

POSITION STATEMENT

APPROPRIATE AND EFFECTIVE REGULATIONS FOR MEDICAL GASES WITHIN 21 CFR PARTS 201, 205, AND 210/211

Question

Consistent with Section 1112 of the 2012 *Food and Drug Administration Safety and Innovation Act's* (FDASIA) Congressional direction to the Federal Food and Drug Administration (FDA), what modifications need to be made to the existing regulations to make them appropriate and effective for designated medical gases or combinations thereof for labeling, wholesale distribution, and good manufacturing practice (GMP) compliance?

Answer

This position statement reflects the Compressed Gas Association's (CGA) consensus position for how FDA's regulations for finished pharmaceuticals found in Title 21 of the U.S. *Code of Federal Regulations* (21 CFR) Parts 201 (labeling), 205 (wholesale distribution), and 210 and 211 (GMPs), should be revised for designated medical gases or combinations thereof. This position is consistent with established and long standing industry practice yielding safe and efficacious designated medical gases and consistent with the Congressional intent in the FDASIA identifying the need for revisions to 21 CFR [1, 2].¹

This position statement is intended to be used by the industry to assist in communicating its positions on labeling, wholesale distribution, and GMPs when federal and state inspectors apply regulations that are either unnecessary or unsafe for designated medical gases or combinations thereof during facility inspections. A copy of this position statement has been provided to FDA's Center for Drug Evaluation and Research (CDER) Office of Compliance and is consistent with the proposed regulatory changes CGA provided to FDA in May 2013. As of the printing of this document FDA has not communicated disagreement or questioned any recommended change.

This position statement contains the positions presented to FDA in CGA's May 2013 letter proposing specific changes to 21 CFR Parts 201, 205, and 210/ 211 to make them effective and appropriate. To facilitate communication and assure consistent rationales to enforcement personnel, the industry developed the proposed changes to the existing regulations and those that are appropriate for designated medical gases. The sections within this document which cover the regulations are formatted to provide the current regulation modified to be appropriate for designated medical gases and an explanation why there is a difference.

NOTE—CGA's modifications to the regulations identify new text with underlines and deleted text with strikeouts.

This position statement is intended to address requirements for:

- Designated medical gases or combinations thereof; and
- Other medical gas as defined in Section 575(2) of FDASIA that may be approved via a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) for which the sponsor has shown through a science-based risk management plan that the positions detailed in this document are appropriate.

This position statement is not intended to address requirements for:

- Medical gases approved via an NDA or ANDA prior to July 8, 2012; or
- Medical gases approved in the future via an NDA or ANDA that contain the same active ingredient moiety as a medical gas approved via an NDA or ANDA prior to July 8, 2012.

¹ References are shown by bracketed numbers and are listed in order of appearance in the reference section.

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Compliance with 21 CFR § 201 Labels and Labeling

The 21 CFR Part 201 section specifically associated with medical gases, 21 CFR 201.161, was developed in the 1970's and the following significant modifications address additional medical gases contained in FDASIA and eliminate gases that are not. The FDA Draft Guidance for Industry on Certification Process for Designated Medical Gases (FDA-2012-D-1197) references a 1987 Compliance Policy Guide (CPG 435.100) and a 1972 proposed rule on oxygen labeling. That 1972 proposed rule, implementing a proposed policy, was never adopted and was subsequently officially rescinded. The industry standards based on safety for labeling are and have been very different from the rescinded proposed rule that was referenced in the draft certification guidance and are reflected in the changes to § 201.161.

In addition to significant modification of § 201.161 to include labeling requirements for additional designated medical gases or combinations thereof, other requirements within this part require modification. We are proposing to codify in § 201.1(b) the historic FDA position that medical gas container filling operations is manufacturing (identified as "subsequent manufacturers" as opposed to "original manufacturers" in other discussions with FDA). This also has implications with other sections of this part and other parts of 21 CFR. In addition to deeming designated medical gases approved drugs, FDASIA also permits the combination of designated gases to be manufactured requiring a change to labeling requirements for combinations. Given medical gas containers are refilled without relabeling and their type and size vary significantly, various requirements must be modified to reflect this uniqueness. To minimize the effect on existing regulations, we have exempted medical gases from several sections of Part 201 and have included the appropriate requirements in § 201.161.

