Guidance for Industry

Current Good Manufacturing Practice for Medical Gases

DRAFT GUIDANCE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)
May 2003

Compliance

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide recommendations on how to comply with the current good manufacturing practice (CGMP) regulations as they apply to manufacturing, filling, transfilling, cascading, transferring, and distributing compressed and cryogenic medical gases. The recommendations should help manufacturers, fillers, and distributors[2] comply with CGMP requirements to ensure the identity, strength, quality, and purity of medical gases. This guidance also provides recommendations to medical gas manufacturers on how to comply with certain aspects of the PDMA final rule (i.e., 21 CFR part 205). This guidance is not intended to be an all-inclusive listing of all relevant CGMP; instead, it covers certain sections of the CGMP regulations followed by a discussion of recommendations that the Agency considers acceptable means of meeting the requirements.

Three previous documents were published on current good manufacturing practice for medical gases. FDA's first guideline on compressed medical gases was issued in June of 1981 and revised in 1983. In February of 1989, FDA issued another revision of the guideline to address the evolving home care area, including the delivery of oxygen to patients at home. This guidance builds on the previous guidelines. It provides details on the filling of high-pressure cylinders and cryogenic containers and includes new information on CGMP policy for large cryogenic containers, as well as discussion of CGMP relating to storage tank installation, carbon dioxide and helium manufacturing, and emergency medical services. Once finalized, this version of the guidance will supersede those earlier guidelines.

[1] This guidance has been prepared by the Division of Manufacturing and Product Quality in the Office of Compliance of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this document, the term *manufacturer* includes fillers, transfillers, cascaders, distributers, and transferers of medical gases.

FDA's guidance documents, including this guidance, 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

Medical gases (e.g., oxygen, carbon dioxide, helium, nitrogen, nitrous oxide, medical air, and combinations of these) are drugs within the meaning of section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 321(g)(1)) and pursuant to section 503(b)(1)(A) of the Act (21 U.S.C. 353(b)(1)(A) are required to be dispensed by prescription.

Medical gases are considered adulterated under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)) if the methods used in, or the facilities or controls used during their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with CGMP. The CGMP regulations are intended to ensure that a drug meets the safety requirements of the Act and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. Medical gases are finished drug products and are subject to the CGMP regulations at 21 CFR parts 210 and 211. Manufacturers of medical gases must follow the requirements in the CGMP regulations to comply with section 501(a)(2)(B). For example, each time a medical gas is filled into another container, finished product testing must be performed in accordance with § 211.165(a).

Medical gases that are not produced and handled in accordance with CGMP regulations can cause serious injury or death to the patients who use them. A number of injuries and deaths have resulted from mix-ups of medical gases associated with CGMP violations including:

- Mislabeling (in some cases the container had two or more labels)
- Inadequate training, including training of medical gas filling personnel as well as delivery personnel
- Inadequate finished product testing
- Inadequate quality control unit
- Failure to qualify equipment prior to use (e.g., stainless steel hoses, large cryogenic containers)
- Inadequate written procedures for manufacturing, processing, testing

The Attachment, Medical Gas Mix-Ups, describes in detail some of the adverse events that the Agency has investigated, including mix-ups that have resulted in serious injury or death.

FDA can take several courses of action when a CGMP violation is found: (1) issue a warning letter; (2) seize gas-related products (including storage tanks, high-pressure cylinders, vehicles containing permanently mounted large cryogenic containers, tankers, and/or cryogenic home containers on the company's premises and trucks); (3) seek an injunction; and/or (4) initiate

prosecution. FDA may also recommend disapproval of certain government contracts with the manufacturer. FDA can also notify the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration) of the violation. This may affect Medicare reimbursement for that company's products. FDA has issued numerous warning letters and on many occasions has successfully pursued seizure actions, injunctions, prosecutions, civil contempt actions, and inspectional warrants to enforce the CGMP regulations as they apply to medical gases.

III. ORGANIZATION AND PERSONNEL

A. Responsibilities of the Quality Control Unit

Medical gases are subject to the requirements in 21 CFR § 211.22 - Responsibilities of quality control unit (QCU).

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

The QCU must have the responsibility for approving or rejecting all procedures or specifications affecting the identity, strength, quality, and purity of the drug product (§ 211.22(c)).

The responsibilities and procedures applicable to the QCU must be in writing and must be followed (§ 211.22(d)).

We recommend that the QCU perform more than a testing function, be independent of the production process, and have both quality assurance and quality control responsibilities. Ideally, the QCU would participate in and have final responsibility for all functions that could affect product quality. The corporate QCU would be responsible for reviewing and approving all written procedures, even those written by each individual location's organizational units.

We recommend that all individuals who are part of the QCU be identified in the manufacturer's operating procedures. In a well-structured and well-defined corporate structure, the QCU would be included as a separate unit. A small medical gas manufacturer can designate a single individual as the QCU.

We recommend that QCU individuals receive adequate CGMP training on a continuing basis, including quality assurance training.

B. Personnel Qualifications

Medical gases are subject to the requirements in § 211.25 - Personnel qualifications.

Each person engaged in the manufacturing, filling, processing, packing, or holding of a medical gas must have the education, training, and experience, or a combination thereof, to enable that person to perform the assigned functions. Training must be in the particular operations that the employee performs and in current good manufacturing practice regulations as they relate to the employee's functions. Training in the CGMP regulations must be conducted by qualified individuals on a continuing basis and with sufficient frequency to ensure that employees remain familiar with CGMP requirements applicable to them (§ 211.25(a)).

FDA recommends that CGMP training not be conducted in one massive training session. Rather, it should be presented in smaller more manageable sessions held throughout the year, or at a minimum be held once a year. We recommend that the specific type of training received or covered, the time, and the attendance at each session be documented, and records of the training be maintained.

Regulations at § 211.25(c) require an adequate number of qualified personnel be available to perform and supervise the manufacturing, processing, or holding of medical gases.

Useful training information and training materials are available as shown below.

- The following FDA Internet sites:

  http://www.fda.gov/cder/dmpq/gases.htm

  www.fda.gov/cder/dmpq/cgmpregs.htm

  www.fda.gov/oc/industry
- Title 21 of the Code of Federal Regulations, Parts 210 and 211, available at: www.access.gpo.gov/nara
- Qualified suppliers who offer CGMP training
- A qualified medical gas consultant or consulting firm
- Industry or professional associations

The Agency recommends that each manufacturer establish and follow written training procedures for all truck drivers specific to their function, including CGMP training. Truck drivers responsible for delivery of medical gases should be trained to examine the drug label and distinguish between medical gases and industrial gases, prior to unloading a container.

We recommend that all manufacturers who allow their drivers to connect large cryogenic containers to customer gas supply systems train their drivers in the specifics of those supply systems. We recommend cargo tanker drivers who fill medical gases into storage tanks also be trained.

We recommend that an individual responsible for performing an odor test not have an ailment (e.g., a cold or allergies) that would adversely affect his or her sense of smell. Likewise,

employees responsible for performing the inspection for the standardized colors should be able to distinguish colors.

C. Consultants

Medical gases are subject to the requirements in § 211.34 - Consultants.

Consultants advising on the manufacturing, processing, packing, or holding of medical gases must have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. A company must maintain records stating the name, address, and qualifications of any consultants and the type of services they provide (§ 211.34).

We recommend that consultants hired to provide assistance in achieving CGMP compliance have sufficient medical gas education, training, and/or experience.

IV. BUILDINGS AND FACILITIES

A. Design and Construction

Medical gases are subject to the requirements in § 211.42 - Design and construction features.

Any building or buildings used in the manufacture, processing, packing, or holding of a medical gas must be of a suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations (§ 211.42(a)).

Buildings must have adequate space for the orderly placement of equipment and materials to prevent mix-ups and to prevent contamination (§ 211.42(b)).

Operations must be performed within specifically defined areas of adequate size. There must be separate or defined areas or other such control systems for the manufacturer's operations as are necessary to prevent contamination or mix-ups (§ 211.42(c)).

The Agency recommends that buildings be maintained in good physical condition, kept clean, and have a sufficient number of areas for organized sequential operations, such as a well-defined filling area and a well-defined quarantine area. The Agency also recommends the creation of quarantine areas to separate incoming medical gases, high-pressure cylinders, cryogenic containers, manufacturing equipment, rejected containers and closures, and the finished product. No matter how large your operation, we recommend you avoid storing industrial gases and medical gases in close proximity to each other.

We also recommend that delivery vehicles have well-defined, separate areas for medical gases and industrial gases to prevent mix-ups from occurring. For example, medical and industrial gases could be separated physically in the delivery truck, or a manufacturer could use a unique identifier to distinguish medical gases from industrial gases. The Agency recommends the use of 360-degree wrap-around label to identify medical gases in large cryogenic containers. If a

manufacturer applies a 360-degree wrap-around label to its large cryogenic containers, this could serve as the control system for preventing mix-ups, as long as a manufacturer has established adequate driver training, adequate written procedures, and proper stock inventory systems.

B. Security

Medical gas manufacturers are wholesale distributors who are subject to the requirements of § 205.50 - Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.

All facilities used for medical gas distribution must be secure from unauthorized entry (§ 205.50(b)(1)).

Entry into areas where medical gases are held must be limited to authorized personnel (§ 205.50(b)(1)(iii)). We recommend areas where nitrous oxide is held be especially secure.

The security requirements of § 205.50(b) apply to all facilities used for medical gas distribution. FDA interprets this regulation to include all facilities where loaded medical gas delivery trucks are parked prior to making deliveries, including at an employee's home when a loaded medical gas delivery truck is driven there and parked overnight for early morning runs.

A manufacturer could use an alarm system to secure the building and keep loading docks secure, rather than open and easily accessible.

V. EQUIPMENT

A. Equipment Cleaning and Maintenance

Medical gases are subject to the requirements in § 211.67 - Equipment cleaning and maintenance.

Equipment must be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the medical gas beyond the official or other established requirements (§ 211.67(a)).

