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PS-42_2—201X DRAFT

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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 the 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, 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.

Title 21—Food and Drugs,
Chapter I—Food and Drug Administration,
Department of Health and Human Services
Subchapter C—Drugs: General

Proposed Changes to 21 CFR § 201

Subpart A—General Labeling Provisions

§ 201.1 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.

(c) If no person performs all of the applicable operations listed in paragraph (b) of this section, no person may be represented as manufacturer except as follows:

(1) If the person performs more than one half of the applicable operations listed in paragraph (b) of this section and acknowledges the contribution of other persons who have performed the remaining applicable operations by stating on the product label that "Certain manufacturing operations have been performed by other firms."; or

(2) If the person performs at least one applicable operation listed in paragraph (b) of this section and identifies by appropriate designation all other persons who have performed the remaining applicable operations, e.g., "Made by (Person A), Filled by (Person B), Sterilized by (Person C)"; or

(3) If the person performs at least one applicable operation listed in paragraph (b) of this section and the person is listed along with all other persons who have performed the remaining applicable operations as "joint manufacturers." A list of joint manufacturers shall be qualified by the phrase "Jointly Manufactured By ----------," and the names of all of the manufacturers shall be printed together in the same type size and style; or

(4) If the person performs all applicable operations listed in paragraph (b) of this section except for those operations listed in paragraph (d) of this section. For purposes of this paragraph, person, when it identifies a corporation, includes a parent, subsidiary, or affiliate company where the related companies are under common ownership and control.

(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).

(e) A person performs an operation listed in paragraph (b) of this section only if the operation is performed, including the performance of the appropriate in-process quality control operations, except laboratory testing of samples taken during processing, as follows:

(1) By individuals, a majority of whom are employees of the person and, throughout the performance of the operation, are subject to the person's direction and control;

(2) On premises that are continuously owned or leased by the person and subject to the person's direction and control; and

(3) On equipment that is continuously owned or leased by the person. As used in this paragraph, person, when it identifies a corporation, includes a parent, subsidiary, or affiliate company where the related companies are under common ownership and control.

(f) The name of the person represented as manufacturer under paragraph (b) or (c) of this section must be the same as either (1) the name of the establishment (as defined in §207.3(b) of this chapter) under which that person is registered at the time the labeled product is produced or (2) the registered establishment name of a parent, subsidiary, or affiliate company where the related companies are under common ownership and control. In addition, the name shall meet the requirements of paragraph (g) of this section.

(g) The requirement for declaration of the name of the manufacturer, packer, or distributor shall be deemed to be satisfied, in the case of a corporate person, only by the actual corporate name, except that the corporate name may be the name of a parent, subsidiary, or affiliate company where the related companies are under common ownership and control. The corporate name may be preceded

or followed by the name of the particular division of the corporation. “Company,” “Incorporated,” etc., may be abbreviated or omitted and “The” may be omitted. In the case of an individual, partnership, or association, the name under which the business is conducted shall be used.

(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.

(i) The statement of the place of business shall include the street address, city, State, and ZIP Code. For a foreign manufacturer, the statement of the place of business shall include the street address, city, country, and any applicable mailing code. The street address may be omitted if it is shown in a current city directory or telephone directory. The requirement for inclusion of the ZIP Code shall apply to consumer commodity labels developed or revised after July 1, 1969. In the case of non-consumer packages, the ZIP Code shall appear either on the label or the labeling (including the invoice).

(j) If a person manufactures, packs, or distributes a drug or drug product at a place other than the person's principal place of business, the label may state the principal place of business in lieu of the actual place where such drug or drug product was manufactured or packed or is to be distributed, unless such statement would be misleading.

(k) Paragraphs (b), (c), (d), (e), and (f) of this section, do not apply to the labeling of drug components.

(l) A drug product is misbranded under section 502(a) of the act if its labeling identifies a person as manufacturer, packer, or distributor, and that identification does not meet the requirements of this section.

(m) This section does not apply to biological drug products that are subject to the requirements of section 351 of the Public Health Service Act, 42 U.S.C. 262.

[45 FR 25775, Apr. 15, 1980; 45 FR 72118, Oct. 31, 1980, as amended at 48 FR 37620, Aug. 19, 1983; 81 FR 60212, Aug. 31, 2016]

§ 201.10 Drugs; statement of ingredients.

Regulation modified to be appropriate for medical gases

(a) The ingredient information required by section 502(e) of the Federal Food, Drug, and Cosmetic Act shall appear together, without any intervening written, printed, or graphic matter, except the proprietary names of ingredients, which may be included with the listing of established names, and such statements that are specifically required for certain ingredients by the act or regulations in this chapter.

(b) The term ingredient applies to any substance in the drug, whether added to the formulation as a single substance or in admixture with other substances.

(c) The labeling of a drug may be misleading by reason (among other reasons) of:

(1) The order in which the names of the ingredients present in the drug appear in the labeling, or the relative prominence otherwise given such names.

(2) Failure to reveal the proportion of, or other fact with respect to, an ingredient present in such drug, when such proportion or other fact is material in the light of the representation that such ingredient is present in such drug.

(3) The employment of a fanciful proprietary name for a drug or ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness or composition when, in fact, the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name.

(4) The featuring in the labeling of inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation.

(5) Designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.

(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.), <u>if all ingredients are designated medical gases the statement of percentage shall be in accordance with 201.161 (f).</u>

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 (c). 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.

(e) A derivative or preparation of a substance named in section 502(e) of the act is an article derived or prepared from such substance by any method, including actual or theoretical chemical action.

(f) If an ingredient is a derivative or preparation of a substance specifically named in section 502(e) of the act and the established name of such ingredient does not indicate that it is a derivative or preparation of the parent substance named in section 502(e) of the act, the labeling shall, in conjunction with the listing of the established name of such ingredient, declare that such article is a derivative or preparation of such parent substance.

(g) (1) If the label or labeling of a prescription drug bears a proprietary name or designation for the drug or any ingredient thereof, the established name, if such there be, corresponding to such proprietary name or designation shall accompany such proprietary name or designation each time it is featured on the label or in the labeling for the drug; but, except as provided in this subparagraph, the established name need not be used with the proprietary name or designation in the running text of the label or labeling. On any label or page of labeling in which the proprietary name or designation is not featured but is used in the running text, the established name shall be used at least once in the running text in association with such proprietary name or designation and in the same type size used in such running text: Provided, however, That if the proprietary name or designation is used in the running text in larger size type, the established name shall be used at least once in association with, and in type at least half as large as the type used for, the most prominent presentation of the proprietary name or designation in such running text. If any labeling includes a column with running text containing detailed information as to composition, prescribing, side effects, or contraindications and the proprietary name or designation is used in such column but is not featured above or below the column, the established name shall be used at least once in such column of running text in association with such proprietary name or designation and in the same type size used in such column of running text: Provided, however, That if the proprietary name or designation is used in such column of running text in larger size type, the established name shall be used at least once in association with, and in type at least half as large as the type used for, the most prominent presentation of the proprietary name or designation in such column of running text. Where the established name is required to accompany or to be used in association with the proprietary name or designation, the established name shall be placed in direct conjunction with the proprietary name or designation, and the relationship between the proprietary name or designation and the established name shall be made clear by use of a phrase such as “brand of” preceding the established name, by brackets surrounding the established name, or by other suitable means.

(2) The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

(h) (1) In the case of a prescription drug containing two or more active ingredients, if the label bears a proprietary name or designation for such mixture and there is no established name corresponding to such proprietary name or designation, the quantitative ingredient information required on the label by section 502(e) of the act shall be placed in direct conjunction with the most prominent display of the proprietary name or designation. The prominence of the quantitative ingredient information shall bear a reasonable relationship to the prominence of the proprietary name.

(2) If the drug is packaged in a container too small to bear the quantitative ingredient information on the main display panel, the quantitative ingredient information required by section 502(e) of the act may appear elsewhere on the label, even though the proprietary name or designation appears on the main display panel of the label; but side- or back-panel placement shall in this case be so arranged and printed as to provide size and prominence of display reasonably related to the size and prominence of the front-panel display.

(i) A drug packaged in a container too small or otherwise unable to accommodate a label with sufficient space to bear the information required for compliance with section 502(e)(1) (A)(ii) and (B) of the act shall be exempt from compliance with those clauses: Provided, That:

(1) The label bears:

(i) The proprietary name of the drug;

(ii) The established name, if such there be, of the drug;

(iii) An identifying lot or control number; and

(iv) The name of the manufacturer, packer, or distributor of the drug; and

(2) All the information required to appear on the label by the act and the regulations in this chapter appears on the carton or other outer container or wrapper if such carton, outer container, or wrapper has sufficient space to bear such information, or such complete label information appears on a leaflet with the package.

[40 FR 13998, Mar. 27, 1975, as amended at 67 FR 4906, Feb. 1, 2002]

§ 201.18 Drugs; significance of control numbers.

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 (~~g~~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.

Subpart B—Labeling Requirements for Prescription Drugs and/or Insulin

§ 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 (i).

