meet any of its specifications (§§ 211.192, 211.198(a)). When an investigation is conducted, the written record must include the investigation findings and follow-up (§ 211.198(b)(2)). These records should include the following:

- Date the complaint was received.
- Action initially taken, including dates and identity of the person taking the action.

[26] The description should facilitate investigative follow-up and identify adverse trends or patterns (e.g., a recurring container or container closure defect).

- Follow-up action taken, including any investigation or corrective action and whether other batches of product were potentially affected.

- Final outcome regarding the issues raised by the complaint.

J. Certificate of Analysis

When manufacturers use COAs to demonstrate medical gas conformance to applicable specifications, the COAs should contain the following information:

- Manufacturer name and complete address.
- Supplier name and complete address (if available).
- Product name (e.g., Oxygen USP).
- An air liquefaction statement, as appropriate.
- Lot number or other unique identification number.
- Analytical results for all USP-NF monographs or other testing (e.g., impurities).
- Test method used to perform the analysis.
- Manufacturer or supplier signature and date.

See also section III.A.2, Quality Agreements With Suppliers.

XII. RETURNED MEDICAL GAS

For the purposes of this guidance, FDA does not consider gas remaining in high-pressure cylinders or cryogenic containers that are returned for refilling to be returned medical gas.

For medical gas that is returned, FDA recommends that the container be vented.

Medical gases that have been improperly stored must not be salvaged and returned to the marketplace (§ 211.208).

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 specific medical gas.

On rare occasions and only under strict control, adapters can be used to fill mixtures of medical gases. However, manufacturers should have written procedures detailing system checks and controls to prevent mix-ups or contamination, and to promptly identify and quarantine compromised gases if a mix-up or contamination should occur.

XIV. GLOSSARY

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

Air separation units (ASUs): ASUs 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. ASUs are original manufacturers.

Chemical synthesizers: Chemical synthesizers or processors produce medical gas by chemical reaction (e.g., nitrous oxide by thermal degradation of ammonium nitrate) or by reprocessing feeder gas. Feeder gas is often the waste stream of other industrial manufacturing operations, which is then purified and treated to manufacture a medical gas.

Cryogenic medical gas containers: Containers used to hold a low-temperature, low-pressure liquid product. They can be divided into:

- **Cryogenic medical gas home containers:** Containers designed to hold liquid oxygen at a patient's residence.

- **Portable medical gas cryogenic containers:** Containers that are capable of being transported and are intended to be connected to a medical gas supply system within a hospital, health care entity, nursing home, other facility, or home health care setting, or that are base units used to fill small cryogenic containers for use by individual patients. The term does not include 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, such as portable liquid oxygen containers, as defined in 21 CFR 868.5655.

Designated medical gas: A drug that is manufactured or stored in a liquefied, nonliquefied, or cryogenic state; is administered as a gas; and is identified in section 575(1) of the FD&C Act (e.g., Oxygen USP, Carbon Dioxide USP, Nitrogen NF, Nitrous Oxide USP, Helium USP, Medical Air USP).

Manufacturer: Any person or firm that manufactures a medical gas, which includes producing, cascading, distributing, filling, mixing, purifying, separating, transferring, and transfilling medical gases. This includes original manufacturers.

Original manufacturer: The original manufacturer of the medical gas, that is, the person or entity that initially produces the gas by chemical reaction, physical separation, compression of atmospheric air, or other means, including ASUs and chemical synthesizers or processors as well as transfillers who manufacture medical gas by mixing other gases.

Transfillers: Transfillers manufacture medical gas by transferring the gas, either in a liquid or gaseous state, from a larger container into smaller containers. Manufacturers who 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 procedure uses the same personnel, equipment, and batch of component.