Written procedures must be established and followed (§ 211.67(b), (4), (5), & (6)), including maintenance and cleaning schedules, removal or obliteration of previous batch identification, protection of clean equipment from contamination prior to use, and inspection of equipment for cleanliness immediately prior to use.

We recommend that equipment used in the manufacture of medical gas (e.g., manifolds, pigtails, valve assemblies, hoses, and gauges) be cleaned at initial use and if exposed to a contaminant. We recommend that hoses used to fill cryogenic containers have protective end caps to prevent contamination from insects, dirt, debris, and other materials. We also recommend that high-pressure cylinders exposed to the elements be provided with protective caps or some other

protective device, applied to the valve opening to prevent contamination. See related clarifications in § 211.80(b).

We recommend that storage tanks (especially those installed at a health care facility, nursing home, or hospital), tractor trailers, rail cars, high-pressure cylinders, and cryogenic containers prior to the introduction of a medical gas be cleaned in the following circumstances: when they previously contained industrial gases; when they are first received, whether new or used; and when they are or could be, contaminated.

B. Equipment Calibration

Medical gases are subject to the requirements in § 211.68 - Automatic, mechanical, and electronic equipment.

Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems can be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is used, it must be routinely calibrated, inspected, or checked according to a written program designed to ensure proper performance (§ 211.68(a)). Written records of those calibration checks and inspections must be maintained (§ 211.68(a)).

The Agency recommends that medical gas manufacturers use either the equipment manufacturer recommended calibration schedule or a schedule based on their own historical data. A company can reference the equipment manufacturer instruction manual in its written procedures if the manual is available for use at the manufacturing site.

We recommend that vacuum gauges undergo two calibrations. The first calibration, performed daily, would ensure that the needle on the gauge returns to zero. This check can be performed with no vacuum present, and recorded on either a batch production record or a separate log. The second calibration would ensure that vacuum gauges are calibrated based on standards established by the National Institute of Standards and Technology (NIST) on an annual basis at a minimum. Low pressure gauges and flow meters used in filling cryogenic home containers would not require calibration.

We recomment that thermometers be calibrated in accordance with manufacturer recommendations, and that the calibrations be documented in a separate log.

We also recommend that medical gas companies ensure that check valves used in a supply system to prevent the back flow of a foreign product or contaminant into the lines create a proper seal and cannot be compromised. This recommendation applies to check valves placed at various points in a supply line to protect the pump, manifold, or other equipment from over-pressurization or an undesirable back flow. Check valves do not need to be qualified if they are intended to act only as an added safety feature and do not prevent the cross contamination of gases or do not affect product identity, strength, purity, or quality.

C. Computerized Systems

Medical gases are subject to the requirements in § 211.68 - Automatic, mechanical, and electronic equipment.

Appropriate controls must be exercised over computer or related systems to ensure that changes in master production and control records or other records are instituted only by authorized personnel (§ 211.68(b)). Input to and output from the computer or related system of records or data must be checked for accuracy (§ 211.68(b)). The degree and frequency of input/output verification must be based on the complexity and reliability of the computer or related system (§ 211.68(b)).

The Agency recommends that computerized systems, including hardware and software, used in the manufacturing, processing, and holding of medical gases be validated. The depth and scope of the validation depends on the diversity, complexity, and significance of the computerized application. Commercially available software that has been qualified does not need the same level of testing as software that has been specifically developed for a company.

The Agency recommends that computerized systems have sufficient controls to prevent unauthorized access or changes to data and to preclude omissions in data. The Agency also recommends that records be kept of any changes made to data, including who made the change, when the change was made, and the previous entry.

We recommend that any change to computerized systems be made according to specified procedures and would be formally authorized, documented, and tested. We recommend that records of all changes, including modifications and enhancements made to hardware, software, and any other critical component of the system be kept as long as the manufacturer is still using that system.

VI. COMPONENTS, CONTAINERS, AND CLOSURES

A. General Recommendations

Medical gases are subject to the requirements in §§ 211.80 - 211.94: Control of components and drug product containers and closures.

Manufacturers must have written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and medical gas containers and closures (§ 211.80(a)). Containers and closures must at all times be handled and stored in a manner to prevent contamination (§ 211.80(b)).

Each medical gas container and closure, upon receipt and before acceptance, must be examined visually for appropriate labeling as to contents, container damage, and contamination (§ 211.82(a)). Containers and closures must be stored under quarantine until they have been tested or examined, as appropriate (§ 211.82(b)).

Medical gas containers and closures must be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit (QCU) (§ 211.84(a)). The containers must be opened, sampled, and resealed in a manner designed to prevent contamination (§ 211.84(c)(2)). Each medical gas container and closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant must be examined against established specifications for such contamination (§ 211.84(d)(5)).

Rejected containers and closures must be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable (§ 211.89).

Medical gas containers and closures must not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements (§ 211.94(a)). Container closure systems must provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product (§ 211.94(b)). Containers and closures must be clean (§ 211.94(c)). Medical gas containers and closures are used repeatedly and therefore play a critical role in ensuring that the drug product provided to the patient has the appropriate identity, strength, quality, and purity. Containers and closures used for medical gases are integral parts of the drug delivery system. We recommend they undergo strict inspections and examinations prior to the introduction of the drug product. In addition, we advise medical gas manfacturers to determine valve assembly compatibility prior to installation on a high-pressure cylinder and during the lifetime of the valve.

To avoid the possibility of contamination, we recommend that all high-pressure cylinders and cryogenic containers used for medical gases be dedicated to medical use only.

1. Prefill Inspections for Cylinders

We recommend that the following prefill inspections be performed on each medical gas cylinder prior to the start of the filling operation. Cylinders failing any of these procedures would be quarantined to prevent their use in any subsequent filling operation. We recommend that medical gas manufacturers document all prefill inspections on a batch production record.

Hydrostatic testing date inspection: Hydrostatic tests offer assurance of the integrity of a cylinder. Ultrasonic inspection of steel high-pressure cylinders can be performed instead of internal visual and hydrostatic testing. We recommend that manufacturers consult U.S. Department of Transportation (DOT) requirements pertaining to hydrostatic testing of certain cylinders as appropriate (see, e.g., 49 CFR 180.209).

External examination: We recommend that each cylinder be examined externally for dents, arc burns, dings, oil, grease, and other signs of damage, including fire or thermal damage, that can cause a cylinder to be unacceptable or unsafe for use. Any cylinder found to have any of these conditions would be removed from service and placed in an appropriate quarantine area until their suitability has been determined by the QCU.

Venting or blowing down: If any gas is present in a cylinder, venting or blowing down a cylinder can be performed until atmospheric pressure occurs. We recommend that cylinders containing liquid be inverted and drained.

Odor test: The odor test is a very important prefill test for detecting the presence of any foreign gas or odor. Do not perform this test on carbon dioxide, nitrous oxide, toxic, or corrosive gases. If a cylinder is empty (contains no pressure), a medical gas can be introduced into the cylinder at a predetermined pressure, and an odor test can be performed on the resulting gas. Use only medical gases, as an industrial gas could contain industrial contaminants.

Do not confuse this odor test with the finished product odor test conducted under § 211.165(a) and required by the USP.

Hammer or dead ring test: One way to determine if a cylinder has internal corrosion is by performing a hammer or dead ring test. This test consists of lightly tapping the cylinder sidewall with a hammer-like instrument. A cylinder in good condition will make a clear bell-like ring, while a dull ring indicates possible internal corrosion. All cylinders that produce a dull ring would be quarantined until their suitability has been determined. This procedure cannot be performed on aluminum or fiber wrapped cylinders because the test would not indicate internal corrosion. A hammer test works best on empty unpressurized cylinders with a 10-year test date (stamped into the cylinder shoulder area). It is not necessary to test cylinders with a 5-year test date.

Valve assembly examination: The Agency recommends that the valve assembly be appropriate for the medical gas being dispensed and be examined for debris, oil, or grease. The inspection would examine whether any of the threads on the valve or on top of the valve stem are damaged; whether the handwheel or valve stem is bent; and whether there are indications of damage, corrosion inside the valve, or excessive heat or fire damage.

Color code examination: The following colors are used by the medical gas industry in the United States to aid in identifying a medical gas. We recommend manufacturers use them.

- Carbon Dioxide - gray;
- Helium - brown;
- Medical Air - yellow;
- Nitrogen - black;
- Nitrous Oxide - blue;
- Oxygen - green; and
- Blends of medical gases use a combination of the corresponding color for each component gas. For example, oxygen and carbon dioxide would be green and gray.

Color coding alone cannot be relied on for identification of the medical gas; use color coding in addition to examining the product label on the cylinder.

Label inspection: We recommend that the label on the cylinder be inspected and that obsolete labels or labels containing outdated lot numbers be removed. A label on an empty cylinder does not need to be removed if it is in good condition and is identical to the label that will be used for the filled cylinder. We suggest that you ensure that cylinders bear only one manufacturer or filler's label and that you not apply new labels on top of an old label.

Residual gas removal: We recommend that residual gases be removed from medical gas cylinders by means of a vacuum pump prior to filling a medical gas.

All the above inspections can be documented on a batch production record.

2. Prefill Inspections for Cryogenic Home Containers

The FDA recommends that the following prefill inspections be performed on all cryogenic home containers (patient-specific containers):

- An external inspection for any signs of damage, oil, or grease that would cause the container to be unacceptable for use
- An inspection of the inlet and outlet connection for any signs of damage, oil, or grease
- An inspection of the volume or quantity of contents gauge to ensure that it is operating properly
- An inspection of the drug label to ensure correctness.

All the above inspections can be documented on a batch production record.

3. Dedication of Large Cryogenic Containers to Medical Use Only

To avoid the possibility of industrial contaminants, we recommend that large cryogenic containers used to contain medical gases be dedicated to medical service only.