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 Requirements on content and format of labeling for human prescription drug and biological products.

Regulation modified to be appropriate for medical gases

(a) General requirements. Prescription drug labeling described in §201.100(d) must meet the following general requirements:

(1) The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.

(2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with Sec. §314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

(3) The labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness. Conclusions based on animal data but necessary for safe and effective use of the drug in humans must be identified as such and included with human data in the appropriate section of the labeling.

(b) Categories of prescription drugs subject to the labeling content and format requirements in Sec. §201.56(d) and 201.57.

(1) The following categories of prescription drug products are subject to the labeling requirements in paragraph (d) of this section and §201.57 in accordance with the implementation schedule in paragraph (c) of this section:

(i) Prescription drug products for which a new drug application (NDA), biologics license application (BLA), or efficacy supplement was approved by the Food and Drug Administration (FDA) between June 30, 2001 and June 30, 2006;

(ii) Prescription drug products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006; or

(iii) Prescription drug products for which an NDA, BLA, or efficacy supplement is submitted anytime on or after June 30, 2006.

(2) Prescription drug products not described in paragraph (b)(1) of this section are subject to the labeling requirements in paragraph (e) of this section and §201.80.

(c) Schedule for implementing the labeling content and format requirements in Sec. §201.56(d) and 201.57. For products described in paragraph (b)(1) of this section, labeling conforming to the requirements in paragraph (d) of this section and §201.57 must be submitted according to the following schedule:

(1) For products for which an NDA, BLA, or efficacy supplement is submitted for approval on or after June 30, 2006, proposed conforming labeling must be submitted as part of the application.

(2) For products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006, or that has been approved any time from June 30, 2005, up to and including June 30, 2006, a supplement with proposed conforming labeling must be submitted no later than June 30, 2009.

(3) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2004, up to and including June 29, 2005, a supplement with proposed conforming labeling must be submitted no later than June 30, 2010.

(4) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2003, up to and including June 29, 2004, a supplement with proposed conforming labeling must be submitted no later than June 30, 2011.

(5) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2002, up to and including June 29, 2003, a supplement with proposed conforming labeling must be submitted no later than June 30, 2012.

(6) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2001, up to and including June 29, 2002, a supplement with proposed conforming labeling must be submitted no later than June 30, 2013.

(d) Labeling requirements for new and more recently approved prescription drug products. This paragraph applies only to prescription drug products described in paragraph (b)(1) of this section and must be implemented according to the schedule specified in paragraph (c) of this section.

(1) Prescription drug labeling described in §201.100(d) must contain the specific information required under §201.57(a), (b), and (c) under the following headings and subheadings and in the following order:

Highlights of Prescribing Information
- Product Names, Other Required Information
- Boxed Warning
- Recent Major Changes
- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations

Full Prescribing Information: Contents

Full Prescribing Information
- Boxed Warning
- 1 Indications and Usage
- 2 Dosage and Administration
- 3 Dosage Forms and Strengths
- 4 Contraindications
- 5 Warnings and Precautions
- 6 Adverse Reactions
- 7 Drug Interactions
- 8 Use in Specific Populations
  - 8.1 Pregnancy
  - 8.2 Labor and delivery
  - 8.3 Nursing mothers
  - 8.4 Pediatric use
  - 8.5 Geriatric use
- 9 Drug Abuse and Dependence
  - 9.1 Controlled substance
  - 9.2 Abuse
  - 9.3 Dependence
- 10 Overdosage
- 11 Description
- 12 Clinical Pharmacology
  - 12.1 Mechanism of action
  - 12.2 Pharmacodynamics
  - 12.3 Pharmacokinetics
- 13 Nonclinical Toxicology
  - 13.1 Carcinogenesis, mutagenesis, impairment of fertility
  - 13.2 Animal toxicology and/or pharmacology
- 14 Clinical Studies
- 15 References
- 16 How Supplied/Storage and Handling
- 17 Patient Counseling Information

(2) Additional nonstandard subheadings that are used to enhance labeling organization, presentation, or ease of use (e.g., for individual warnings or precautions, or for each drug interaction) must be assigned a decimal number that corresponds to their placement in labeling. The decimal numbers must be consistent with the standardized identifying numbers listed in paragraph (d)(1) of this section (e.g., subheadings added to the "Warnings and Precautions" section must be numbered 5.1, 5.2, and so on).

(3) Any reference in Highlights to information appearing in the full prescribing information must be accompanied by the identifying number (in parentheses) corresponding to the location of the information in the full prescribing information.

(4) Omit clearly inapplicable sections, subsections, or specific information. If sections or subsections required under paragraph (d)(1) of this section are omitted from the full prescribing information, the heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of Contents: "* Sections or subsections omitted from the full prescribing information are not listed."

(5) Any risk information that is required under §201.57(c)(9)(iv) is considered "appropriate pediatric contraindications, warnings, or precautions" within the meaning of section 505A(l)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355A(l)(2)), whether such information appears in the "Contraindications," "Warnings and Precautions," or "Use in Specific Populations" section of labeling.

(e) Labeling requirements for older prescription drug products <u>other than designated medical gases or combinations thereof that are labeled in accordance with the requirements of 201.161</u>. 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).

(1) Prescription drug labeling described in §201.100(d) must contain the specific information required under §201.80 under the following section headings and in the following order:

Description
Clinical Pharmacology
Indications and Usage
Contraindications
Warnings
Precautions
Adverse Reactions
Drug Abuse and Dependence
Overdosage
Dosage and Administration
How Supplied

(2) The labeling may contain the following additional section headings if appropriate and if in compliance with §201.80(l) and (m):

Animal Pharmacology and/or Animal Toxicology
Clinical Studies
References

(3) Omit clearly inapplicable sections, subsections, or specific information.

(4) The labeling may contain a "Product Title" section preceding the "Description" section and containing only the information required by §201.80(a)(1)(i), (a)(1)(ii), (a)(1)(iii), and (a)(1)(iv) and

§201.100(e). The information required by §201.80(a)(1)(i) through (a)(1)(iv) must appear in the "Description" section of the labeling, whether or not it also appears in a "Product Title."

(5) The labeling must contain the date of the most recent revision of the labeling, identified as such, placed prominently immediately after the last section of the labeling.

(6) The requirement in §201.80(f)(2) to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling must be implemented no later than June 30, 2007.

[71 FR 3986, Jan. 24, 2006, as amended at 79 FR 72101, Dec. 4, 2014]

Subpart D—Exemptions from Adequate Directions for Use

§ 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, ~~T~~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.

(1) The statement "Rx only" and

(2) The recommended or usual dosage and

(3) The route of administration, if it is not for oral use; and

(4) The quantity or proportion of each active ingredient, as well as the information required by section 502 (d) and (e); and

(5) If it is for other than oral use, the names of all inactive ingredients, except that:

(i) Flavorings and perfumes may be designated as such without naming their components.

(ii) Color additives may be designated as coloring without naming specific color components unless the naming of such components is required by a color additive regulation prescribed in subchapter A of this chapter.

(iii) Trace amounts of harmless substances added solely for individual product identification need not be named. If it is intended for administration by parenteral injection, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection it need not be named.

(6) An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug.

(7) A statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its identity, strength, quality, and purity. Where there are standards and test procedures for determining that the container meets the requirements for specified types of containers as defined in an official compendium, such terms may be used. For example, "Dispense in tight, light-resistant container as defined in the National Formulary". Where standards and test procedures for determining the types of containers to be used in dispensing the drug product are not included in an official compendium, the specific container or types of containers known to be adequate to maintain the identity, strength, quality, and purity of the drug products shall be described. For example, "Dispense in containers which (statement of specifications which clearly enable the dispensing pharmacist to select an adequate container)": Provided, however, That in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, but which are packaged within an outer container from which they are removed for dispensing or use, the information required by paragraph (b) (2), (3), (5), and (7) of this section may be contained in other labeling on or within the package from which it is to be dispensed; the information referred to in paragraph (b)(1) of this section may be placed on such outer container only; and the information required by paragraph (b)(6) of this section may be on the crimp of the dispensing tube. The information required by this paragraph (b)(7) is not required for prescription drug products packaged in unit-dose, unit-of-use, on other packaging format in which the manufacturer's original package is designed and intended to be dispensed to patients without repackaging.

(c) (1) Labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented; and

(2) If the article is subject to section 505 of the act, the labeling bearing such information is the labeling authorized by the approved new drug application or required as a condition for the certification or the exemption from certification requirements applicable to preparations of insulin or antibiotic drugs.

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug (other than dose information required by paragraph (b)(2) of this section and §201.105(b)(2) contains:

(1) Adequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which

it is advertised or represented; and if the article is subject to section 505 of the act, the parts of the labeling providing such information are the same in language and emphasis as labeling approved or permitted, under the provisions of section 505, and any other parts of the labeling are consistent with and not contrary to such approved or permitted labeling; and

(2) The same information concerning the ingredients of the drug as appears on the label and labeling on or within the package from which the drug is to be dispensed.