Proposed Changes to 21 CFR § 201

§ 201.1(b) Drugs; name and place of business of manufacturer, packer, or distributor

Regulation modified to be appropriate for medical gases

- (a) A drug or drug product (as defined in §320.1 of this chapter) in finished package form is misbranded under section 502 (a) and (b)(1) of the act if its label does not bear conspicuously the name and place

of business of the manufacturer, packer, or distributor. This paragraph does not apply to any drug or drug product dispensed in accordance with section 503(b)(1) of the act.

- (b) As used in this section, and for purposes of section 502 (a) and (b)(1) of the act, the manufacturer of a drug product is the person who performs all of the following operations that are required to produce the product: (1) Mixing, (2) granulating, (3) milling, (4) molding, (5) lyophilizing, (6) tableting, (7) encapsulating, (8) coating, (9) sterilizing, and (10) filling sterile, aerosol, or gaseous drugs into dispensing containers, and (11) filling designated medical gases or combinations thereof into containers by any of the following processes: (a) liquid to liquid, (b) liquid to gas, or (c) gas to gas.

Rationale for modification

Although filling of medical gases has historically been considered a “manufacturing activity” included in (b)(10), i.e., filling...gaseous drugs into dispensing containers, a new operation (11) is added to explicitly indicate the filling of designated medical gases/ gas mixtures by the three methods identified in CGA’s proposed Guidance for Certification of Designated Medical Gases as a manufacturing activity for purposes of 21 CFR Part 201 (and 21 CFR Parts 207 and 210/211) to resolve any current regulatory uncertainty that subsequent manufacturers are manufacturers of designated medical gases although they may not be original manufacturers and therefore may not be required to certify.

§ 201.1(d) Drugs; name and place of business of manufacturer, packer, or distributor

Regulation modified to be appropriate for medical gases

- (d) The Food and Drug Administration finds that it is the common practice in the drug industry to contract out the performance of certain manufacturing operations listed in paragraph (b) of this section. These operations include: (1) Soft-gelatin encapsulating, (2) aerosol filling, (3) sterilizing by irradiation, (4) lyophilizing, and (5) ethylene oxide sterilization, and (6) designated medical gas filling or combinations of designated medical gas filling.

Rationale for modification

Added operation (6) to 201.1(d) to reflect that filling may be performed under contract and relates to new (b)(11).

§ 201.1(h) Drugs; name and place of business of manufacturer, packer, or distributor

Regulation modified to be appropriate for medical gases

- (h) (1) Except as provided in this section, no person other than the manufacturer, packer, or distributor may be identified on the label of a drug or drug product.
- (2) The appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacturer of the product. That representation is false and misleading, and the drug product is misbranded under section 502(a) of the act, if the person is not the manufacturer of the product in accordance with this section. Permanent stamped markings on containers or closures for designated medical gas or combination thereof that are required by an agency other than FDA are not considered labeling for the purposes of this part.
- (3) If the names of two or more persons appear on the label of a drug or drug product, the label may identify which of the persons is to be contacted for further information about the product.
- (4) If a trademark appears on the drug or drug product label or appears as a mark directly on the drug product (e.g., tablet or capsule), the label may identify the holder or licensee of the trademark. The label may also state whether the person identified holds the trademark or is licensee of the trademark.
- (5) If the distributor is named on the label, the name shall be qualified by one of the following phrases: “Manufactured for -----”, “Distributed by -----”, “Manufactured by ----- for -----”, “Manufactured for -----by -----”, “Distributor: -----”, “Marketed by -----”. The qualifying phrases may be abbreviated.

- (6) If the packer is identified on the label, the name shall be qualified by the phrase "Packed by -----" or "Packaged by -----". The qualifying phrases may be abbreviated.
- (7) If the owner of a container filled with a designated medical gas or combination thereof is distributing supplier filled and labeled product, the name and address of the container owner may appear on a separate label from the product label to designate to whom the empty container should be returned to, provided the name on the separate label is qualified by the phrase "Property of -----". The firm adding this separate label shall not be considered a "relabeler" for purposes of registration and listing under § 207 of this part.

Rationale for modification

For subsection (2)—Permanent DOT required stamped markings must be explicitly excluded from this regulation given both federal and state investigators have commented that these marking are "labeling." Permanent DOT markings are required to satisfy transportation regulations.