4. Prefill Inspections of Large Cryogenic Containers

We recommend the following prefill inspections be performed on large cryogenic containers:

- An external examination for any signs of damage, oil, or grease that could cause the container to be unacceptable for use
- An inspection of the inlet and outlet connections for any signs of damage, oil, or grease and to ensure that they are the correct fittings for the corresponding medical gas. Permanently attach all connections or fittings to the container.
- An inspection of the label for correctness.
- An examination for a 360-degree wrap-around label applied on the sidewall of the cylinder, as close to the top portion of the container as possible, but below the top weld seam. These labels are designed to repeat the drug product name (e.g., Medical Oxygen) in the appropriate color around the entire container. See the "Color Code

Examination" discussed above under section *1. Prefill Inspections for Cylinders;* and in the Glossary under "Wrap-around" Label.

We recommend all the above inspections be documented on a batch production record.

5. Prefill Inspections for Permanently Mounted Cryogenic Containers

We recommend that the following prefill inspections be performed on permanently mounted cryogenic containers:

- An external examination for any signs of damage, oil, or grease
- An inspection of the inlet and outlet connections for any signs of damage, oil, or grease
- An inspection of the product label

B. Retesting of Containers

Containers and closures must be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the QCU in accordance with § 211.84 as necessary (e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the medical gas container or closure) (§ 211.87).

VII. PRODUCTION AND PROCESS CONTROLS

A. Written Procedures

Manufacturers must have written procedures for production and process controls designed to ensure that medical gases have the identity, strength, quality, and purity they purport or are represented to possess. These written procedures, including any changes, must be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the QCU (§ 211.100(a)).

Written production and process control procedures must be followed in the execution of the various production and process control functions and must be documented at the time of performance (§ 211.100(b)).

To guarantee batch uniformity and integrity of medical gases, written procedures must be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures must be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the drug product (§ 211.110(a)).

The Agency recommends that the corporate QCU not allow the local QCU to establish and implement written procedures that have not been reviewed and approved by the corporate QCU.

Written procedures provide a basis for the uniform performance of a function and a step-by-step description of how to perform a specific task, function, or operation, regardless of its size or complexity. We recommend the procedures be readily available to all employees and be read, understood, and followed by them.

We recommend that a manufacturer or individual, especially a manufacturer filling multiple gases, have data on file demonstrating the amount of vacuum evacuation required to remove all contaminants from high-pressure cylinders. We also recommend that the manufacturer have data demonstrating that each different gas it fills would be removed by the established vacuum evacuation limit.

We recommend that portable racks, such as those added to the main header or manifold via pigtails, be evaluated to ensure that the cylinders being filled on the portable rack are being properly vacuum evacuated and are being filled to the correct pressure, as indicated by the net content statement on the label.

We recommend that automated filling systems (that is, systems that fill from large cryogenic containers into high pressure cylinders) be validated to provide assurance that the filling is done to the correct pressure.

B. Charge-in of Components

Written production and control procedures must include the following, which are designed to ensure that the medical gases produced have the identity, strength, quality, and purity they purport or are represented to possess (§ 211.101):

- The batch must be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient (§ 211.101(a)).

- Components for medical gas manufacturing must be weighed, measured, or subdivided as appropriate (§ 211.101(b)).

- Each component must be added to the batch by one person and verified by a second person (§ 211.101(d)).

The Agency recommends that all high-pressure cylinders and cryogenic containers be filled according to the net content statement indicated on the label in accordance with section 502(b)(2) of the act. This includes blends or mixtures of medical gases (i.e., multiple gases). The net content statement can be the same as the fill pressure or the service pressure. Refer to § 201.51, Declaration of net quantity of contents, for further information.

1. Temperature/Pressure Readings (Boyle's Law)

A medical gas in a high-pressure cylinder increases in pressure as the temperature of the gas rises. Overfilled cylinders could reach dangerously high pressures if exposed to elevated temperatures, even if the pressure at room temperature is safe. This temperature rise can be properly compensated for during filling, so that the cylinder contents do not exceed the net content statement on the label. A temperature/pressure chart or other temperature/pressure calculation algorithms can be used to adjust the filling pressure so that the proper contents are achieved (this is usually stated as the pressure at 70°F with appropriate tolerances). We recommend that temperatures measured on the wall of a cylinder during filling operations not exceed 130°F. Before the filling is complete, the temperature and pressure reading would be recorded on the batch production record.

To ensure that high-pressure cylinders have the correct contents as indicated on the label, the manufacturer can attach a thermometer to one cylinder per manifold-filling sequence and adjust the temperature and pressure readings according to a temperature pressure chart. We recommend that, when filling cylinders one at a time (also known as the cascade method), each cylinder have a thermometer attached to it.

If a "+" symbol follows the hydrostatic testing date, the cylinder can be overfilled by 10 percent unless the valve is equipped with a fusible, metal-backed safety. It is critical not to overfill aluminum cylinders.

2. Valve Assembly Leak Testing

The Agency recommends that a valve assembly leak test be performed during the cylinder filling operation. Each valve assembly would be tested for valve packing leaks, safety plug leaks, and other valve leaks using an appropriate leak detection solution. The test would be performed while the cylinder is under pressure with the cylinder valve open. The leak detection solution would be sprayed on and around the entire valve assembly. A leak would be indicated when bubbles appear in the solution. We recommend the solution be oxygen compatible and not contain any hydrocarbons. Solutions containing soap are not recommended because they can corrode the valve stem and can leave a residue.

After the filling of high-pressure cylinders, and after all valves have been closed, we recommend a second valve assembly leak test be performed to detect any valve outlet leaks. If any leaks are detected, the cylinder would be removed from service and quarantined until repaired.

The two valve assembly leak tests provide assurance that the cylinder contents do not leak out during storage or shipment, resulting in a partially filled or empty cylinder that would not contain sufficient contents for a patient.

3. Heat of Compression

During the filling of high-pressure cylinders, we recommend a heat-of-compression check be performed by lightly touching the exterior of each and every cylinder. A warm cylinder indicates that the cylinder is filling properly; a cool or cold cylinder indicates that the cylinder may not be filling properly. Such a situation would be investigated.

C. Calculation of Yield

Actual yields and percentages of theoretical yield must be determined at the conclusion of each appropriate phase of manufacturing, processing, packing, or holding of medical gases. Such calculations must be performed by one person and independently verified by a second person (§ 211.103).

FDA recognizes that accurate inventory records and reconciliation of use are difficult to maintain for liquefied gases. Normal losses of gas occur through vaporization, the filling process, and venting and could reach 10 percent or more. The FDA does not expect the reconciliation to be 100 percent accurate. A manufacturer's procedures for reconciling the use of medical gases can include allowances for normal storage and operating losses. The procedures would include provisions for further investigation when unexplained discrepancies occur, such as losses beyond established normal levels.

VIII. PACKAGING AND LABELING CONTROLS

A. Materials Examination and Usage

Medical gases are subject to the requirements in § 211.122 - Materials examination and usage criteria.

There must be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, and examination of labeling and packaging materials, and these written procedures must be followed. Labeling and packaging materials must be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a medical gas (§ 211.122(a)).

Records must be maintained for each shipment received of each different labeling indicating receipt, examination, and whether accepted or rejected (§ 211.122(c)).

Labels for each different medical gas must be stored separately with suitable identification. Access to the storage area must be limited to authorized personnel (§ 211.122(d)).

Obsolete and outdated labels must be destroyed (§ 211.122(e)).

If cut labeling is used, labeling operations must include one of the following special control procedures (§ 211.122(g)):

- Dedication of labeling lines to each different strength of each different medical gas (§ 211.122(g)(1))
- Use of appropriate electronic or electromechanical equipment to conduct a 100 percent examination for correct labeling during or after completion of finishing operations

- Use of visual inspection to conduct a 100 percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination must be performed by one person and independently verified by a second person (§ 211.122(g)(3))

Upon receipt from the printer, labels would be counted to verify the quantity received and would be examined to ensure correctness when compared against the master label.

We recommend that labels be locked in a secure area with access limited to authorized personnel. Different medical gas labels would be stored separately. We recommend that industrial labels be stored in a separate area.

It is industry practice to apply labels by hand, therefore, we recommend a second person verify the correctness of the label and document the verification. In light of recent deaths and injuries, this examination is critical to ensure that the correct label has been applied to a container of medical gas.

B. Labeling Control

Medical gases are subject to the requirements in § 211.125 - Labeling issuance.

Strict control must be exercised over labeling issued for use in medical gas labeling operations (§ 211.125(a)).

Labeling materials issued for a batch must be carefully examined for identity and conformity to the labeling specified in the master or batch production records (§ 211.125(b)).

Procedures must be used to reconcile the quantities of labeling issued, used, and returned, and must require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued if the discrepancies are outside narrow preset limits based on historical operating data (§ 211.125(c)). However, this paragraph does not apply to the 360-degree wrap-around label that is applied to large cryogenic containers.

The Agency recommends that all labels be issued by authorized personnel only. Before release of issued labels to an employee, we recommend a representative label be checked against the master label to ensure correctness.

C. Packaging and Labeling Operations

Medical gases are subject to the requirements in § 211.130 - Packaging and labeling operations.

There must be written procedures designed to ensure that correct labels and labeling are used for medical gases; such written procedures must be followed. These procedures must incorporate the following features (§ 211.130):

- Prevention of mix-ups and cross contamination by physical or spatial separation from operations on other medical gases (§ 211.130(a))
- Identification of the medical gas with a lot or control number that permits determination of the history of the manufacture and control of the batch (§ 211.130(c))
- Examination of labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record (§ 211.130(d))

We recommend manufacturers consider each batch of medical gas a separate entity with unique filling procedures to help ensure that the batch is uniform and consistent. Assigning a single lot number to an entire day's production is not appropriate. Each manifold filling sequence; each uninterrupted filling sequence; and each filled cryogenic container, storage tank, and trailer would be considered a new lot and be assigned a unique lot number.

In addition, we recommend each large cryogenic container containing liquid oxygen for delivery to patients at home, whether portable or permanently mounted in a van or a truck, be considered a lot and be assigned a unique lot number. Cryogenic home containers filled at a patient's home do not need a lot number. However, we recommend that cryogenic home containers filled on site or by a third party in advance for future delivery be given a lot number.