(3) The information required, and in the format specified, by Sec. §201.56, 201.57, and 201.80.

(e) All labeling described in paragraph (d) of this section bears conspicuously the name and place of business of the manufacturer, packer, or distributor, as required for the label of the drug under §201.1.

(f) Reminder labeling which calls attention to the name of the drug product but does not include indications or dosage recommendations for use of the drug product is exempted from the provisions of paragraph (d) of this section. This reminder labeling shall contain only the proprietary name of the drug product, if any; the established name of the drug product, if any; the established name of each active ingredient in the drug product; and, optionally, information relating to quantitative ingredient statements, dosage form, quantity of package contents, price, the name and address of the manufacturer, packer, or distributor or other written, printed, or graphic matter containing no representation or suggestion relating to the drug product.

- If the Commissioner finds that there is evidence of significant incidence of fatalities or serious injury associated with the use of a particular prescription drug, he may withdraw this exemption by so notifying the manufacturer, packer, or distributor of the drug by letter.

- Reminder labeling, other than price lists and catalogs solely intended to convey price information including, but not limited to, those subject to the requirements of §200.200 of this chapter, is not permitted for a prescription drug product whose labeling contains a boxed warning relating to a serious hazard associated with the use of the drug product.

- Reminder labeling which is intended to provide consumers with information concerning the price charged for a prescription for a particular drug product shall meet all of the conditions contained in §200.200 of this chapter.

- Reminder labeling, other than that subject to the requirements of §200.200 of this chapter, is not permitted for a drug for which an announcement has been published pursuant to a review of the labeling claims for the drug by the National Academy of Sciences/National Research Council (NAS/NRC), Drug Efficacy Study Group, and for which no claim has been evaluated as higher than “possibly effective.”

- If the Commissioner finds the circumstances are such that reminder labeling may be misleading to prescribers of drugs subject to NAS/NRC evaluation, such reminder labeling will not be allowed and the manufacturer, packer, or distributor will be notified either in the publication of the conclusions on the effectiveness of the drug or by letter.

[40 FR 13998, Mar. 27, 1975, as amended at 40 FR 58799, Dec. 18, 1975; 42 FR 15674, Mar. 22, 1977; 43 FR 37989, Aug. 25, 1978; 44 FR 20659, Apr. 6, 1979; 44 FR 37467, June 26, 1979; 45 FR 25777, Apr. 15, 1980; 63 FR 26698, May 13, 1998; 64 FR 400, Jan. 5, 1999; 67 FR 4906, Feb. 1, 2002; 71 FR 3996, Jan. 24, 2006]

§ 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.

(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 drugs that are to be used only by or on the prescription or other order of a licensed veterinarian; or

(ii) In the possession of a retail, hospital, or clinic pharmacy, or other person authorized under State law to dispense veterinary prescription drugs, who is regularly and lawfully engaged in dispensing drugs that are to be used only by or on the prescription or other order of a licensed veterinarian; or

(iii) In the possession of a licensed veterinarian for use in the course of his professional practice; and

(2) To be dispensed in accordance with section 503(f) of the act.

(b) The label of the drug bears:

(1) The statement “Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian”; and

(2) The recommended or usual dosage; and

(3) The route of administration, if it is not for oral use; and

(4) The quantity or proportion of each active ingredient as well as the information required by section 502(e) of the act; and

(5) If it is for other than oral use, the names of all inactive ingredients, except that:

(i) Flavorings and perfumes may be designated as such without naming their components.

(ii) Color additives may be designated as coloring without naming specific color components unless the naming of such components is required by a color additive regulation prescribed in subchapter A of this chapter.

(iii) Trace amounts of harmless substances added solely for individual product identification need not be named. If it is intended for administration by parenteral injection, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection, it need not be named.

(6) An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug; Provided, however, That in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, but which are packaged within an outer container from which they are removed for dispensing or use, the information required by paragraphs (b) (2), (3), and (5) of this section may be contained in other labeling on or within the package from which it is to be so dispensed, and the information referred to in paragraph (b)(1) of this section may be placed on such outer container only, and the information required by paragraph (b)(6) of this section may be on the crimp of the dispensing tube.

(c) (1) Labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and

precautions under which veterinarians licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented; and

(2) If the article is subject to section 512 or 572 of the act, the labeling bearing such information is the labeling authorized by the approved new animal drug application or contained in the index listing: Provided, however, That the information required by paragraph (c)(1) of this section may be omitted from the dispensing package if, but only if, the article is a drug for which directions, hazards, warnings, and use information are commonly known to veterinarians licensed by law to administer the drug. Upon written request, stating reasonable grounds therefore, the Commissioner will offer an opinion on a proposal to omit such information from the dispensing package under this proviso.

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug (other than dose information required by paragraph (b)(2) of this section and §201.100(b)(2)) contains:

(1) Adequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant warnings, hazards, contraindications, side effects, and precautions, and including information relevant to compliance with the new animal drug provisions of the act, under which veterinarians licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented; and if the article is subject to section 512 or 572 of the act, the parts of the labeling providing such information are the same in language and emphasis as labeling approved, permitted, or indexed under the provisions of section 512 or 572, and any other parts of the labeling are consistent with and not contrary to such approved, permitted, or indexed labeling; and

(2) The same information concerning the ingredients of the drug as appears on the label and labeling on or within the package from which the drug is to be dispensed; Provided, however, That the information required by paragraphs (d)(1) and (2) of this section is not required on the so-called reminder-piece labeling which calls attention to the name of the drug but does not include indications or dosage recommendations for use of the drug.

(e) All labeling, except labels and cartons, bearing information for use of the drug also bears the date of the issuance or the date of the latest revision of such labeling.

(f) A prescription drug intended for both human and veterinary use shall comply with paragraphs (e) and (f) of this section and §201.100.

[40 FR 13998, Mar. 27, 1975, as amended at 42 FR 15674, Mar. 22, 1977; 57 FR 54300, Nov. 18, 1992; 72 FR 69119, Dec. 6, 2007]

§ 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.

[41 FR 6911, Feb. 13, 1976]

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 (I)(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 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)(2), (3) and (4) 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 current 21 CFR 201.161 (g) language does not permit mixtures which are currently allowed by FDASIA and therefore it is deleted and replaced with the modified language reflecting 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.

[81 FR 81696, Nov. 18, 2016]

§ 201.328 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

[81 FR 81696, Nov. 18, 2016]

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.

Title 21—Food and Drugs,
Chapter I—Food and Drug Administration,
Department of Health and Human Services,
Subchapter C—Drugs: General

Part 205 Guidelines for State Licensing of Wholesale Prescription Drug Distributors

Proposed Changes to 21 CFR § 205

§ 205.1 Scope.

This part applies to any person, partnership, corporation, or business firm in a State engaging in the wholesale distribution of human prescription drugs in interstate commerce.

§ 205.2 Purpose.

The purpose of this part is to implement the Prescription Drug Marketing Act of 1987 by providing minimum standards, terms, and conditions for the licensing by State licensing authorities of persons who engage in wholesale distributions in interstate commerce of prescription drugs.

§ 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.

[55 FR 38023, Sept. 14, 1990, as amended at 64 FR 67762, Dec. 3, 1999, 73 FR 59501, Oct. 9, 2008]

§ 205.4 Wholesale drug distributor licensing requirement.

Every wholesale distributor in a State who engages in wholesale distributions of prescription drugs in interstate commerce must be licensed by the State licensing authority in accordance with this part before engaging in wholesale distributions of prescription drugs in interstate commerce.

§ 205.5 Minimum required information for licensure.

(a) The State licensing authority shall require the following minimum information from each wholesale drug distributor as part of the license described in 205.4 and as part of any renewal of such license:

(1) The name, full business address, and telephone number of the licensee;

(2) All trade or business names used by the licensee;

(3) Addresses, telephone numbers, and the names of contact persons for all facilities used by the licensee for the storage, handling, and distribution of prescription drugs;

(4) The type of ownership or operation (i.e., partnership, corporation, or sole proprietorship); and

(5) The name(s) of the owner and/or operator of the licensee, including:

(i) If a person, the name of the person;

(ii) If a partnership, the name of each partner, and the name of the partnership;

(iii) If a corporation, the name and title of each corporate officer and director, the corporate names, and the name of the State of incorporation; and

(iv) If a sole proprietorship, the full name of the sole proprietor and the name of the business entity.

(b) The State licensing authority may provide for a single license for a business entity operating more than one facility within that State, or for a parent entity with divisions, subsidiaries, and/or affiliate companies within that State when operations are conducted at more than one location and there exists joint ownership and control among all the entities.

(c) Changes in any information in paragraph (a) of this section shall be submitted to the State licensing authority as required by such authority.

(Approved by the Office of Management and Budget under control number 0910-0251)

§ 205.6 Minimum qualifications.