For new subsection (7)—The use of a "Property of..." label is current common industry practice to identify the container owner if the container is not filled by the cylinder owner and the cylinder owner is not identified on the main product label. Also the application or use of a "Property of..." label is not an operation requiring registration and listing.

§ 201.10(d)(2) Drugs; statement of ingredients

Regulation modified to be appropriate for medical gases

- (d) (1) If the drug is in tablet or capsule form or other unit dosage form, any statement of the quantity of an ingredient contained therein shall express the quantity of such ingredient in each such unit. If the drug is not in unit dosage form, any statement of the quantity of an ingredient contained therein shall express the amount of such ingredient in a specified unit of weight or measure of the drug, or the percentage of such ingredient in such drug. Such statements shall be in terms that are informative to licensed practitioners, in the case of a prescription drug, and to the layman, in the case of a nonprescription drug.
- (2) A statement of the percentage of an ingredient in a drug shall, if the term percent is used without qualification, mean percent weight-in-weight, if the ingredient and the drug are both solids, or if the ingredient is a liquid and the drug is a solid; percent weight in volume at 68 [deg]F. (20 [deg]C.), if the ingredient is a solid and the drug is a liquid; and percent volume in volume at 68 [deg]F. (20 [deg]C.), if both the ingredient and the drug are liquids, except that alcohol shall be stated in terms of percent volume of absolute alcohol at 60 [deg]F. (15.56 [deg]C.), if all ingredients are designated medical gases the statement of percentage shall be in accordance with 201.161 (f).

Rationale for modification

Combinations of designated medical gases are not addressed in (d)(2) as the ingredient is a gas and the drug is a gas and are currently expressed in percent volume/volume as identified in 201.161 (f). This change is required to express the ingredients of mixtures of designated medical gases in percent volume/volume. Medical Air, which may be manufactured by mixing oxygen and nitrogen in appropriate proportions, is exempted from this proposed change. To bring all labeling requirements for designated medical gases or combinations thereof into one location under 201.161.

§ 201.18 Drugs; significance of control numbers

Regulation modified to be appropriate for medical gases

The lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package. An incorrect lot number may be regarded as causing the article to be misbranded. See 201.161 (d) for lot numbers on containers of designated medical gas or combinations thereof.

Rationale for modification

Because medical gas containers are reused, they are typically labeled with product labeling that is also reused (unless damaged). Lot numbers change each time the container is filled, therefore historic and current industry practice is to use a separate decal that contains the lot number as opposed to placing the lot number on the main product label. The lot number decal is removed prior to or during the filling process and replaced prior to release with a new lot number decal. The revision to 201.161(d) will codify this practice and keep all designated medical gas labeling requirements in one section.

§ 201.51 Declaration of net quantity of contents*Regulation modified to be appropriate for medical gases*

- (a) The label of a prescription or insulin-containing drug in package form shall bear a declaration of the net quantity of contents. This shall be expressed in the terms of weight, measure, numerical count, or a combination of numerical count and weight or measure. The statement of quantity of drugs in tablet, capsule, ampule, or other unit dosage form shall be expressed in terms of numerical count; the statement of quantity for drugs in other dosage forms shall be in terms of weight if the drug is solid, semi-solid, or viscous, or in terms of fluid measure if the drug is liquid. When the drug quantity statement is in terms of the numerical count of the drug units, it shall be augmented to give the weight or measure of the drug units or the quantity of each active ingredient in each drug unit or, when quantity does not accurately reflect drug potency, a statement of the drug potency.
- (b) Statements of weight of the contents shall in the case of prescription drugs be expressed in terms of avoirdupois pound, ounce, and grain or of kilogram, gram, and subdivisions thereof. A statement of liquid measure of the contents shall in the case of prescription drugs be expressed in terms of the U.S. gallon of 231 cubic inches and quart, pint, fluid-ounce, and fluid-dram subdivisions thereof, or of the liter and milliliter, or cubic centimeter, and shall express the volume at 68 [deg]F. (20 [deg]C.). A statement of the liquid measure of the contents in the case of insulin-containing drugs shall be expressed in terms of the liter and milliliter, or cubic centimeter, and shall express the volume at 68 [deg]F. (20 [deg]C.).
- (c) The declaration shall contain only such fractions as are generally used in expressing the quantity of the drug. A common fraction shall be reduced to its lowest terms; a decimal fraction shall not be carried out to more than three places, except in the case of a statement of the quantity of an active ingredient in a unit of a drug.
- (d) The declaration shall appear as a distinct item on the label and, in the case of large volume parenterals, may be embossed on the glass.
- (e) The declaration shall accurately reveal the quantity of drug in the package exclusive of wrappers and other material packed therewith.
- (f) A statement of the quantity of a prescription or insulin-containing drug in terms of weight or measure applicable to such drug, under the provisions of paragraph (a) of this section, shall express with prominence and conspicuousness the number of the largest whole unit, as specified in paragraph (b) of this section, that are contained in the package. Any remainder shall be expressed in terms of common or decimal fractions of such unit or in terms of the next smaller whole unit and common or decimal fractions thereof.
- (g) The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large. In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the minimum quantity and the variation above the stated measure shall comply with the excess volume prescribed by the National Formulary or the U.S. Pharmacopeia for filling of ampules. In the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight. Variations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary.