For safety reasons, we recommend each medical gas container bear only one drug label containing the appropriate information. Do not place a current label on top of an obsolete label.

In accordance with 502(b)(2) of the Act, all medical gas cylinders and cryogenic containers must bear a label with an accurate statement of the net contents. We recommend that the net contents appear on the body label or shoulder label and not on (1) a removable tag, (2) a certificate of analysis, or (3) a small separate sticker.

If a medical gas company sells medical oxygen to emergency medical services for emergency use, the label would contain the statement:

> For emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation. For all other medical applications, Rx Only.[3]

FDA would not prohibit the sale of medical oxygen with this labeling to emergency medical services (see Glossary for definition of an EMS) without a prescription.

We recommend the labeling for large permanently mounted containers, trailers, and rail cars bear a statement consisting of "Name of the Medical Gas, Refrigerated Liquid USP or NF," such as "Oxygen Refrigerated Liquid USP."

[3] See September 19, 1996, citizen petition response in docket 87P-0167.

The Agency recommends the use of a 360-degree wrap-around label to identify medical gases in large cryogenic containers.

D. Drug Product Inspection

Medical gases are subject to the requirements in § 211.134 – Drug product inspection.

Labeled products must be examined during finishing operations to provide assurance that containers in the lot have the correct label (§ 211.134(a)).

A representative sample of units must be collected at the completion of finishing operations and must be visually examined for correct labeling (§ 211.134(b)).

Results of these examinations must be recorded in the batch production or control records (§ 211.134(c)).

Only one medical gas label would appear on a cylinder or container, and the manufacturer of the medical gas would apply the label in accordance with section 502(b) of the act.

E. Expiration Dating

Medical gases are subject to the requirements in § 211.137 - Expiration dating.

To ensure that a medical gas meets applicable standards of identity, strength, quality, and purity at the time of use, each container must bear an expiration date determined by appropriate stability testing described in § 211.166 (§ 211.137(a)).

Expiration dates must be related to any storage conditions stated on the label, as determined by stability studies described in § 211.166 (§ 211.137(b)).

Expiration dates must appear on the labeling in accordance with the requirements of § 201.17 (§ 211.137(d)).

New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations (§ 211.137(g)).

The Agency recommends that high-pressure cylinders stored for long periods of time, such as those provided to patients as a backup to their oxygen concentrator, be monitored to ensure they contain the correct net contents (i.e., pressure). We recommend that companies, especially home care companies and durable medical equipment suppliers, establish and follow a written plan to periodically verify the pressure (i.e., net content) of each high-pressure cylinder stored at a patient's home and that the results be documented.

IX. HOLDING AND DISTRIBUTION

A. Warehousing Procedures

Medical gases are subject to the requirements in § 211.142 - Warehousing procedures.

Manufacturers must develop and follow written procedures describing the warehousing of medical gases. Procedures must include (§ 211.142):

- Quarantine of medical gases before release by the QCU (§ 211.142(a))
- Storage of medical gases under appropriate conditions (§ 211.142(b))

The Agency recommends that separate areas be designated for the following: (1) empty containers, (2) full containers, (3) in-process containers, (4) different types of medical gases, (5) rejected containers and closures, (6) medical gases that have been released, and (7) medical gases that have not been released. We also recommend that industrial gases, containers, and equipment be stored separately from medical gases, containers, and equipment.

We recommend medical gas containers be stored under protective covering and not be subject to temperature extremes. Based on this recommendation, storage areas would be clean, dry, well ventilated, and free of combustible materials. Also all valve assemblies, hoses, and other relevant equipment would be protected from contamination such as insect infestation.

B. Distribution Procedures and Recalls

Medical gases are subject to the requirements in § 211.150 - Distribution procedures.

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

We recommend that manufacturers have procedures to explain who would evaluate distribution information if a recall were necessary, how a recall would be initiated, who would be informed about the recall, and what would be done with the recalled product.

The Agency recommends that delivery vehicles have well-defined, separate areas for medical gases and industrial gases to prevent mix-ups from occurring. For example, medical and industrial gases can be separated physically in the delivery truck, or a manufacturer can use a unique identifier to distinguish medical gases from industrial gases. As mentioned above, the Agency recommends the use of a 360-degree wrap-around label to identify medical gases in large cryogenic containers. If a manufacturer applies a 360-degree wrap-around label to its large cryogenic containers, and the manufacturer has established adequate driver training, written procedures, and proper stock inventory systems, physical separation on a delivery vehicle is not critical.

We recommend that handheld computer devices or computers used during distribution operations be validated to ensure proper performance.

X. LABORATORY CONTROLS

A. General Controls

Medical gases are subject to the requirements in § 211.160 - Laboratory control general requirements.

The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by Subpart I of 21 CFR Part 211, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, must be drafted by the appropriate organizational unit and reviewed and approved by the QCU. The requirements in Subpart I of 21 CFR Part 211 must be followed and must be documented at the time of performance (§ 211.160(a)).

The Agency recommends that a manufacturer follow the specifications for the specific medical gas as described in the respective monograph of the current U.S. Pharmacoepia/National Formulary (USP/NF), or a manufacturer can establish its own specifications capable of producing equivalent or better-than-USP results.

Medical gases approved under a new drug application (NDA) or covered by an investigational new drug application (IND) would comply with the specifications established in the application.

Although a primary objective of the USP is to ensure the identity, strength, quality, and purity of a product, it is impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. Contaminants can arise from a change in the source of material or from a change in processing, or contaminants can be introduced from extraneous sources. We recommend that a manufacturer use tests suitable for detecting such occurrences in addition to the tests provided in the individual monograph (refer to the USP General Notices, Foreign Substances and Impurities).

In the past, deaths and injuries have resulted from adulterated products that contained contaminants or impurities that were not detected. In one example, a carbon dioxide (CO_2) manufacturer in Tennessee failed to include an analysis for hydrogen cyanide in its finished product testing. As a result, the manufacturer released several large liquid batches of medical CO_2 that were contaminated with this deadly toxin. The source of this problem was the lack of an agreement between the supplier and the CO_2 manufacturer requiring notification of any change in the manufacturing process. Fortunately, the problem was discovered before any injury occurred. Our investigation found the supplier of the raw material had changed the manufacturing process, which resulted in elevated hydrogen cyanide levels. Because testing for hydrogen cyanide was not performed, an adulterated drug product was released.

1. Sampling Plan

We recommend that a sampling plan describe the following:

- How many cylinders or cryogenic containers will be tested
- When the testing will occur
- What acceptance criteria will be used for selecting samples
- What action will be taken if test results are outside established specifications

2. USP Oxygen Monograph

Medical gas manufacturers can establish their own testing specifications that meet or exceed the requirements of the USP or can use the USP specifications.

USP Testing Specifications - Specifications recommend that the potency of oxygen not be less than 99.0 percent by volume. Oxygen produced by the air liquefaction process is exempt from tests for carbon dioxide and carbon monoxide. However, if there is no documentation that the oxygen is produced by the air liquefaction process, we recommend that two additional impurity tests for carbon dioxide and for carbon monoxide be performed.

Note: The official method is explained below. The Agency recommends that you check periodically with the USP to determine if the official method has changed or has been modified.

The ORSAT testing method uses a calibrated 100-ml buret, copper wire, and an ammonium chloride - ammonium hydroxide solution mixed together and equilibrated by agitation with the copper wire. Prior to the introduction of a sample from a pumped cylinder, a series of analyses (minimum of 3 runs) using a calibration standard would be performed to properly age the test solution and to eliminate any air bubbles that may have become trapped in the apparatus. The Agency recommends that a manufacturer not proceed with testing a filled or pumped cylinder until these analyses are completed. A 100-ml sample of the unknown gas would be drawn into the buret, agitated, and measured. An identification test, using a carbon dioxide detector tube, would be performed at the same time.

Note: The ammonium chloride - ammonium hydroxide solution used in this method would be expected to bear an expiration date supported by appropriate stability studies.

The USP Oxygen Monograph requires a finished drug product odor test to be performed on each container undergoing testing.

The Agency recommends that USP tests not be performed on an industrial gas in an attempt to convert it to a medical gas.

The accuracy of the USP procedure is $\pm$0.1 percent.

3. Calibration of Instruments

Laboratory controls must include the calibration of 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 (§ 211.160(b)(4)).

Oxygen analyzers and other instruments can be calibrated at intervals specified in the instructions from the equipment manufacturer. The FDA recommends that gas manufacturers not use other medical or industrial gases as the basis for calibrating their instruments.

We recommend that standards be certified to ensure the proper level of precision and accuracy as reported on the certificate of analysis (COA).

We also recommend that each COA for a medical gas calibration standard be specific for that cylinder and provide the following information:

- Name and address of the calibration standard supplier
- Name of the product
- Lot number or unique identification number specific for each cylinder
- Analytical methodology used to assay the calibration standard
- Actual analytical results (for example, 99.9 percent nitrogen)
- The responsible person's signature and the date signed

B. Testing and Release for Distribution

Medical gases are subject to the requirements in § 211.165 - Testing and release for distribution.

For each batch of medical gas, there must be appropriate laboratory determination of satisfactory conformance to final specifications, prior to release (§ 211.165(a)).

The Agency recommends that each manufacturer determine the specific testing to be performed on any incoming medical gas and on medical gases delivered to a consignee, customer, or patient. We recommend that testing methods conform to official specifications (i.e., the USP testing methodology or a validated test procedure capable of producing equivalent or better-than-USP test method performance).

If batch results do not conform to specifications, retesting is not recommended unless a thorough investigation is performed in accordance with established written procedures.[4]

For high-pressure cylinders filled on a multiple outlet manifold, the Agency recommends that one or more cylinders from each manifold filling sequence be assayed for identity, strength, and

[4] A draft guidance, on *Investigating Out-of-Specification Test Results for Pharmaceutical Production* was issued on September 30, 1998.