(a) The State licensing authority shall consider, at a minimum, the following factors in reviewing the qualifications of persons who engage in wholesale distribution of prescription drugs within the State:

(1) Any convictions of the applicant under any Federal, State, or local laws relating to drug samples, wholesale or retail drug distribution, or distribution of controlled substances;

(2) Any felony convictions of the applicant under Federal, State, or local laws;

(3) The applicant's past experience in the manufacture or distribution of prescription drugs, including controlled substances;

(4) The furnishing by the applicant of false or fraudulent material in any application made in connection with drug manufacturing or distribution;

(5) Suspension or revocation by Federal, State, or local government of any license currently or previously held by the applicant for the manufacture or distribution of any drugs, including controlled substances;

(6) Compliance with licensing requirements under previously granted licenses, if any;

(7) Compliance with requirements to maintain and/or make available to the State licensing authority or to Federal, State, or local law enforcement officials those records required under this section; and

(8) Any other factors or qualifications the State licensing authority considers relevant to and consistent with the public health and safety.

(b) The State licensing authority shall have the right to deny a license to an applicant if it determines that the granting of such a license would not be in the public interest.

§ 205.7 Personnel.

The State licensing authority shall require that personnel employed in wholesale distribution have appropriate education and/or experience to assume responsibility for positions related to compliance with State licensing requirements.

§ 205.8 Violations and penalties.

(a) State licensing laws shall provide for the suspension or revocation of licenses upon conviction of violations of Federal, State, or local drug laws or regulations, and may provide for fines, imprisonment, or civil penalties.

(b) State licensing laws shall provide for suspension or revocation of licenses, where appropriate, for violations of its provisions.

§ 205.50 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.

(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 f~~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.

Rationale for modification

Designated medical gases or combinations thereof are not subject to theft and diversion and this language is consistent with the Model Act for the Wholesale Distribution of Medical Gases published by the National Association of Boards of Pharmacy (NABP).

(c) *Storage.* All prescription drugs, other than designated medical gases, shall be stored at appropriate temperatures and under appropriate conditions in accordance with requirements, if any, in the labeling of such drugs, or with requirements in the current edition of an official compendium, such as the United States Pharmacopeia/National Formulary (USP/NF).

Rationale for modification

The identity, strength, quality, and purity of designated medical gases are not impacted by storage conditions. Current industry standards require storage of cylinders to be protected from sunlight when ambient temperature exceeds 52 °C (125 °F). This requirement is to protect against cylinder over- pressurization but would have no impact on the product itself.

(1) If no storage requirements are established for a prescription drug, the drug may be held at "controlled" room temperature, as defined in an official compendium, to help ensure that its identity, strength, quality, and purity are not adversely affected.

(2) Appropriate manual, electromechanical, or electronic temperature and humidity recording equipment, devices, and/or logs shall be utilized to document proper storage of prescription drugs.

(3) The recordkeeping requirements in paragraph (f) of this section shall be followed for all stored drugs.

(d) Examination of materials.

(1) Upon receipt, each outside shipping container shall be visually examined for identity and to prevent the acceptance of contaminated prescription drugs or prescription drugs that are

otherwise unfit for distribution. This examination shall be adequate to reveal container damage that would suggest possible contamination or other damage to the contents.

(2) Each outgoing shipment shall be carefully inspected for identity of the prescription drug products and to ensure that there is no delivery of prescription drugs that have been damaged in storage or held under improper conditions.

(3) The recordkeeping requirements in paragraph (f) of this section shall be followed for all incoming and outgoing prescription drugs.

(e) *Returned, damaged, and outdated prescription drugs.*

(1) Prescription drugs that are outdated, damaged, deteriorated, misbranded, or adulterated shall be quarantined and physically separated from other prescription drugs until they are destroyed or returned to their supplier.

(2) Any prescription drugs whose immediate or sealed outer or sealed secondary containers have been opened or used shall be identified as such, and shall be quarantined and physically separated from other prescription drugs until they are either destroyed or returned to the supplier.

(3) If the conditions under which a prescription drug has been returned cast doubt on the drug's safety, identity, strength, quality, or purity, then the drug shall be destroyed, or returned to the supplier, unless examination, testing, or other investigation proves that the drug meets appropriate standards of safety, identity, strength, quality, and purity. In determining whether the conditions under which a drug has been returned cast doubt on the drug's safety, identity, strength, quality, or purity, the wholesale drug distributor shall consider, among other things, the conditions under which the drug has been held, stored, or shipped before or during its return and the condition of the drug and its container, carton, or labeling, as a result of storage or shipping.

(4) The recordkeeping requirements in paragraph (f) of this section shall be followed for all outdated, damaged, deteriorated, misbranded, or adulterated prescription drugs.

(f) *Recordkeeping.*

(1) Wholesale drug distributors shall establish and maintain inventories and records of all transactions regarding the receipt and distribution or other disposition of prescription drugs. These records shall include the following information:

(i) The source of the drugs, including the name and principal address of the seller or transferor, and the address of the location from which the drugs were shipped;

(ii) The identity and quantity of the drugs received and distributed or disposed of; and

(iii) The dates of receipt and distribution or other disposition of the drugs.

(2) Inventories and records shall be made available for inspection and photocopying by authorized Federal, State, or local law enforcement agency officials for a period of 3 years after the date of their creation.

(3) Records described in this section that are kept at the inspection site or that can be immediately retrieved by computer or other electronic means shall be readily available for authorized inspection during the retention period. Records kept at a central location apart from the inspection site and not electronically retrievable shall be made available for inspection within 2 working days of a request by an authorized official of a Federal, State, or local law enforcement agency.

(g) *Written policies and procedures.* Wholesale drug distributors shall establish, maintain, and adhere to written policies and procedures, which shall be followed for the receipt, security, storage, inventory, and distribution of prescription drugs, including policies and procedures for identifying, recording, and reporting losses or thefts, and for correcting all errors and inaccuracies in inventories. Wholesale drug distributors shall include in their written policies and procedures the following:

(1) A procedure whereby the oldest approved stock of a prescription drug product is distributed first. The procedure may permit deviation from this requirement, if such deviation is temporary and appropriate.

(2) A procedure to be followed for handling recalls and withdrawals of prescription drugs. Such procedure shall be adequate to deal with recalls and withdrawals due to:

(i) Any action initiated at the request of the Food and Drug Administration or other Federal, State, or local law enforcement or other government agency, including the State licensing agency;

(ii) Any voluntary action by the manufacturer to remove defective or potentially defective drugs from the market; or

(iii) Any action undertaken to promote public health and safety by replacing of existing merchandise with an improved product or new package design.

(3) A procedure to ensure that wholesale drug distributors prepare for, protect against, and handle any crisis that affects security or operation of any facility in the event of strike, fire, flood, or other natural disaster, or other situations of local, State, or national emergency.

(4) A procedure to ensure that any outdated prescription drugs shall be segregated from other drugs and either returned to the manufacturer or destroyed. This procedure shall provide for written documentation of the disposition of outdated prescription drugs. This documentation shall be maintained for 2 years after disposition of the outdated drugs.

(h) *Responsible persons.* Wholesale drug distributors shall establish and maintain lists of officers, directors, managers, and other persons in charge of wholesale drug distribution, storage, and handling, including a description of their duties related to wholesale distribution and a summary of their qualifications.

Rationale for modification

The duties and summary qualifications should be limited to those directly related to wholesale distribution.

(i) *Compliance with Federal, State, and local law.* Wholesale drug distributors shall operate in compliance with applicable Federal, State, and local laws and regulations.

(1) Wholesale drug distributors shall permit the State licensing authority and authorized Federal, State, and local law enforcement officials to enter and inspect their premises and delivery vehicles, and to audit their records and written operating procedures, at reasonable times and in a reasonable manner, to the extent authorized by law.

(2) Wholesale drug distributors that deal in controlled substances shall register with the appropriate State controlled substance authority and with the Drug Enforcement Administration (DEA), and shall comply with all applicable State, local, and DEA regulations.

(j) *Salvaging and reprocessing.* Wholesale drug distributors shall be subject to the provisions of any applicable Federal, State, or local laws or regulations that relate to prescription drug product salvaging or reprocessing, including parts 207, 210, and 211 of this chapter.

[55 FR 38023, Sept. 14, 1990, as amended at 64 FR 67763, Dec. 3, 1999]

Compliance with 21 CFR § 210/211 cGMPs (currently limited to information as presented in May 2013 letter to FDA)

The following modifications to existing regulations, consistent with the longstanding industry practice, are based on the significant variances between manufacturing, processing, packing and holding of medical gases versus manufacturing, processing, packing and holding of traditional pharmaceuticals such as pills or injectables.

Title 21—Food and Drugs,
Chapter I—Food and Drug Administration,
Department of Health and Human Services,
Subchapter C—Drugs: General

Part 210 Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General

Proposed Changes to 21 CFR § 210

§ 210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in parts 211, 225, and 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211, 225, and 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

(c) Owners and operators of establishments engaged in the recovery, donor screening, testing (including donor testing), processing, storage, labeling, packaging, or distribution of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in 1271.3(d) of this chapter, that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act), are subject to the donor-eligibility and applicable current good tissue practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211, 225, and 226 of this chapter. Failure to comply with any applicable regulation set forth in this part, in parts 211, 225, and 226 of this chapter, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter with respect to the manufacture, processing, packing or holding of a drug, renders an HCT/P adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action.