- (h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.
- (i) Designated medical gases or combinations thereof are exempt from this section and shall comply with 201.161 (f).

Rationale for modification

The net quantity of contents for designated medical gases or combinations thereof must be expressed in terms appropriate for the modality of the product and the size of the container. These requirements are included in 201.161 containing all other labeling requirements for designated medical gases or combinations thereof.

§ 201.56(e) Requirements on content and format of labeling for human prescription drug and biological products

Regulation modified to be appropriate for medical gases

- (e) Labeling requirements for older prescription drug products other than designated medical gases or combinations thereof that are labeled in accordance with the requirements of 201.161. This paragraph applies only to approved prescription drug products not described in paragraph (b)(1) of this section.

Rationale for modification

Because FDASIA has approved designated medical gases that are “older” prescription drugs that were not previously approved, designated medical gases or combinations thereof that meet the requirements of 201.161 and other applicable portions of the labeling regulations, must now be explicitly exempted from 201.56(e).

§ 201.100 Prescription drugs for human use

Regulation modified to be appropriate for medical gases

A drug subject to the requirements of section 503(b)(1) of the act shall be exempt from section 502(f)(1) if all the following conditions are met:

- (a) The drug is:
 - (1) (i) In the possession of a person (or his agents or employees) regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale distribution of prescription drugs; or
 - (ii) In the possession of a retail, hospital, or clinic pharmacy, or a public health agency, regularly and lawfully engaged in dispensing prescription drugs; or
 - (iii) In the possession of a practitioner licensed by law to administer or prescribe such drugs; or
 - (iv) A designated medical gas in the possession of a person who is cleaning or purging medical gas containers, including medical gas pipelines; and
- (2) It is to be dispensed in accordance with section 503(b)
- (b) Other than designated medical gases or combinations thereof in compliance with 201.161, ~~the~~ the label of the drug bears:

Rationale for modification

For subparagraph (a): Designated medical gases may be used to test or purge medical gas containers after manufacture or repair, or in the course of preparing pipelines for medical gas use, and persons should be lawfully permitted to obtain a designated gas for such purposes.

For subparagraph (b): According to section 576(a)(3)(A)(ii) of the Food Drug and Cosmetic Act, added by FDASIA, designated medical gases or combinations thereof are now addressed in the revised 201.161.

§ 201.105 Veterinary drugs

Regulation modified to be appropriate for medical gases

A drug subject to the requirements of section 503(f)(1) of the act shall be exempt from section 502(f)(1) of the act if all the following conditions are met, or if it is a designated medical gas or combination thereof that it is in compliance with 201.161:

Rationale for modification

Designated medical gases or combinations thereof may be used for veterinary use, and do not require any different information than that provided for human drugs as specified in the revised 201.161.

§ 201.128 Meaning of “intended uses”

Regulation modified to be appropriate for medical gases

The words intended uses or words of similar import in Sec. § 201.5, 201.115, 201.117, 201.119, 201.120, and 201.122 refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put. Designated medical gases or combinations thereof are exempt from this section provided they are not marketed for uses other than those provided in Section 576(a)(3)(A)(i) of the Act.