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

1. Liquid-to-Liquid Filling; Oxygen Only

This section pertains to the filling of liquid medical oxygen into cryogenic home containers, either at a patient's home (curbside), or on site. Due to the unique nature of this operation, the Agency recognizes that testing for conformance to final specifications prior to release is impractical. Therefore, FDA recommends using the following procedures.

a. Testing of the incoming liquid oxygen

In lieu of testing, the home care company (HCC) can (1) witness the testing for identity and strength of the large cryogenic container(s) performed by the supplier for each container received, (2) document that the testing has been witnessed, and (3) obtain a valid COA for each container. The employee responsible for witnessing the testing would have been trained on the analytical methodology used by their supplier. Training would be documented by the employee's company.

If the testing is not witnessed and the HCC chooses to rely on a valid COA, the Agency recommends that the HCC perform a specific identity test. The HCC would also periodically verify the reliability of the supplier's analysis. This can be done by (1) visiting the supplier to verify that the supplier is following appropriate written testing procedures, (2) observing the supplier's analytical testing, including calibration of the analyzer, and (3) documenting that steps 1 and 2 have been taken. Alternatively, to periodically verify the reliability of the supplier's analysis, the HCC can submit to a third party a sample from a recent delivery to be analyzed for conformance with the USP requirements or established specifications.

If an HCC does not follow the above methods or chooses to test the large cryogenic containers, the Agency recommends that full testing on the incoming medical oxygen (each large cryogenic container) be performed.

b. Testing of an oxygen storage tank used to fill large vehicle-mounted cryogenic containers

If a new shipment of oxygen is combined in a storage tank with a previously received, tested, and approved lot, we recommend that the manufacturer test the combined product and approve it before use. If the storage tank is located on the company's premises and is used to fill vehicle-mounted containers or cryogenic home containers, the Agency recommends an identity and strength test be performed by sampling from the storage tank after each oxygen delivery and prior to the filling of any cryogenic containers.

After the storage tank has been tested, the company can forego testing a large cryogenic container filled from the storage tank if:

- No other storage tank is located on the premises

- The container is dedicated to the delivery of medical oxygen for home care use only
- The container has not been completely emptied (i.e., gaseous pressure below 15 pounds per square inch in gauge) and has not been out of service
- A valid COA is received with each delivery and is maintained on file

c. Testing of cryogenic home containers

It is important to exercise control over the home container during the filling operation. We recommend that appropriate methods be developed to control situations where external contamination may occur, such as failing to cap or cover the ends of a filling hose to prevent dirt, debris, or insect infestation.

Testing of a cryogenic home container is less of a concern if:

- Liquid oxygen is the only liquid being filled on the premises
- The incoming liquid oxygen is tested according to one of the methods outlined above under Testing of Incoming Liquid Oxygen or Testing of an Oxygen Storage Tank
- The container is filled by the company that owns it

If any other medical gas is filled on site or if the incoming liquid oxygen is not tested by one of the testing methods discussed above, we recommend all filled cryogenic home containers be tested for conformance with USP or established specifications.

If cryogenic home containers are filled by another individual or another company prior to release to the patient, we recommend that the manufacturer distributing the containers inspect each container to ensure that a correct label including a lot number has been applied.

2. Liquid-To-Gas; Filling Large Cryogenic Containers

This section pertains to medical gas companies, such as welding supply companies, who fill multiple gases, both industrial and medical. In this situation, the potential for mix-ups is greatest. The Agency recommends that the incoming product be tested for full USP or established specifications immediately after each lot is received. This can be done either by taking a sample directly from the storage tank or by testing one cylinder from the first medical filling sequence.

Each filled large cryogenic container would be tested prior to release. Cryogenic containers usually contain a residual product and a commingling of new and old product would result in a new batch or lot. This new batch or lot would be analyzed and assigned a new batch or lot number. A valid COA would be provided with each cryogenic container.

3. Liquefied (gas on top of liquid) Compressed Gas

The pressure in a closed container containing carbon dioxide or nitrous oxide increases as the temperature rises. A cylinder filled at a safe pressure at normal temperatures can reach a dangerously high pressure at high ambient temperatures. Therefore, the Agency recommends that nitrous oxide and carbon dioxide be filled individually as liquids on a scale where the pressure does not indicate the amount filled. Instead, we recommend these cylinders be filled individually, and the weight not exceed 68 percent of the weight of water the cylinder will hold at 60°F (15.6 C).

The Agency recommends that one of the cylinders filled during an uninterrupted filling sequence be tested for conformance with specifications prior to release. For both carbon dioxide and nitrous oxide, a specific carbon dioxide identification test would be conducted concurrently with the assay in accordance with USP monograph.

4. Gas Mixtures

If a product is a mixture of two gases, the Agency recommends that each cylinder of the blended product be tested for the identity and strength of one of the gases, usually the active ingredient. In addition, an identity test for the other gas would be performed on one cylinder from the manifold filling sequence. For product mixtures containing three gases, each cylinder of the blended product would be tested for the identity and strength of two of the gases, and one cylinder from each manifold filling sequence would be tested for the identity of the third gas.

5. Liquid Nitrogen

An assay of the finished product using the official gas chromatographic method would not be necessary for a manufacturer who receives shipments of medical nitrogen. However, we recommend a manufacturer meet all of the following conditions:

- A valid COA is received with each delivery and the product is designated Nitrogen NF
- The filling system has dedicated lines, and these supply lines are traceable from the storage tank to the filling manifold. If there is a possibility that another gas, either industrial or medical, could be introduced and could contaminate the product, we recommend that USP testing and a test for the absence of the contaminating gas be performed.
- Testing for the lack of oxygen (less than or equal to 1.0 percent) is performed with an oxygen analyzer that has been validated against the USP methodology
- Initially and at appropriate intervals, testing for complete specifications is recommended. Once the reliability of the supplier is established, a manufacturer can rely upon the supplier's certificate of analysis. Auditing the supplier's testing and manufacturing is an additional measure that would be used to determine that the product complies with the USP. This testing can be performed by the manufacturer, by a third party, or by a contract-testing laboratory.

To ensure that they receive medical nitrogen, we recommend that manufacturers use suppliers registered with FDA.

In light of several reported injuries due to patient exposure to toxic compounds contained in a supply of contaminated *industrial* nitrogen used to power surgical or dental equipment, the FDA strongly recommends the use of *medical* nitrogen by hospitals and dentist offices, even when the nitrogen is used for industrial purposes in those settings.[5]

C. Alternate Testing Methods

The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the manufacturer must be established and documented. We recommend that such validation and documentation be accomplished in accordance with § 211.194(a)(2).

We recommend that any alternative testing method (e.g., spectrophotometer, handheld analyzers) used to analyze a medical gas be compared against the official testing methodology.

We also recommend that each medical gas manufacturer maintain a copy of the entire validation study, including the actual data generated for each analyzer by model number that demonstrates USP equivalence and any changes made to the analytical methodology, such as a different column length or a different carrier gas. Validation of alternate methods can be performed in accordance with USP Validation of Compendia Methods.

D. Stability Testing

Medical gases are subject to the requirements in § 211.166 – Stability Testing.

There must be a written testing program designed to assess the stability characteristics of medical gases. The results of such stability testing must be used in determining appropriate storage conditions and expiration dates. The written program must be followed and must include (' 211.166(a)):

- Reliable, meaningful, and specific test methods (§ 211.166(a)(3))
- Testing of the medical gas in the same container-closure system as that in which the medical gas is marketed (§ 211.166(a)(4))

An adequate number of batches of each medical gas must be tested to determine an appropriate expiration date, and a record of such data must be maintained (§ 211.166(b)).

The Agency recommends that the testing program take into account the compatibility of the valve assembly, the acceptability of the valve packing and the valve seal used, the type of cylinder, and any other factor that can have an effect on the stability of the medical gas. Each medical gas would be tested for stability in the exact container closure system that it is marketed

[5] Compressed Gas Association, Inc., Saftey Alert (SA-6) Use of Nitrogen NF for Surgical Air Tools.

in, such as steel high-pressure cylinders, aluminum high-pressure cylinders, and cryogenic containers.

E. Reserve Samples

Reserve samples of compressed medical gases do not need to be retained (§ 211.170).

XI. RECORDS AND REPORTS

Medical gases are subject to the requirements on records and reports in §§ 211.180 - 198.

A. Record Retention

Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of medical gas must be retained for at least 1 year after the expiration date of the batch (§ 211. 180(a)).

All records required under this part, 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)). The records or copies thereof are subject to photocopying or other means of reproduction as part of such an inspection (§ 211.180(c)). Records that can be immediately retrieved from another location by computer or other electronic means will be considered as meeting the requirements of this paragraph (§ 211. 180(c)).

Records required under this part may be retained either as original records or as true copies such as photocopies or other accurate reproductions of the original records (§ 211.180(d)).

Records can be kept on paper or electronically. Electronic records must comply with the requirements of 21 CFR part 11.

Medical gas manufacturers are required to maintain a number of documents and records including:

- Equipment cleaning and use logs (§ 211.182)
- Computer and process validation data (§ 211.68)
- Analyzer validation studies and data (§ 211.194)
- Label reconciliation logs (§ 211.184)
- Master production records (§ 211.186)
- Batch production records (§ 211.188)
- Analytical equipment calibration logs (§ 211.194(d))
- Testing records (§ 211.194)
- Stability studies (§ 211.194(e))
- Complaint files (§ 211.198)

The Agency recommends that medical gas manufacturers also maintain training records and certificates of analysis.

B. Equipment Cleaning and Use Log

Medical gases are subject to the requirements in § 211.182 – Equipment cleaning and use log.

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use must be included in individual equipment logs that show the date, time, product, and lot number of each batch processed (§ 211.182). In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use must be part of the batch record (§ 211.182). The persons performing and double-checking the cleaning and maintenance must date and sign or initial the log indicating that the work was performed (§ 211.182).

Equipment cleaning and use logs can be maintained for trailers, rail cars, and storage tanks, especially those installed at a health care facility or a hospital.

C. Component, Drug Product Container, Closure, and Labeling Records

Medical gases are subject to the requirements in § 211.184 - Component, drug product container, closure, and labeling records.