[43 FR 45076, Sept. 29, 1978, as amended at 69 FR 29828, May 25, 2004; 74 FR 65431, Dec. 10, 2009]

§ 210.2 Applicability of current good manufacturing practice regulations.

(a) The regulations in this part and in parts 211, 225, and 226 of this chapter as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use; and in part 1271 of this chapter as they are applicable to a human cell, tissue, or cellular or tissue-based product (HCT/P) that is a drug (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part, in parts 211, 225, and 226 of this chapter, in parts 600 through 680 of this chapter, and in part 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

(c) An investigational drug for use in a phase 1 study, as described in 312.21(a) of this chapter, is subject to the statutory requirements set forth in 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter. However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or phase 3 study, as described in 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a phase 2 or phase 3 study or the drug has been lawfully marketed, the drug for use in the phase 1 study must comply with part 211.

[69 FR 29828, May 25, 2004, as amended at 73 FR 40462, July 15, 2008; 74 FR 65431, Dec. 10, 2009]

§ 210.3 Definitions.

Regulation modified to be appropriate for medical gases

(a) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in Parts 211 through 226 of this chapter.

(b) The following definitions of terms apply to this part and to Parts 211 through 226 of this chapter.

(1) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.).

(2) *Batch* means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(3) *Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

(4) *Drug product* means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

(5) *Fiber* means any particulate contaminant with a length at least three times greater than its width.

(6) *Non-fiber-releasing filter* means any filter, which after any appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered

(7) *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

(8) *Inactive ingredient* means any component other than an ``active ingredient."

(9) *In-process material* means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

(10) *Lot* means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

(11) *Lot number, control number, or batch number* means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.

(12) *Manufacture, processing, packing, or holding of a drug product* includes packaging and labeling operations, testing, and quality control of drug products.

(13) The term *medicated feed* means any Type B or Type C medicated feed as defined in 558.3 of this chapter. The feed contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated feeds is subject to the requirements of Part 225 of this chapter.

(14) The term *medicated premix* means a Type A medicated article as defined in 558.3 of this chapter. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of Part 226 of this chapter.

(15) *Quality control unit* means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

(16) *Strength* means:

(i) The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or

(ii) The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

(17) *Theoretical yield* means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

(18) *Actual yield* means the quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular drug product.

(19) *Percentage of theoretical yield* means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.

(20) *Acceptance criteria* means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

(21) *Representative sample* means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.

(22) *Gang-printed labeling* means labeling derived from a sheet of material on which more than one item of labeling is printed.

(23) *Designated medical gas* means a drug that is manufactured or stored in a liquefied, nonliquefied, or cryogenic state; is administered as a gas; and is defined in section 575(1) of the Act.

Rationale for modification

Designated medical gases are a new and unique subset of approved drug products.

[43 FR 45076, Sept. 29, 1978, as amended at 51 FR 7389, Mar. 3, 1986; 58 FR 41353, Aug. 3, 1993; 73 FR 51931, Sept. 8, 2008; 74 FR 65431, Dec. 10, 2009]

Title 21—Food and Drugs
Chapter I—Food and Drug Administration
Department of Health and Human Services
Subchapter C—Drugs: General

Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals

Proposed Changes to 21 CFR § 211

Subpart A—General Provisions

§ 211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products (excluding positron emission tomography drugs) for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter as they pertain to drug products; in parts 600 through 680 of this chapter, as they pertain to drugs that are also biological products for human use; and in part 1271 of this chapter, as they are applicable to drugs that are also human cells, tissues, and cellular and tissue-based products (HCT/Ps) and that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); supplement and do not supersede the regulations in this part unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, or in parts 600 through 680 of this chapter, or in part 1271 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

(c) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this part shall not be enforced for OTC drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use. Therefore, until further notice, regulations under part 110 of this chapter, and where applicable, parts 113 to 129 of this chapter, shall be applied in determining whether these OTC drug products that are also foods are manufactured, processed, packed, or held under current good manufacturing practice.

[43 FR 45077, Sept. 29, 1978, as amended at 62 FR 66522, Dec. 19, 1997; 69 FR 29828, May 25, 2004; 74 FR 65431, Dec. 10, 2009; 80 FR 56168, Sept. 17, 2015]

§ 211.3 Definitions.

The definitions set forth in 210.3 of this chapter apply in this part.

Subpart B—Organization and Personnel

§ 211.22 Responsibilities of quality control unit

Regulation modified to be appropriate for medical gases

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.

(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

(e) For designated medical gases, personnel assigned to the facility quality control unit may perform other functions not related to quality. However when performing quality control functions personnel are under the direction of the quality control unit.

Rationale for modification

Change to clarify the requirements for designated medical gas manufacturers this would include; the requirement to address small business or small plant operations structure because these quality control units are not full time separate functions, these individuals may perform other manufacturing or distribution functions accordingly.

§ 211.25 Personnel qualifications.

(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

(b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

(c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

§ 211.28 Personnel responsibilities.

Regulation modified to be appropriate for medical gases

(a) Where the potential for contamination exists, ~~P~~personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.

(b) Personnel shall practice good sanitation and health habits.

(c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

(d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to

report to supervisory personnel any health conditions that may have an adverse effect on drug products.

Rationale for modification

Health and sanitation habits are not critical to protect designated medical gases or combinations thereof from contamination because closed pressurized systems are used to manufacture and fill medical gases and are not affected by employee hygiene. For designated medical gases or combinations thereof, specific clothing and apparel requirements may be necessary to ensure safe operations but have no impact on the identity, strength, quality and purity of the designated medical gas.

§ 211.34 Consultants.

Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C—Buildings and Facilities

§ 211.42 Design and construction features.

Regulation modified to be appropriate for medical gases

(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.

(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.

(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas for the firm's operations to prevent contamination or mixups as follows:

(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;

(2) Holding rejected components, drug product containers, closures, and labeling before disposition;

(3) Storage of released components, drug product containers, closures, and labeling;

(4) Storage of in-process materials;

(5) Manufacturing and processing operations;

(6) Packaging and labeling operations;

(7) Quarantine storage before release of drug products;

(8) Storage of drug products after release;

(9) Control and laboratory operations;

(10) Aseptic processing, which includes as appropriate:

(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;

(ii) Temperature and humidity controls;

(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;

(iv) A system for monitoring environmental conditions;

(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;

(vi) A system for maintaining any equipment used to control the aseptic conditions.

(d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

(e) For designated medical gases or combinations thereof, buildings and facilities shall be a suitable size and have adequate space for the orderly placement of equipment and materials to prevent mix-ups of incoming supply gases, cylinders, valves, labels, in-process materials, filled cylinders, and rejected materials.

Rationale for modification

Designated medical gases or combinations thereof are filled and stored in a closed pressurized system and are not affected by environmental conditions such as dust and dirt. Aseptic processing is not applicable.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

§ 211.44 Lighting.

Regulation modified to be appropriate for medical gases

As appropriate, ~~A~~adequate lighting shall be provided ~~in all areas~~.

Rationale for modification

Adequate lighting shall be provided in areas where persons are performing functions such as reading procedures, instructions, labels, gauges, scales, and test equipment. Not all areas need to be lighted (tanker storage, etc.).

§ 211.46 Ventilation, air filtration, air heating and cooling

Regulation modified to be appropriate for medical gases

(a) Adequate ventilation shall be provided.

(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

(c) Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.

(d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

(e) For designated medical gases or combinations thereof, products are processed in closed pressurized system and therefore not subject to requirements 211.46(a) – (d).

Rationale for modification

Designated medical gases or combinations thereof do not require controlled environments to protect the product. No potential for environmental contamination exists as, closed pressurized systems are used to manufacture and fill medical gases.

§ 211.48 Plumbing.

(a) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40 CFR part 141. Water not meeting such standards shall not be permitted in the potable water system.

(b) Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphonage.

[43 FR 45077, Sept. 29, 1978, as amended at 48 FR 11426, Mar. 18, 1983]

§ 211.50 Sewage and refuse.

Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

§ 211.52 Washing and toilet facilities.

Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.

§ 211.56 Sanitation.

Regulation modified to be appropriate for medical gases

(a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition. Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

(b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

(c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135).

(d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

(e) 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

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.

§ 211.58 Maintenance.

Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.

Subpart D—Equipment

§ 211.63 Equipment design, size, and location.

Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

§ 211.65 Equipment construction.

Regulation modified to be appropriate for medical gases

(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(c) Designated medical gas systems shall have the appropriate engineering controls, procedures, validations, or combinations thereof (adapter controls, etc.) to prevent mix-ups, cross-contamination of the systems, or filling of containers from the wrong supply source.

Rationale for modification

The modifications require medical gas specific controls including the use of gas property specific connections for designated medical gases or combinations thereof as identified in CGA V-1 to address the potential for cross product contamination.