Rationale for modification

The intended uses of designated medical gases are specified in FDASIA. During the negotiation of FDASIA, FDA negotiators indicated that they would use section 201.161 to create appropriate labeling for designated medical gases or combinations thereof that addressed appropriate warnings and intended use.

Subpart E—Other Exemptions

§ 201.161 Medical gases.

Regulation modified to be appropriate for medical gases

- (a) ~~Oxygen, nitrogen, carbon dioxide, helium, and nitrous oxide~~ Designated medical gases intended for drug use, and medically appropriate combinations of any of these gases intended for drug use, are exempted from the requirements of § 201.5 and § 201.100(b)(2) and (3), and (c)(1), provided that, where applicable, the requirements of §§ 201.328 and 211.94(e)(2) of this chapter are met and the labeling bears, in addition to any other information required by the Federal Food, Drug, and Cosmetic Act, the following:

Rationale for modification

211.161(a) – The exemption historically presented in 201.161 now includes all designated medical gases or combinations thereof not just the ones listed per the Containers and Closures Rule. 201.161(a) is modified to explicitly exempt designated medical gases or combinations thereof from adequate directions for use contained in 201.5.

Medical air (as detailed in (1)(iii) below) and carbon monoxide (not detailed in 201.161 at this time) are designated medical gases per FDASIA and must follow the labeling requirements for oxygen, nitrogen, carbon dioxide, helium, and nitrous oxide.

- (1) (i) In the case of oxygen, a warning statement providing that uninterrupted use of high concentrations of oxygen over a long duration, without monitoring its effect on oxygen content of arterial blood, may be harmful; that oxygen should not be used on patients who have stopped breathing unless used in conjunction with resuscitative equipment; and, in the case of oxygen that may be provided without a prescription for use in the event of depressurization or other environmental oxygen deficiency, or for oxygen deficiency or for use in emergency resuscitation when administered by properly trained personnel, a warning statement providing that oxygen may be used for emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation, and that for all other medical applications a prescription is required.
- (ii) In the case of nitrogen, carbon dioxide, helium, nitrous oxide, and medically appropriate combinations of any of the gases listed in paragraph (a) of this section, a warning statement providing that the administration of the gas or gas combination (as applicable) may be hazardous or contraindicated; and that the gas or gas combination (as applicable) should be used only by or under the supervision of a licensed practitioner who is experienced in the use and administration of the gas or gas combination (as applicable) and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications, and side effects and the precautions to be taken.
- (iii) In the case of medical air, a warning statement providing that administration of medical air may be hazardous or contraindicated; and should be used only by or under the supervision of a licensed practitioner who is experienced in the use and administration of medical air and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications, and side effects and the precautions to be taken, and a statement providing medical air may be used for breathing support without a prescription when used by properly trained personnel, and for all other medical applications a prescription is required.

Rationale for modification

21 CFR 201.161(a)(1)(iii) reflects what has historically been used on medical air.

- (2) Any needed directions concerning the conditions for transportation, storage and warnings against the inherent dangers in the handling of the specific compressed gas, as required by any other federal agency and as specified in Compressed Gas Association (CGA) publication C-7 or supplemental statements per the current USP.

Rationale for modification

21 CFR 201.161(a)(2) modified to include directions and conditions to be placed on the label for compliance with proper transportation regulations (Department of Transportation (DOT)) and employee safety regulations (Occupational Safety and Health Administration (OSHA)) and includes all of the industry precautionary handling statements in CGA C-7 and is consistent with current industry practice and USP exceptions for oxygen and medical air.

- (b) If nitrogen is provided as a designated medical gas in the form of cryogenic liquid in an open top dewar the "Rx only" statement and the warning statements specified in (a)(1)(ii), of this section are not required;

Rationale for modification

201.161(b) – Because of the change in 201.161(a) and to be consistent with the new containers and closures rule a specific exemption for the RX only statement was needed for open top nitrogen dewars. 21 CFR 201.161 (b) reflects the labeling appearing on open top nitrogen dewars filled with liquid nitrogen NF that is not inhaled and is not administered as a gas.

- (c) Combinations of designated medical gases other than medical air, intended for drug use are exempted from the requirements of § 201.100(b) (4), provided the label of the drug bears the proportion of each designated medical gas expressed in percent volume/volume.