These records must include the following (§ 211.184):

- The identity and quantity of each shipment of each lot of medical labeling
- The results of any test or examination performed (including those performed as required by § 211.82(a), ' 211.84(d), or § 211.122(a)) and the conclusions derived therefrom
- Documentation of the examination and review of labels and labeling for conformity with established specifications in accordance with §§ 211.122(c) and 211.130(c)
- The disposition of rejected medical gas containers, closures, and labeling

D. Master Production and Control Records

Medical gases are subject to the requirements in § 211.186 – Master Production and Control Records.

To ensure uniformity from batch to batch, master production and control records for each medical gas, including each batch size thereof, must be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person (§ 211.186(a)). The preparation of master production and control records must be described in a written procedure, and the written procedures must be followed (§ 211.186(a)).

Master production and control records must include (§ 211.186(b)):

- A description of the medical gas containers and closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling (§ 211.186(b)(8))

- Complete manufacturing and control instructions, sampling, and testing procedures, specifications, special notations, and precautions to be followed (§ 211.186(b)(9))

The Agency recommends that a manual containing all of the above be on site and available to personnel to ensure that individuals are able to perform their assigned functions

E. Batch Production and Control Records

Medical gases are subject to the requirements in § 211.188 – 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 relating to the production and control of each batch. These record must include (§ 211.188):

- An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed (§ 211.188(a))

- Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including (§ 211.188(b)):

  --Dates (§ 211.188(b)(1))
  --Inspection of the packaging and labeling area before and after use (§ 211.188(b)(6)
  --Complete labeling control records (§ 211.188(b)(8))
  --Description of medical gas containers and closures (§ 211.188(b)(9))
  --Any sampling performed (§ 211.188(b)(10))
  --Identification of the persons performing and directly supervising or checking each significant step in the operations (§ 211.188(b)(11))
  --Any investigation made according to § 211.192 (§ 211.188(b)(12))
  --Results of examinations made in accordance with § 211.134 (§ 211.188(b)(13))

The Agency recommends that the records include documentation of the following:

- Prefill inspections
- Number and size of the cylinders or cryogenic containers filled
- Filling inspections
- Post-fill inspections
- Lot number assigned
- Final temperature and pressure results
- Initials of the filler and/or analyst

- Signature of the individual who checked the entries for accuracy and completeness

Historically, the industry has used pumper's logs or filler's logs as batch production records. This is appropriate as long as the logs contain all of the relevant information. A batch production record acts as a snapshot of the actual production at the time of its performance. One batch production record would document the filling of high-pressure cylinders and a separate record would document the filling of cryogenic containers.

Based on the requirements of § 211.188, batch production records would include an item-by-item entry. A manufacturer would not use a single entry to indicate that all of the significant steps have been performed, nor a check mark or other symbol when an actual value should be recorded, such as temperature and pressure readings, purity, and identity results.

F. Production Record Review

Medical gases are subject to the requirements in § 211.192 – Production record review.

All medical gas production and control records, including those for packaging and labeling, must be reviewed and approved by the QCU to determine compliance with all established, approved written procedures before a batch is released or distributed (§ 211.192). Any unexplained discrepancy or the failure of a batch to meet any of its specifications must be thoroughly investigated (§ 211.192). A written record of the investigation must be made and must include conclusions and follow-up (§ 211.192).

Any test result that is outside of the established limits would be considered an unexplained discrepancy or the failure of a batch to meet its specifications.

The Agency recommends that the release of a drug product from an air separation plant or unit (ASU) not be performed by a third-party consignee (usually known as a transporter or a trucking company). That is, the third-party consignee receiving the product would not sign as the ASU's QCU to release the product.

For ASUs where filling occurs at night, the ASU's QCU would be responsible for the release of the product, prior to distribution. For swap agreements, the manufacturer having its trailers filled would be responsible for and would have its own QCU review and approve the cleaning of any trailers that have contained industrial product, prior to filling with a medical gas.

G. Laboratory Records

Medical gases are subject to the requirements in § 211.194 – 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, as follows (§ 211.194(a)):

- A description of the sample received for testing with identification of source (that is, location from where the sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing (§ 211.194(a)(1))

- A statement of each method used in the testing of the sample. The statement must indicate the location of the data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested (§ 211.194(a)(2))

- A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific medical gas and lot tested (§ 211.194(a)(4))

- A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors (§ 211.194(a)(5))

- The initials or signature of the person who performs each test and the date(s) the tests were performed (§ 211.194(a)(7))

- The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards (§ 211.194(a)(8))

Complete records must be maintained of any modification of an established method employed in testing (§ 211.194(d)). Such records must include the reason for the modification and 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 (§ 211.194(b)).

Complete records must be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions (§ 211.194(c)).

Complete records must be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by § 211.160(b)(4) (§ 211.194(d)).

Complete records must be maintained of all stability testing performed in accordance with § 211.166 (§ 211.194(e)).

The Agency recommends that when using a handheld oxygen analyzer to perform an identity test, the actual value obtained be recorded, and the manufacturer establish written procedures describing an acceptable range that meets the accuracy of the analyzer.

The suitability of all testing methods must be verified under actual conditions of use (' 211.194(a)(2)).

When testing is done by a gas chromatographic method specified in a USP monograph (such as the assay method for Nitrogen NF), the Agency recommends the chromatographic system used be adjusted to meet all system suitability requirements listed in the monograph. We recommend that after tests are run to verify that the requirements have been met, the results be documented. For monograph methods that lack specific system suitability requirements, the section on system suitability in USP "Chromatography" can be used as a guide.

When an alternative testing methodology is employed, we recommend that the methodology be validated against an official test method and the method be carried out under substantially the same conditions that prevailed during the validation study. If the testing environment is substantially different, some additional on-site "spot check" tests of the method, perhaps with a small number of standard gases, would help show that its 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. We recommend such an on-site spot check also be made if the analyzer is installed as part of a control or alarm system. The results of these tests would be fully documented. Certain changes made to instrumentation may be substantive enough that they would be considered a change in the method itself; these changes would require additional documentation of accuracy and reliability (see § 211.194(b), above) or a new validation study.

H. Liquid Supply (Certificate of Analysis (COA))

The medical gas industry routinely relies on COAs to reduce the amount of finished product testing performed. For example, if a COA lists all of the impurities tested for by a supplier, then it would be unnecessary for a manufacturer to perform a test for the listed impurities on the finished drug product. If no COA is received, the Agency recommends that the finished drug product testing include all impurities listed in the USP monograph or established specifications for each medical gas.

In addition, the COA for medical oxygen usually contains the *air liquefaction statement* as required by the USP, and as a result, it would be unnecessary for a manufacturer to test for carbon dioxide and carbon monoxide impurities. If a manufacturer does not maintain the air liquefaction statement for its medical oxygen, the Agency recommends that the manufacturer perform testing for carbon dioxide and carbon monoxide impurities.

We also recommend that a COA contain the following information and would accompany all incoming deliveries of liquid medical gas:

- Supplier’s name and complete address
- Name of the product (e.g., oxygen USP, carbon dioxide USP, nitrogen NF, nitrous oxide USP, helium USP, or medical air USP)
- An air liquefaction statement, where appropriate
- Lot number or other unique identification number
- Actual analytical results for full USP monograph testing, (e.g., 99.5 percent oxygen)

- Test method used to perform the analysis. If an analyzer is used, the specific model number is indicated.
- Supplier's signature and the date
- Signature of the employee witnessing any testing at a supplier, if applicable

If a company relies on a COA to reduce the amount of testing required by the USP, we recommend the company establish the reliability of the supplier's analysis at appropriate intervals. This can be accomplished by the manufacturer, by a third party, or by a contract-testing laboratory.

I. Distribution Records

Medical gases are subject to the requirements in § 211.196 – Distribution records.

Distribution records must contain the name and strength of the product and description of the dosage form, name and address of the consignee, and date and quantity shipped (§ 211.196).

A manufacturer must establish and follow written procedures that include a system whereby the distribution of each lot of a medical gas can be determined if a recall becomes necessary, as required in § 211.150. For compressed medical gases, distribution records are not required to contain lot or control numbers.

J. Complaint Files

Medical gases are subject to the requirements in § 211.198 – Complaint files.

Written procedures describing the handling of all written and oral complaints regarding a medical gas must be established and followed (§ 211.198(a)). Such procedures must include provisions for review by the QCU, of any complaint involving the possible failure of a medical gas to meet any of its specifications and, for such a medical gas, a determination as to the need for an investigation in accordance with § 211.192 (§ 211.198(a)). Such procedures must include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience, which is required to be reported to the Food and Drug Administration in accordance with § 301.305 (§ 211.198(a)).

A written record of each complaint must be maintained in a file designated for medical gas complaints (§ 211.198(b)). The file regarding such medical gas complaints must be maintained at the establishment where the medical gas involved was manufactured, processed, or packed, or the file may be maintained at another facility if the written records in the file are readily available for inspection at that other facility (§ 211.198(b)).

The Agency recommends that complaint records include, where known:

- Name of the drug product
- Name and address of complainant

- Name (and, where appropriate, title) and telephone number of the person submitting the complaint
- Nature of the complaint
- Date the complaint is received
- Action initially taken, including dates and identity of person taking the action
- Follow-up action taken
- Response provided to the originator of complaint, including the date the response was sent
- Final outcome regarding the issues raised by the complaint

Where an investigation under § 211.192 is conducted, the written record must include the findings of the investigation and follow-up (211.198(b)(2)). The record or copy of the record of the investigation must be maintained at the establishment where the investigation occurred in accordance with § 211.180(c) (§ 211.198(b)(2)).

K. Reporting Deaths and Injuries

The following is intended to clarify current adverse event reporting requirements.

In accordance with § 310.305, manufacturers of prescription medical gases must establish and maintain records and must make reports to FDA of all serious, unexpected adverse drug experiences, such as deaths or life-threatening adverse events, associated with the use of their medical gases. More information can be obtained on FDA's web site, at http://www.fda.gov/medwatch/report/mfg.htm.