§ 211.67 Equipment cleaning and maintenance

Regulation modified to be appropriate for medical gases

(a) Equipment and utensils shall 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 drug product beyond the official or other established requirements.

(b) Where appropriate to protect the drug product, ~~W~~written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment;

(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;

(4) Removal or obliteration of previous batch identification;

(5) Protection of clean equipment from contamination prior to use;

(6) Inspection of equipment for cleanliness immediately before use.

Rationale for modification

Designated medical gases are manufactured and filled utilizing pressurized closed systems and equipment should not be cleaned between batches and lots. Significant cleaning is performed when initially assembled and prior to commissioning. Unnecessary cleaning introduces a contaminant (the cleaning solution) which must be completely removed prior to using the system.

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in §§ 211.180 and 211.182.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51931, Sept. 8, 2008]

§ 211.68 Automatic, mechanical, and electronic equipment

Regulation modified to be appropriate for medical gases

(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

(b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

(c) For designated medical gases, automatic, mechanical, or electronic equipment used in the manufacture of medical gases shall be routinely calibrated, inspected, and checked to ensure proper performance. Written procedures and records as applicable shall be established and maintained following the equipment manufacturer's recommendation or scientifically sound methods.

Computer systems (including back-up systems and programmable logic controllers) shall be appropriately qualified and validated to demonstrate suitability of the hardware and/or software to perform tasks in a consistent and reproducible manner. The depth and scope of the validation is dependent on the diversity, complexity, and criticality of the system.

Firms using computerized systems that records, stores, and uses data, that computer system requires validation in accordance with 21 CFR Part 11. Computers used in a laboratory setting may require validation based on the stored data and how it is used.

In addition, automated analysis and/or automated loading systems used by firms for the bulk distribution of product shall be validated. This equipment can be used for the analyst signature for the release of bulk designated medical products provided that the requirements as defined in the *USP–NF* are met for a specific gas and the requirements in 21 CFR Part 11 have been satisfied.

Appropriate change control shall be used whenever modifications are made to computer systems.

Rationale for modification

This section as currently written is not adequate for designated medical gases. The modifications clarify the specific requirements for the equipment used in the manufacturing of designated medical gases, including appropriate change control for medical gases.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995; 73 FR 51932, Sept. 8, 2008]

§ 211.72 Filters.

Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may be used when it is not possible to manufacture such products without the use of these filters. If use of a fiber-releasing filter is necessary, an additional nonfiber-releasing filter having a maximum nominal pore size rating of 0.2 micron (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. The use of an asbestos-containing filter is prohibited.

[73 FR 51932, Sept. 8, 2008]

Subpart E—Control of Components and Drug Product Containers and Closures

§ 211.80 General requirements.

Regulation modified to be appropriate for medical gases

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.

(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.

(c) Bagged or boxed components of drug product containers or closures<u>, other than designated medical gas containers,</u> shall be stored off the floor and suitably spaced to permit cleaning and inspection.

(d) Each container or grouping of containers for components or drug product containers~~,~~ or closures <u>other than designated medical gas containers and closures,</u> shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

Rationale for modification

For subparagraph (c)—Designated medical gases are filled utilizing pressurized closed systems that protects the integrity of the drug product. They are designed to be stored on the ground due to the size and weight of the actual containers. Storage conditions have no impact to the identity, strength, quality, and purity of the designated medical gas containers or components.

For subparagraph (d)—These requirements do not apply to new or re-used designated medical gas containers and closures as they are inspected immediately prior to use in the manufacturing operations. Additionally, there are no distinctive incoming lot codes for medical gas cylinders and valves.

§ 211.82 Receipt and storage of untested components, drug product containers, and closures.

Regulation modified to be appropriate for medical gases

(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination. <u>This section does not apply to designated medical gases.</u>

(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released. Storage within the area shall conform to the requirements of § 211.80. This section does not apply to designated medical gases.

Rationale for modification

The specific requirements for medical gases are better explained and identified in new section 211.85.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

§ 211.84 Testing and approval or rejection of components, drug product containers, and closures.

Regulation modified to be appropriate for medical gases

(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by § 211.170.

(c) Samples shall be collected in accordance with the following procedures:

(1) The containers of components selected shall be cleaned where necessary, by appropriate means.

(2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.

(3) Sterile equipment and aseptic sampling techniques shall be used when necessary.

(4) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.

(5) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.

(6) Containers from which samples have been taken shall be marked to show that samples have been removed from them.

(d) Samples shall be examined and tested as follows:

(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

(3) Containers and closures shall be tested for conformance with all appropriate written procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the

manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.

(4) When appropriate, components shall be microscopically examined.

(5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.

(6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.

(f) This section does not apply to designated medical gases.

Rationale for modification

The specific requirements for medical gases are better explained and identified in new section 211.85.

[43 FR 45077, Sept. 29, 1978, as amended at 63 FR 14356, Mar. 25, 1998; 73 FR 51932, Sept. 8, 2008]

§ 211.85 Testing and approval or rejection of designated medical gas components, containers, and closures.

Current regulation

§ 211.85 does not currently exist.

Regulation modified to be appropriate for medical gases

(a) Cylinders, valves, and liquid containers, shall be examined for appropriate quality and integrity characteristics prior to filling. Any rejected items shall be handled in accordance with section 211.189.

(b) Supply gases or supply gases commingled with existing inventory shall be examined, sampled, tested, and approved or rejected as appropriate prior to the release of any containers filled.

(c) Cylinders, valves and liquid containers, shall be inspected for conformance with appropriate written procedures. In lieu of such inspection by the manufacturer, a statement of verification that the cylinders, valves or liquid containers may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's capabilities through auditing or other established means.

(d) A firm shall verify that the incoming product's labeling identifies the product as United States Pharmacopoeia (USP) or National Formulary (NF). If an acceptable certificate of analysis (COA) is provided, only an identity test is required on the commingled product prior to use. If no COA is provided, full compendial testing is required using one of the following methods:

(1) sampling the commingled product in the storage tank or supply container directly;

(2) sampling a high pressure cylinder that has been previously evacuated to proper levels and then filled with this supply; or

(3) sampling a liquid cylinder that has been emptied of any residual product and properly purged or evacuated and then filled with this supply.

(e) A receiving firm shall assign a unique identification number to the commingled product for traceability. A unique identification number shall be assigned or the supplier's unique lot number shall be used for containers that will be directly used as a supply.

(f) The sample shall be tested for USP/NF specifications. Testing shall be performed using either official USP/NF test methods or validated equivalent methods and documented according to a firm's procedure.

(g) The quality control unit (QCU) shall review the receipt and testing documentation for the supply gas and either approve the supply gas for use or reject it.

(h) For home care companies or for single source locations (filling medical liquid containers only):

(1) In lieu of full compendial testing, a COA may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on the sample of such component, and provided that the manufacturer establishes the reliability of the supplier's analyses at appropriate intervals either through witnessing the supplier performing the test or having a third party verify the supplier's results. If witnessing is relied upon, the medical gas manufacturer shall be trained on the supplier's method of analysis and that training shall be documented. A formal letter of agreement addressing trailer qualification between the manufacturer and the competitor can be part of the purchase agreement or an appendix to the contract. As an alternative, a COA from the last load or any other form of documentation agreed to by the manufacturer and the competitor can be used to satisfy this requirement.

(2) The information on a COA shall contain at a minimum:

(i) supplier's name;

(ii) name of the product (including an air liquefaction statement for oxygen USP);

(iii) lot number or other unique identification number;

(iv) actual analytical result obtained for strength, and all other tests performed;

(v) test method(s) used for analysis; and

(vi) supplier representative's signature and the date of the signature.

Rationale for modification

To ensure the integrity of designated medical gas containers and closures, a separate regulation is necessary. Section 211.85 was developed to address the uniqueness of bulk material, commingled product, and qualification procedures that could not be addressed through modification of existing regulations.

- *Cylinders and valves that are received may not be identified for medical service upon receipt. Service is determined prior to fill. These requirements do not apply to new or re-used medical gas containers and closures as they are inspected as part of the pre-fill process.*
- *Testing of commingled product as opposed to testing a sample from the delivery prior to commingling.*
- *Testing of components has historically included testing concurrent with first use at the time that final product testing is being performed on the filled final product container.*
- *Unique circumstances with home care companies or single source locations filling medical liquid containers only.*

§ 211.86 Use of approved components, drug product containers, and closures.

Regulation modified to be appropriate for medical gases

Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate. This section does not apply to designated medical gas components, containers, or closures.

Rationale for modification

Bulk designated medical gases are commingled in large cryogenic vessels and therefore there is no stock rotation. Single component gases contained in high pressure or liquid containers do not expire therefore stock rotation is not required. High pressure cylinders, liquid containers, and valves are inspected prior to each use.

§ 211.87 Retesting of approved components, drug product containers, and closures.

Regulation modified to be appropriate for medical gases

Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit 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 component, drug product container, or closure. This section does not apply to designated medical gas components, containers, or closures.