Rationale for modification

201.161 (c) replaces 21 CFR 201.100 (b) (4) and replaces the requirement for expression of mixtures in 201.10 (d) (2).

- (d) A designated medical gas or combination thereof is exempted from the requirements of § 201.100(b) (6), provided it bears an identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug, which for medical gas containers, may appear on an ancillary decal.

Rationale for modification

201.161 (d) replaces 21 CFR 201.100 (b) (6). Because medical gas containers are reused, they are typically labeled with product labeling that is also reused (unless damaged). Lot numbers change each time the container is filled, therefore historic and current industry practice is to use a separate decal that contains the lot number as opposed to placing the lot number on the main product label. The lot number decal is removed prior to or during the filling process and replaced prior to release with a new lot number decal. The proposed revision will codify this practice.

- (e) A designated medical gas or combination thereof is exempted from the requirements of § 201.100(e), provided all labeling conspicuously bears the name and place of business of the manufacturer, packer, or distributor, as required for the label of the drug under § 201.1.

Rationale for modification

201.161 (e) replaces 21 CFR 201.100 (e).

- (f) Designated medical gases or combinations thereof shall bear a declaration of the nominal net quantity of contents as a distinct item on the label or on an ancillary decal as follows:
- (1) if in a gaseous state in a high pressure final use container, it shall be expressed in liters or cubic feet based on the filled pressure at 70 [deg]F;
 - (2) if in a liquefied compressed gas state in a high pressure final use container shall be expressed in gaseous liters or by an appropriate net weight statement;
 - (3) if in a liquefied state in a portable cryogenic final use container shall be expressed in gaseous liters, liquid liters (if identified as a liquid measure), gallons or by an appropriate net weight statement at the time of fill;
 - (4) if in a refrigerated liquid transport, a high pressure tube transport, (i.e., non-final use containers), labeling for net quantity of contents is not required;
 - (5) if in a large non-portable cryogenic storage container, or high pressure storage bank (i.e., supplies product via pipeline), labeling for net quantity of contents is not required.

Rationale for modification

21 CFR 201.161 (f) - The net quantity of contents for designated medical gases must be expressed in terms appropriate for the modality of the product and the size of the container and reflect nominal values. When the container is not a final use container directly available to patients or the care giver (e.g. large storage tank, bulk trailer, etc.), the container labeling should be specifically exempted from a net quantity statement. The net quantity of contents declaration historically and currently is provided on the same ancillary decal used for identifying the lot or control number for the container(s) and permits a sample of what was placed on the containers to be included with the appropriate batch record.

- (g) This labeling exemption does not apply to mixtures of any one or more of these gases with oxygen or with each other. If oxygen is provided as a designated medical gas in the form of cryogenic liquid in a cryogenic final use container that is classified as a medical device the warning statements specified in (a)(1)(i) and (a)(2) of this section are not required, provided the device label provides adequate directions for use in accordance with the device approval;

Rationale for modification

The proposed language reflects the labeling appearing on liquid home oxygen vessels.

- (h) If a designated medical gas is provided in a container that will not be used as a final use container (i.e., transport, railcar, storage tank, storage bank) the container must be identified with the name of the product contained in accordance with all federal requirements (however the designation as USP or NF is not required) and is exempt from the requirements of (a), (b) (c) and (d) of this section provided the accompanying documentation identifies the product as USP or NF;

Rationale for modification

21 CFR 201.161 (h) exempts non-final use containers from labeling requirements targeted for communication to the end user.

§ 201.328(a) Labeling of medical gas containers.

Regulation modified to be appropriate for medical gases

- (a) Portable cryogenic medical gas containers. For the purposes of this section a “portable cryogenic medical gas container” is one that is capable of being transported and is intended to be attached to a medical gas supply system within a hospital, health care entity, nursing home, other facility, or home health care setting, or ~~is a base unit~~ used to fill small cryogenic gas containers for use by individual patients. The term does not include cryogenic containers that are not designed to be connected to a medical gas supply system, e.g., tank trucks, trailers, rail cars, or ~~small cryogenic gas containers utilizing proprietary connections for use by individual patients (including portable liquid oxygen units as defined at § 868.5655 of this chapter).~~

Rationale for modification

(a) The term "base unit" is common vernacular in the home health care segment of the medical gas industry as the device that is maintained at the patient's residence that is filled with oxygen USP. Although "portable" it is not typically moved (except when being filled). This device utilizes proprietary connections and is also used to fill truly portable containers for patient mobility.