According to § 310.305(b) Definitions – an adverse drug experience is any adverse event associated with the use of a drug in humans, whether or not considered drug related. This would include problems with valves, such as valve seat combustion resulting in a release of chlorine gas, contamination from cleaning solutions, and mix-ups that result in an adverse event to a patient.

We also encourage hospitals, nursing homes, and other health care facilities dispensing medical gases to report serious adverse events and product problems associated with the use of those gases. They can report adverse events directly to the medical gas manufacturer. Or, they can report to **MedWatch**, the FDA's voluntary reporting program, in one of the following four ways:

- Online at http://www.accessdata.fda.gov/scripts/medwatch/
- By telephone at 1-800-FDA-1088
- By FAX at 1-800-FDA-0178
- By mail to:

  MedWatch
  Food and Drug Administration (HF-2)
  5600 Fishers Lane
  Rockville, MD 20857-9787

XII. RETURNED AND SALVAGED DRUG PRODUCTS

A. Returned Drug Products

Medical gases are subject to the requirements in § 211.204 – Returned drug products.

Returned medical gases must be identified as such and held (§ 211.204). If the conditions under which returned medical gases have been held, stored, or shipped before or during their return, or if the condition of the drug product, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the medical gas, the returned medical gas must be destroyed unless examination, testing, or other investigations prove the medical gas meets appropriate standards of safety, identity, strength, quality, or purity (§ 211.204).

B. Drug Product Salvaging

Medical gases are subject to the requirements in § 211.208 – Drug product salvaging.

Medical gases that have been subjected to improper storage conditions must not be salvaged and returned to the marketplace (§ 211.208).

XIII. AIR SEPARATION PLANTS OR UNITS (ASU)

ASUs separate atmospheric air into the constituent gases of oxygen, nitrogen, and argon by using a purification process of cleaning, compressing, and cooling. ASUs are generally highly computerized and have very few employees in attendance during operations, which usually take place 24 hours a day, 7 days a week. ASUs are drug manufacturers and as such must comply with all relevant CGMP regulations.

The Agency recommends that an ASU that receives deliveries of a drug product into its storage tanks from outside sources perform finished product testing on the incoming supply, prior to accepting the delivery. Appropriate COAs would be maintained.

The Agency plans to develop and publish a separate guidance on the validation of the manufacturing process and computerized systems at ASUs.

XIV. STORAGE TANK INSTALLATIONS AT HEALTH CARE FACILITIES

This section pertains to the installation of a storage tank that will contain a medical gas, usually oxygen, at a hospital, nursing home, or long-term health care facility. During the installation of a storage tank and associated equipment (i.e., equipment used for the delivery of medical gases — usually oxygen — to hospitals, nursing homes, clinics, and long-term health care facilities), following CGMP would be very important for manufacturers or individuals installing the storage tank. CGMP would also be important any time the system is exposed to a possible contaminant

or impurity, such as installation of a new valve or piping. The company would determine the stage of the installation where problems or contamination may occur and ensure compliance. CGMP would be applicable to activities involving all equipment that is part of the medical gas storage and delivery mechanism, including the storage tank that holds the drug product, all related equipment such as piping and valves, and all other equipment up to the wall leading into the facility.

For storage tank filling, we recommend a focus on the following aspects of CGMP:

- Establish a QCU and written procedures
- Perform training for service technicians in their job functions and in CGMP
- Qualify all equipment for medical use, including delivery vehicles and storage tanks
- Audit contracted cleaning firms
- Develop and follow detailed written procedures
- Calibrate testing equipment
- Test finished products prior to introduction of the drug product into the supply system
- Use USP equivalent testing methodology
- Log equipment cleaning and use, especially for storage tanks
- Maintain batch production records
- Provide COAs to the receiving facility with each delivery
- Maintain documentation

If a third party is contracted to install a health care facility storage tank and associated equipment, the supplier of the medical gas would determine whether the system has been installed in accordance with CGMP. This determination would be made prior to introducing the medical gas into the supply system and would be fully documented. The supply firm would consider itself responsible for the actions of the third party installer.

XV. MEDICAL GAS MIX-UPS

FDA has investigated a number of deaths and injuries resulting from medical gas mix-ups. In all of these incidents, the injuries and deaths could have been prevented if the manufacturer had followed the CGMP and industry standards.[6] Specific CGMP deviations noted repeatedly included:

- § 211.100(a & b): Failure to establish and follow adequate written procedures
- § 211.25(a): Failure to provide adequate CGMP training to all persons involved with the handling and delivery of a medical gas
- § 211.42(c): Inadequate storage areas on delivery vehicles for the storing of medical gases and industrial gases

[6] See CGA standards.

In particular, over the past several years, FDA has received reports from separate hospitals, nursing homes, and clinics involving 7 deaths and 15 injuries to patients who were thought to be receiving medical oxygen when in fact they were receiving a toxic industrial gas, (e.g., nitrogen). The Agency recommends the following steps to help prevent similar deaths or injuries from occurring:

- Ensure that all employees involved in the manufacturing, processing, packaging, or holding of medical gases have the education, training, and experience, or any combination thereof, to enable them to perform their assigned functions.
- Ensure that employees understand that they are handling a drug. Make sure they learn how to examine the label on each container before delivering the container or connecting the container to a supply system. Make sure employees know what to do if a label does not match the invoice or the connections do not fit (e.g., possibly not accept the product and/or notify their supervisor immediately).
- Be aware that most fittings or connectors are permanently attached on all large cryogenic containers used to deliver medical gases.
- Never remove fittings and connectors. If an employee is unable to connect a container to a supply system, he or she would contact the supplier immediately. This is especially true for oxygen.
- Ensure that written procedures are developed and followed. Train employees regularly on how to perform the procedures.
- Ensure that separate storage areas for medical and industrial gases are identified and used on each delivery vehicle.
- Make sure that all large cryogenic containers are dedicated to medical use and are not used for industrial gases.
- Ensure that all cryogenic containers have clear labeling, such as a 360-degree wrap-around label on the sidewalls. The wrap-around label would be placed as close to the top portion of the container as possible, but below the top weld seam, and would contain and repeat the product name (e.g., *Medical Oxygen Medical Oxygen Medical Oxygen)* and be the appropriate color (e.g., green for oxygen).
- Make sure only one drug label is applied to a container. Never apply a label on top of another label.
- Provide each consignee (e.g., hospital, nursing home, and clinic) with a copy of FDA's Public Health Advisory, *Guidance to Hospitals, Nursing Homes, and Other Health Care Facilities*.

XVI. CARBON DIOXIDE AND HELIUM MANUFACTURERS AND WHOLESALE DISTRIBUTORS

Manufacturers of medical carbon dioxide and medical helium also are subject to CGMP requirements. The Agency recommends that manufacturers perform process and computer systems validation and have a written agreement with the raw material manufacturer to be notified of any changes in the manufacturing process or the quality of the raw material. We also recommend that manufacturers perform an initial *fingerprinting* or characterization of the incoming raw material for any contaminants or impurities that could affect the quality, strength, purity, or identity of the finished drug product.

Carbon dioxide and helium manufacturers, as well as shippers, wholesale distributors, jobbers, and transporters that fill these medical gases into or out of rail cars, storage tanks, trailers, and containers are required to comply with CGMP, including the following:

- Process validation and computer systems validation (§ 211.68)
- Establishment of a QCU and written procedures (§ 211.22)
- In-process testing (§ 211.110)
- Lot numbering (§ 211.80(d))
- Written operating procedures (§§ 211.80(a) and 211.100)
- Calibration of analytical equipment (§ 211.160(b)(4))
- Testing of the finished product via USP or equivalent testing methodology (§ 211.165)
- Batch production records (§ 211.188)
- Maintaining documentation (§ 211.180)

The Agency also recommends that carbon dioxide and helium manufacturers, as well as shippers, wholesale distributor jobbers, and transporters that fill these medical gases into or out of rail cars, storage tanks, trailers, and containers, do the following:

- Conduct training, including for CGMP
- Test residual gas in tankers, trailers, and rail cars prior to filling

The Agency recommends that all tankers or trailers used for the delivery of carbon dioxide be dedicated to medical use only.

XVII. EMERGENCY MEDICAL SERVICE (EMS)

An EMS can follow this guidance to comply with CGMP when filling small high-pressure cylinders. Given the limited nature of the operation, an EMS would emphasize:

- CGMP training
- Operating procedures
- Procedures for accurate labeling
- Receiving oxygen from reliable sources
- Performing pre-fill inspections
- Traceability, so that a recall can be performed if necessary

XVIII. GAS-TO-GAS ADAPTERS

For safety reasons, ***avoid the use of*** gas-to-gas adapters of any kind to circumvent the specific medical gas valves and connections associated with a specific medical gas. The Agency recommends that companies only use adapters that reduce or expand the connection size for a specific medical gas while still maintaining the proper connection system. This practice would be described in written procedures.

Adapters can be used when filling mixtures or blends. However, documented written procedures detailing a system of checks will help prevent mix-ups or contamination. We recommend that adapters be under strict control and be kept under limited access.

XVIX. ALTERNATIVE APPROACHES

As noted, this guidance represents FDA's current thinking on CGMP for medical gases. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach can be used if that approach satisfies the applicable statutes and regulations. In the event you have ideas, questions, or concerns regarding an alternative approach, we encourage you to contact the Director of the Division of Manufacturing and Product Quality in the Office of Compliance of the Center for Drug Evaluation and Research at FDA.

ATTACHMENT: MEDICAL GAS MIX-UPS

The purpose of this section is to highlight the serious consequences of failing to follow CGMP in the production and delivery of medical gases.