Rationale for modification

Designated medical gas components, containers, and closures are not impacted by the length of storage or storage conditions. Designated medical gases are maintained in closed pressurized systems and are not affected by environmental conditions.

§ 211.89 Rejected components, drug product containers, and closures.

Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

§ 211.94 Drug product containers and closures.

Regulation modified to be appropriate for medical gases

(a) Drug product containers and closures shall 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.

(b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product

(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

(e) Medical gas containers and closures must meet the following requirements—

(1) Gas specific use outlet connections. Portable cryogenic medical gas containers that are not manufactured with permanent gas use outlet connections (e.g., those that have been silver brazed) must have gas-specific use outlet connections that are attached to the valve body so that they cannot be readily removed or replaced (without making the valve inoperable and preventing

the containers' use) except by the manufacturer. For the purposes of this paragraph, the term "manufacturer" includes any individual or firm that fills high-pressure medical gas cylinders or 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 with unique connections for use by individual patients ~~(including portable liquid oxygen units as defined at § 868.5655 of this chapter)~~.

(2) Label and coloring requirements. The labeling specified at § 201.328(a) of this chapter must be affixed to the container in a manner that does not interfere with other labeling ~~and such that it is not susceptible to becoming worn or inadvertently detached during normal use~~. Each such label as well as materials used for coloring medical gas containers must be reasonably resistant to fading, durable when exposed to atmospheric conditions, and not readily soluble in water.

Rationale for modification

(e)(1): 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.

(e)(2): The requirement for labeling to be not susceptible to becoming worn or inadvertently detached during normal use is impossible to achieve given the unique characteristics of the way medical gases are delivered, handled and used and the fact that medical gas fillers have no control over the storage and handling at the user facility. Any label on the side of the container is susceptible to damage and other than a label which is placed on the shoulder, all other items considered labels, will be damaged and replaced as industry has done for decades. Unlike traditional pharmaceutical containers, medical gas containers including the labeling attached to the containers are intended to be reused multiple times. Current industry practice us to inspect all levels and container color as part of the prefill inspection and when necessary replace the label or bring the container into color code compliance prior to it being released for distribution. Containers are typically inspected along the distribution chain to assure they are and remain properly labeled. Missing or improper label condition will cause the container not to be distributed to the end user.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008; 81 FR 81697, Nov. 18, 2016]

Subpart F—Production and Process Controls

§ 211.100 Written procedures; deviations.

(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

§ 211.101 Charge-in of components.

Regulation modified to be appropriate for medical gases

Written production and control procedures shall include the following, which are designed to assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess:

(a) The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient, except for designated medical gas combinations. For designated medical gas combinations, the batch shall be formulated with the intent to provide 100 percent of the label or established amount of ingredients within acceptable tolerances.

(b) Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate, except for designated medical gases. If a component is removed from the original container to another, the new container shall be identified with the following information:

(1) Component name or item code;

(2) Receiving or control number;

(3) Weight or measure in new container;

(4) Batch for which component was dispensed, including its product name, strength, and lot number.

(c) Weighing, measuring, or subdividing operations for components shall be adequately supervised, except for designated medical gases. Each container of component dispensed to manufacturing shall be examined by a second person to assure that:

(1) The component was released by the quality control unit;

(2) The weight or measure is correct as stated in the batch production records;

(3) The containers are properly identified.

(d) Component shall be added to the batch by one person and verified by a second person. For designated medical gases, verification by analytical methods may substitute for second person verification.

(e) For designated medical gases or combinations thereof, adding components into in-process supply or final product containers shall be weighed or measured as appropriate. Final product and in-process supply containers shall identify the name of the component or the name and percentage of each component if multiple components, and the unique lot number assigned.

Final product containers shall identify the name of the component or the name and percentage of each component if a mixture.

Rationale for modification

For subparagraph (a) modification: Historically, designated medical gas combinations including medical air have been formulated with allowable tolerances. For example, medical air may contain between 19.5 and 23.5 percent oxygen per the USP monograph.

For subparagraphs (b) – (e) modifications: Designated medical gases are manufactured through continuous processes (e.g. air separation plants) and filled in closed, pressurized systems. Verification of designated medical gas mixtures occurs through analytical testing of each cylinder filled which is a more accurate verification of the process.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

§ 211.103 Calculation of yield.

Regulation modified to be appropriate for medical gases

Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person. The calculation of yield is not required for designated medical gases or combinations thereof.

Rationale for modification

This requirement is not applicable to designated medical gases because there will not be any issues of super potency, subpotency, or contamination (i.e. addition of a component that is not intended to be in the final product because designated gases are single component and containers of mixtures of designated gases are individually tested). Designated medical gas manufacturing is designed to involve natural product loss associated with the vaporization of liquefied gases in the manufacturing process. More detailed rationale can be found in Citizen's Petition 94P-0426/CP1 and CGA's comments to the 2003 Draft Guidance for Medical Gases discussing changes of modality (i.e. liquid to gas) and use of bulk product for industrial as well as medical finished product manufacturing.

[73 FR 51932, Sept. 8, 2008]

§ 211.105 Equipment identification.

Regulation modified to be appropriate for medical gases

(a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

(b) Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

(c) This section does not apply to designated medical gases or combinations thereof.

Rationale for modification

Equipment installed for designated medical gas manufacturing is specific for the gas being filled (e.g. bulk tanks, cryogenic pumps, manifolds, etc.). The manufacturing of bulk medical gases is a continuous process and all the equipment in the plant is necessary for the production process.

§ 211.110 Sampling and testing of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall 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 shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

(1) Tablet or capsule weight variation;

(2) Disintegration time;

(3) Adequacy of mixing to assure uniformity and homogeneity;

(4) Dissolution time and rate;

(5) Clarity, completeness, or pH of solutions;

(6) Bioburden testing.

(b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.

(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

(d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

§ 211.111 Time limitations on production.

When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.

§ 211.113 Control of microbiological contamination.

(a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

§ 211.115 Reprocessing.

(a) Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics.

(b) Reprocessing shall not be performed without the review and approval of the quality control unit.

Subpart G—Packaging and Labeling Control

§ 211.122 Materials examination and usage criteria.

Regulation modified to be appropriate for medical gases

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product.

(b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

(c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.

(d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel.

(e) Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.

(f) Use of gang printing of labeling for different drug products or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color.

(g) If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures:

(1) Dedication of labeling and packaging lines to each different strength of each different drug product.

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

(3) 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 shall be performed by one person and independently verified by a second person.

(h) Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.

(i) For designated medical gases or combinations thereof, labels that meet all appropriate requirements, may be reused if they are legible and properly affixed to the container.

Rationale for modification

This section has been modified to reflect current industry standards and practice which is consistent with historical FDA enforcement. For example, medical gas labels are typically reused multiple times and are inspected to assure continued compliance when the cylinder is refilled.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41353, Aug. 3, 1993; 77 FR 16163, Mar. 20, 2012]

§ 211.125 Labeling issuance.

Regulation modified to be appropriate for medical gases

(a) Strict control shall be exercised over labeling issued for use in drug product labeling operations.

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

(c) Procedures shall be utilized to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with § 211.192. Labeling reconciliation is ~~also~~ waived for designated medical gases, including lot number decals, if a 100% examination for correct labeling is performed in accordance with 211.122(g)(1) or 211.122(g)(3). ~~360° wraparound labels on portable cryogenic medical gas containers.~~

(d) All excess labeling bearing lot or control numbers shall be destroyed.

(e) Returned labeling shall be maintained and stored in a manner to prevent mixups and provide proper identification.

(f) Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

(g) 211.125 (a) - (f) is waived for 360° wraparound labels on portable cryogenic medical gas containers.

Rationale for modification

211.125(c) - Label reconciliation is not appropriate for designated medical gases because designated medical gas labels are reused and 100-percent of designated medical gas cylinders labeling is verified. Product labels may be reused therefore separate decals must be used for lot numbers. These decals are not pre-numbered and therefore reconciliation is not required.

211.125(g) – 360° degree wraparound decals have been used by the industry for well over a decade. FDA now considers them labels. These wraparound decals/labels are neither issued or reconciled. Although FDA exempted wraparound labels from reconciliation in 211.125(c), it is appropriate to waive all requirements listed under 211.125.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993; 81 FR 81697, Nov. 18, 2016]

§ 211.130 Packaging and labeling operations.

Regulation modified to be appropriate for medical gases

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products.

(b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

(c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

(e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

(f) For designated medical gases, drug products shall be identified with a lot number during labeling operations. The net contents and lot number may be applied to the cylinder by use of a separate identification sticker or decal.

Product labels can be reused provided they match the approved current label revisions and all information on the label is readable.

Bulk designated medical gas containers are exempt from this section provided shipping documents follow federally mandated transportation regulations to identify the drug product.

(g) Packaging and labeling operations (211.130) are waived for 360° wraparound labels on portable cryogenic medical gas containers.