- (1) Each portable cryogenic medical gas container must be conspicuously marked with a 360° wraparound label identifying its contents. Such label must meet the requirements of § 211.94(e)(2) of this chapter and the following additional requirements.
- i) If the container holds a single gas, the name of the gas held in the container must be printed on the label in one of the following ways:
 - (A) Using lettering that appears in the color designated for the gas in paragraph (c) of this section and that is printed against a white background, or
 - (B) Using lettering that appears in white against a background that is painted in the color for the gas designated in paragraph (c) of this section.
 - ii) The lettering for the name of the gas on the label must be at least 2 inches high.
 - iii) The name of the gas must be printed continuously around the label and be capable of being read around the entire container.

- iv) The label must be on the sidewall of the container, as close to the top of the container as possible but below the top weld seam.
 - v) A portable cryogenic medical gas container may only be colored in the color or colors designated in paragraph (c) of this section if the gas or gases held within the container correspond to that color or those colors.
- (2) A label on the container (either the 360° wraparound label required in paragraph (a)(1) of this section or a separate label) must include, in conspicuous lettering, the phrase “For Medical Use”, “Medical Gas,” or some similar phrase that indicates the gas is for medical use.
- (b) High-pressure medical gas cylinders. Each high-pressure medical gas cylinder must be colored on the shoulder portion of the cylinder in the color or colors designated in paragraph (c) of this section. The color or colors must be visible when viewed from the top of cylinder.
- (c) Medical gas colors. The colors required to identify medical gases under paragraph (a) and (b) of this section are:

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

Compliance with 21 CFR § 205 Wholesale Distribution

CGA has worked extensively with the National Association of Boards of Pharmacy (NABP) to develop the “Model Rules for the Licensure of Medical Gas and Medical Gas Related Equipment Wholesale Distributors”, and our proposed changes to 21 CFR Part 205 support the NABP Model Rule. The most significant change needed to address the uniqueness of medical gases and to be consistent with this model rule is addressed in our proposed changes to § 205.50 for storage of medical gases in wholesale distribution.

Proposed Changes to 21 CFR § 205

§ 205.3 Definitions

Regulation modified to be appropriate for medical gases

- (a) *Blood* means whole blood collected from a single donor and processed either for transfusion or further manufacturing.
- (b) *Blood component* means that part of blood separated by physical or mechanical means.
- (c) *Drug sample* means a unit of a prescription drug that is not intended to be sold and is intended to promote the sale of the drug.
- (d) *Manufacturer* means anyone who is engaged in manufacturing, preparing, propagating, compounding, processing, packaging, repackaging, or labeling of a prescription drug.
- (e) *Prescription drug* means any human drug required by Federal law or regulation to be dispensed only by a prescription, including finished dosage forms and active ingredients subject to section 503(b) of the Federal Food, Drug, and Cosmetic Act.
- (f) *Wholesale distribution* and *wholesale distribution* means distribution of prescription drugs to persons other than a consumer or patient, but does not include:

- (1) Intracompany sales;
 - (2) The purchase or other acquisition by a hospital or other health care entity that is a member of a group purchasing organization of a drug for its own use from the group purchasing organization or from other hospitals or health care entities that are members of such organizations;
 - (3) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug by a charitable organization described in section 501(c)(3) of the Internal Revenue Code of 1954 to a nonprofit affiliate of the organization to the extent otherwise permitted by law;
 - (4) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug among hospitals or other health care entities that are under common control; for purposes of this section, common control means the power to direct or cause the direction of the management and policies of a person or an organization, whether by ownership of stock, voting rights, by contract, or otherwise;
 - (5) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug for emergency medical reasons; for purposes of this section, emergency medical reasons includes transfers of prescription drugs by a retail pharmacy to another retail pharmacy to alleviate a temporary shortage;
 - (6) The sale, purchase, or trade of a drug, an offer to sell, purchase, or trade a drug, or the dispensing of a drug pursuant to a prescription;
 - (7) The distribution of drug samples by manufacturers' representatives or distributors' representatives; or
 - (8) The sale, purchase, or trade of blood and blood components intended for transfusion.
 - (9) Drug returns, when conducted by a hospital, health care entity, or charitable institution in accordance with 203.23 of this chapter; or
 - (10) The sale of minimal quantities of drugs by retail pharmacies to licensed practitioners for office use.
- (g) Wholesale distributor means any one engaged in wholesale distribution of prescription drugs, including, but not limited to, manufacturers; repackers; own-label distributors; private-label distributors; jobbers; brokers; warehouses, including manufacturers' and distributors' warehouses, chain drug warehouses, and wholesale drug warehouses; independent wholesale drug traders; and retail pharmacies that conduct wholesale distributions.
- (h) Health care entity means any person that provides diagnostic, medical, surgical, or dental treatment, or chronic or rehabilitative care, but does not include any retail pharmacy or any wholesale distributor. Except as provided in 203.22(h) and (i) of this chapter, a person cannot simultaneously be a "health care entity" and a retail pharmacy or wholesale distributor.
- (i) Designated Medical Gas means a drug that is manufactured or stored in a liquefied, nonliquefied, or cryogenic state; and is administered as a gas and is defined in section 575(1) of the Act.
- (j) Emergency use oxygen means oxygen that may be provided without a prescription when in the event of depressurization or other environmental oxygen deficiency; or for oxygen deficiency or for use in emergency resuscitation, when administered by properly trained personnel.

Rationale for modification

For subparagraph (i)—The regulation as proposed requires a definition of designated medical gases, as they are a unique subset of prescription drugs. This definition is consistent with section 575(1) and (2) of FDASIA.

For subparagraph (j)—Although oxygen is a prescription drug, there are certain circumstances when oxygen may be administered without a prescription. This term is used in the proposed modifications to this regulation. This definition is consistent with 576(b)(2)(A) of FDASIA.

§ 205.50(a) Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.

Regulation modified to be appropriate for medical gases

The State licensing law shall include the following minimum requirements for the storage and handling of prescription drugs, and for the establishment and maintenance of prescription drug distribution records by wholesale drug distributors and their officers, agents, representatives, and employees:

- (a) Facilities. All facilities at which prescription drugs are stored, warehoused, handled, held, offered, marketed, or displayed shall:
 - (1) Be of suitable size and construction to facilitate cleaning, maintenance, and proper operations;
 - (2) Have storage areas designed to provide adequate lighting, ventilation, temperature, sanitation, humidity, space, equipment, and security conditions;
 - (3) Have a quarantine area for storage of prescription drugs that are outdated, damaged, deteriorated, misbranded, or adulterated, or that are in immediate or sealed, secondary containers that have been opened;
 - (4) Be maintained in a clean and orderly condition; and
 - (5) Be free from infestation by insects, rodents, birds, or vermin of any kind.
- (6) This section does not apply to designated medical gases or combinations thereof unless necessary to protect the integrity of the drug product.

Rationale for modification

Consistent with the change recommended in § 211.56, designated medical gases or combinations thereof are manufactured and stored in a closed, pressurized system that protects the integrity of the medical gas if the container is exposed to an infestation by rodents, birds, insects, other vermin or other contaminants. Designated medical gases or combinations thereof may be manufactured, filled, and or stored outdoors, which provides additional safety to employees and customers as storing medical gas containers in a confined area may not be safe due the potential for creating an oxygen enriched or oxygen deficient atmosphere.

§ 205.50(b) Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.

Regulation modified to be appropriate for medical gases

(b) Security.

- (1) All facilities used for wholesale drug distribution shall be secure from unauthorized entry.
 - (i) Access from outside the premises shall be kept to a minimum and be well-controlled.
 - (ii) The outside perimeter of the premises shall be well-lighted.
 - (iii) Entry into areas where prescription drugs are held shall be limited to authorized personnel.
- (2) All facilities shall be equipped with an alarm system to detect entry after hours, other than facilities only wholesaling designated medical gases or combinations thereof utilizing other security systems.
- (3) All facilities shall be equipped with a security system that will provide suitable protection against theft and diversion. When appropriate, the security system shall provide protection against theft or diversion that is facilitated or hidden by tampering with computers or electronic records.