On December 7, 2000, a nursing home in Bellbrook, Ohio, reported the death of two patients and the injury of eight patients following a mix-up in the nursing home's oxygen supply system. The nursing home had received a shipment from their supplier of four cryogenic containers supposedly containing medical oxygen. Included in the delivery, however, was a cryogenic container of industrial nitrogen that bore two different labels. The nursing home was running low on oxygen and sent a maintenance employee to connect a new oxygen container to the oxygen supply system. The employee selected the nitrogen container and discovered, correctly, that he was unable to connect the container to the oxygen system. The employee removed a fitting from an empty oxygen container and installed it on the nitrogen container. He then connected the deadly product to the oxygen system. Several days later, two more patients died from exposure to industrial nitrogen, bringing the death toll from this one incident to four.

On December 6, 2000, an industrial nitrogen container was connected to the oxygen supply system at a Medical Center in Springerville, Arizona. The nitrogen container was properly labeled and had the correct nitrogen fitting. The supplier removed the nitrogen fitting and replaced it with an oxygen fitting. A female who had been undergoing a hysterectomy was coming off anesthesia when a ventilator alarm sounded. The anesthesiologist immediately removed the ventilator and started her on an ambu bag. The patient demonstrated no ill effects.

On July 12, 1999, a patient in a California hospital was undergoing dialysis treatment. Since he required a continuous supply of oxygen he was connected to the wall oxygen source during the procedure. Upon completion of dialysis, the oxygen connection was removed from the wall source and reattached to a portable cylinder. The cannula was attached to the patient's existing tracheostomy and the patient was transported to the Intensive Care Unit (ICU). When the patient arrived at the ICU, he was in ventricular fibrillation, became apneic and sustained a cardiac arrest. The patient died. An investigation found that the patient had been attached to a cylinder of carbon dioxide, not oxygen. This cylinder had a green top, was labeled for CO2 and had the specific CO2 valve.

On April 22, 1998, a hospital in Idaho discovered that a large cryogenic container of industrial nitrogen had been connected to their oxygen system supplying the operating rooms, labor and delivery rooms, and the emergency room. When the supplier's truck driver was unable to connect the incompatible nitrogen container fitting to the oxygen supply system, he used a wrench to disconnect the nitrogen fitting and replaced it with an oxygen fitting. Two patients died as a result of this medical gas mix-up.

In October 1997, a hospital in Nebraska received a shipment of large cryogenic containers which were supposed to contain medical oxygen. The shipment included one cryogenic container of industrial argon that was labeled as argon. The hospital was running low on oxygen and sent a maintenance employee to connect a new oxygen container to the oxygen supply system.

Without examining the label, the employee selected the argon container, and, discovering he was unable to connect the container to the oxygen supply system, he removed a fitting from an empty oxygen container, installed it on the argon container, and connected the deadly product to the oxygen supply system. Argon was administered to a patient undergoing minor surgery. The patient died.

On December 2, 1996, a children's home located in New York reported adverse reactions experienced by nine patients due to the inhalation of carbon dioxide. An employee of the home, asked to attach a large cryogenic container of medical oxygen, unknowingly selected a carbon dioxide container from their inventory. He noted that the fitting on the carbon dioxide container was not compatible with the connector on the oxygen supply system. He removed an oxygen fitting from an empty container, installed it on the carbon dioxide container, and attached it to the oxygen supply system. Two patients were injured critically, four patients experienced varying stages of respiratory distress, and three patients recovered with no lasting side effects.

In March of 1996, 11 deaths were associated with contaminated oxygen delivered to a hospital during installation of a new storage tank. A 500-gallon cryogenic container was temporarily connected to the hospital's oxygen supply system with a 50-foot hose. An analysis of the 50-foot hose tested positive for the presence of trichloroethylene (TCE), a standard cleaning chemical that is very toxic to humans.

In December of 1993, a home care company (HCC) that filled liquid oxygen containers authorized an inadequately trained employee to obtain from their supplier a container (GP-45) of medical oxygen. The supplier's employees did not accompany the HCC employee to the loading dock to pick up the medical oxygen. The home care company's employee who failed to examine the label selected a container of argon instead of a container of medical oxygen. The employee loaded the container into the van and went to three patients' homes to fill their containers. When he attempted to fill the cryogenic containers containing oxygen, the discharge line was not compatible with the container fittings. The employee removed a fitting from an empty oxygen container and attached it to the container containing argon, and was able to fill the patients' containers with argon. The next day, the employee became aware of the argon mix-up and retrieved all three containers before the patients used the gas.

In July of 1986, a large welding supply company filled four gray-colored oxygen cylinders with carbon dioxide (CO_2). The cylinders were subsequently sent to a hospital and administered to two patients undergoing surgery. One patient's death was attributed to CO_2 exposure; the other patient was seriously injured. The cylinders had the proper medical oxygen label and the correct oxygen valve. Some hospitals paint their cylinders a certain color to designate a specific unit or room located within the hospital. In this case, the gray-colored cylinders denoted cylinders to be delivered to the surgery rooms only.

In May of 1983, a large welding supply company delivered and connected to a hospital a large cryogenic container thought to contain medical oxygen. The gas was administered to a premature infant, a 46-year-old male, and a 27-year-old female in three separate areas of the hospital. All three patients died. Analysis of the container found that it contained argon instead of oxygen, and the container bore two labels, one label read "Liquid O" while a second label on

the opposite side of the container read "Argon"; the fill line of the container had an argon fitting; and the discharge line had an oxygen fitting.

GLOSSARY

The following terms and definitions are provided to assist the reader in using this guidance document.

Cascading: This operation pertains to gas-to-gas filling of high-pressure cylinders only, and consists of a supply cylinder unit (usually called a *bank*) containing a group of *H* or *K*-sized cylinders, a receiving cylinder unit, a filling manifold, and a vacuum evacuation pump. The first supply cylinder's valve is opened and the gas flows into the smaller cylinder(s) to be filled until equilibrium or the correct net contents is reached. If the smaller cylinder is not full and requires additional pressure or contents, the second supply cylinder's valve is opened and the gas is allowed to flow into the smaller cylinder. This process is repeated to the third, and fourth, etc., supply cylinder until the desired pressure or contents is reached in the smaller cylinder(s). Individual cylinders in the bank are replaced sequentially as their respective pressures or contents are diminished to levels that are ineffective for the transfilling operation.

Certificate of analysis (COA): A single document provided with each shipment of incoming liquid medical gas that undergoes further processing (filling, transfilling). A COA contains all of the required information that would allow the receiving manufacturer to determine if the medical gas is acceptable. A COA can also reduce the amount of finished product testing a manufacturer performs by allowing the manufacturer to rely on the contaminants or impurities testing performed by the supplier and documented on the COA. Otherwise, a manufacturer would test each finished drug product for all contaminants and impurities required by the USP or the manufacturer's established specifications. See above for details.

Cryogenic containers: Containers used to hold a low-temperature, low-pressure liquid product that are similar in design to an insulated thermos bottle with a vacuum between the inner and outer container. They may be portable or permanently mounted in a vehicle, and are commonly known as VGLs (vertical gas liquids), GPs (gas packs), or PLCs (portable liquid containers), or HL119s, MDX 60s, 80s, and 190s. This does not include tankers, trailers, or rail cars.

Cryogenic home containers: Containers designed to hold liquid oxygen at a patient's home under low pressure and very low temperature.

Distributor: An individual or a manufacturer that receives liquid and/or compressed gas in labeled high-pressure cylinders or cryogenic containers and does not manipulate or apply a label to the product. The product is then delivered to a patient or consignee.

Emergency medical services (EMSs): EMSs include fire departments, ambulance companies, and rescue squads that are usually government-affiliated emergency services. EMSs transfill medical oxygen for their own use (no other gases are filled on site other than compressed breathing air) and administer medical oxygen to patients and/or victims in emergency situations.

Handheld oxygen analyzers: Oxygen analyzers that operate on the fuel cell, electrochemical cell, galvanic cell, or polarographic principle. When properly calibrated, these analyzers provide

a specific oxygen identification test result only. They do not have the required USP accuracy for determining potency. We recommend they be validated.

Home care company/home respiratory care company (HCC): Manufacturers that sell durable medical equipment and usually supply liquid oxygen to patients at their home. They may also fill high-pressure cylinders by means of cascading as a back up for their oxygen concentrators.

Oxygen for environmental use: Oxygen that meets USP specifications and is used to support life artificially in environments that are normally deficient. This includes, but is not limited to, space and space simulation capsules, deep submersibles, and scuba systems. This definition excludes oxygen used in chambers or devices. This product is not to be used for inhalation or the medical therapeutic treatment of humans or animals.

Oxygen for industrial use: Oxygen not intended for inhalation or therapeutic treatment of humans or animals. Because of the many contaminants and impurities associated with industrial oxygen, industrial oxygen is not appropriate for breathing purposes.

Oxygen for aircraft use (Aviators Breathing Oxygen (ABO)): Oxygen in fixed or portable oxygen containers or systems intended for commercial or private aircraft use. ABO meets USP specifications for oxygen and has special moisture and/or other limiting characteristics. We recommend against the use of ABO for recreational inhalation or medical therapeutic treatment of humans or animals.

Process validation: Documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (see the FDA guidance, *General Principles of Process Validation*).

Storage tank or stand tank: A large cryogenic stationary holding tank with a capacity of several thousand to several million gallons/liters of a liquid product.

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 lot of component. It does not apply to the filling of high-pressure cylinders on a multiple outlet manifold or rack. The filling of nitrous oxide and carbon dioxide is covered by this definition.

United States Pharmacopeia /National Formulary (USP/NF): A reference containing a select list of articles in the form of monographs. Included in each monograph are the standards for determining the identity, strength, quality, and purity of the articles. Except for medical gases approved under a new drug application or an investigational new drug application, manufacturers can use the specifications for single medical gases described under the individual medical gas monograph. Medical gas mixtures are not listed in the USP.

Wrap-around label: A 360-degree label that encircles and is applied to the top of large cryogenic containers. We recommend the lettering on the label be at least 2¾ inches high and

contain the name of the medical gas. The Agency recommends that the medical gas name be repeated so that the name can be visible when viewed from all angles. We also recommend one of the following: (1) the name of the medical gas (text) in the standard color for that medical gas with a white background or (2) the background in the standard color for that medical gas with the name of the medical gas (text) in white (See Color Code examination).