Rationale for modification

211.130(f) – The first two paragraphs of subparagraph (f) are consistent with modifications in 211.122 and 211.125. Bulk manufacturers do not utilize specific product labels on bulk storage tanks or on bulk trailers, as addressed in the third paragraph of subparagraph (f). Transportation of designated medical gases in bulk trailers must follow DOT regulations.

211.130(g) – Per the rationale for the change in 211.125(g), 360° degree wraparound decals/labels do not require label control.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993]

§ 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.

(a) *General.* The Food and Drug Administration has the authority under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national requirement for tamper-evident packaging of OTC drug products that will improve the security of OTC drug packaging and help assure the safety and effectiveness of OTC drug products. An OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 501 of the act or misbranded under section 502 of the act, or both.

(b) *Requirements for tamper-evident package.*

(1) Each manufacturer and packer who packages an OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale shall package the *product* in a tamper-evident package, if this product is accessible to the public while held for sale. A tamper-evident package is one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design or by the use of one or more indicators or barriers to entry that employ an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term "distinctive by design" means the packaging cannot be duplicated with commonly available materials or through commonly available processes. A tamper-evident package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-evident feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

(2) In addition to the tamper-evident packaging feature described in paragraph (b)(1) of this section, any two-piece, hard gelatin capsule covered by this section must be sealed using an acceptable tamper-evident technology.

(c) Labeling.

(1) In order to alert consumers to the specific tamper-evident feature(s) used, each retail package of an OTC drug product covered by this section (except ammonia inhalant in crushable glass ampules, containers of compressed medical oxygen, or aerosol products that depend upon the power of a liquefied or compressed gas to expel the contents from the container) is required to bear a statement that:

(i) Identifies all tamper-evident feature(s) and any capsule sealing technologies used to comply with paragraph (b) of this section;

(ii) Is prominently placed on the package; and

(iii) Is so placed that it will be unaffected if the tamper-evident feature of the package is breached or missing.

(2) If the tamper-evident feature chosen to meet the requirements in paragraph (b) of this section uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say "For your protection, this bottle has an imprinted seal around the neck."

(d) *Request for exemptions from packaging and labeling requirements.* A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an

exemption is required to be submitted in the form of a citizen petition under 10.30 of this chapter and should be clearly identified on the envelope as a "Request for Exemption from the Tamper-Evident Packaging Rule." The petition is required to contain the following:

(1) The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class.

(2) The reasons that the drug product's compliance with the tamper-evident packaging or labeling requirements of this section is unnecessary or cannot be achieved.

(3) A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration.

(4) Other information justifying an exemption.

(e) *OTC drug products subject to approved new drug applications.* Holders of approved new drug applications for OTC drug products are required under 314.70 of this chapter to provide the agency with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labeling required by this regulation may be made before FDA approval, as provided under 314.70(c) of this chapter. Manufacturing changes by which capsules are to be sealed require prior FDA approval under 314.70(b) of this chapter.

(f) *Poison Prevention Packaging Act of 1970.* This section does not affect any requirements for "special packaging" as defined under 310.3(l) of this chapter and required under the Poison Prevention Packaging Act of 1970.

[54 FR 5228, Feb. 2, 1989, as amended at 63 FR 59470, Nov. 4, 1998]

§ 211.134 Drug product inspection.

Regulation modified to be appropriate for medical gases

(a) Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.

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

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

(d) For designated medical gases, 100% examination of product label is performed during the overall fill process.

Rationale for modification

§ 211.134 (b) is not applicable to designated medical gas manufacturers. Representative sample is inadequate for label inspection of medical gas cylinders because 100% examination is performed. Since containers and labels are reused, labels are inspected prior to fill.

§ 211.137 Expiration dating.

Regulation modified to be appropriate for medical gases

(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in § 211.166.

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

(c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products.

(d) Expiration dates shall appear on labeling in accordance with the requirements of § 201.17 of this chapter.

(e) Homeopathic drug products shall be exempt from the requirements of this section.

(f) Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.

(g) 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. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product.

(h) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

(i) Designated medical gases or combinations thereof shall be exempt from the requirements of this section.

Rationale for modification

Designated medical gases or combinations thereof do not deteriorate over time, are maintained in a closed, pressurized system and are not affected by environmental conditions. CGA's Citizen's Petition 79P-0067/CP requests an exemption from expiration dating for designated medical gases or combinations thereof. This petition includes both high pressure and cryogenic medical gases.

[43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981; 60 FR 4091, Jan. 20, 1995]

Subpart H—Holding and Distribution

§ 211.142 Warehousing procedures.

Regulation modified to be appropriate for medical gases

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

(a) Quarantine of drug products before release by the quality control unit.

(b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected. Designated medical gases or combinations thereof are exempt from § 211.142 (b).

Rationale for modification

Designated medical gases or combinations thereof are stored in a closed, pressurized system and the identity, strength, purity and quality are not impacted by environmental conditions.

§ 211.150 Distribution procedures.

Regulation modified to be appropriate for medical gases

Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

(a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate. Designated medical gases or combinations thereof are exempt from § 211.150 (a).

(b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

Rationale for modification

"First In, First Out" is not necessary for designated medical gases or combinations thereof since they do not expire or degrade over time.

Subpart I—Laboratory Controls

§ 211.160 General requirements.

(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.

(4) 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. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]

§ 211.165 Testing and release for distribution.

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a)(2).

(f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

§ 211.166 Stability testing.

Regulation modified to be appropriate for medical gases

(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:

(1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;

(2) Storage conditions for samples retained for testing;

(3) Reliable, meaningful, and specific test methods;

(4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed;

(5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

(c) For homeopathic drug products, the requirements of this section are as follows:

(1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.

(2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.

(d) Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.

(e) Designated medical gases or combinations thereof are exempt from the requirements of this section.

Rationale for modification

Designated medical gases or combinations thereof do not deteriorate over time. CGA's Citizen's Petition 79P-0067/CP requests an exemption from expiration dating for oxygen USP, nitrogen NF, medical air USP, helium USP, carbon dioxide USP, nitrous oxide USP, mixtures of helium USP and oxygen USP, and mixtures of oxygen USP and carbon dioxide USP. This petition includes both high pressure and cryogenic medical gases.

[43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981]

§ 211.167 Special testing requirements.

(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.

(b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.

(c) For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

§ 211.170 Reserve Samples.

Regulation modified to be appropriate for medical gases

(a) An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is as follows:

(1) For an active ingredient in a drug product other than those described in paragraphs (a) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.

(2) For an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.

(3) For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under 211.137, the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.

(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from

representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with 211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. ~~Reserve samples of compressed medical gases need not be retained.~~ The retention time is as follows:

(1) For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product.

(2) For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days.

(3) For an OTC drug product that is exempt for bearing an expiration date under 211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed.

(c) Medical gases or combinations thereof are exempt from the requirements of this section.

Rationale for modification

Although the exemption from reserve samples was previously contained in 211.170(b), industry believes it should be a separate regulation for designated medical gases or combinations thereof. Designated medical gases or combinations thereof are not the subject of stability issues, therefore retention of samples for future testing is not required.

[48 FR 13025, Mar. 29, 1983, as amended at 60 FR 4091, Jan. 20, 1995]

§ 211.173 Laboratory animals.

Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.

§ 211.176 Penicillin contamination.

If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in `Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD-470), Center for Drug Evaluation and Research, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*

[43 FR 45077, Sept. 29, 1978, as amended at 47 FR 9396, Mar. 5, 1982; 50 FR 8996, Mar. 6, 1985; 55 FR 11577, Mar. 29, 1990; 66 FR 56035, Nov. 6, 2001; 69 FR 18803, Apr. 9, 2004; 81 FR 49897, July 29, 2016]

Subpart J—Records and Reports

§ 211.180 General requirements.

(a) 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 a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products or designated medical gases or combinations thereof lacking expiration dating because they meet the criteria for exemption under § 211.137, 3 years after distribution of the batch.

(b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products or designated medical gases or combinations thereof lacking expiration dating because they meet the criteria for exemption under § 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.

Rationale for modification

211.180(a) and (b) modified to define record retention for designated medical gases or combinations thereof given that designated medical gases do not bear expiration dates. The current industry practice for record retention is 3 years after distribution of a lot.

(c) All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.

(d) Records required under this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.

(e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

(1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.

(2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under § 211.192 for each drug product.

(f) Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under §§ 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

§ 211.182 Equipment cleaning and use log.

Regulation modified to be appropriate for medical gases

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one

product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

For designated medical gases or combinations thereof, cleaning and maintenance is performed on a periodic basis and is not associated with a batch or lot process. Equipment cleaning and non-routine maintenance is documented on separate cleaning or maintenance records.

Rationale for modification

Designated medical gases are manufactured and filled utilizing pressurized closed systems and equipment should not be cleaned between batches and lots. Significant cleaning is performed when initially assembled and prior to commissioning. Unnecessary cleaning could introduce a contaminant.

[73 FR 51933, Sept. 8, 2008]

§ 211.184 Component, drug product container, closure, and labeling records.

Regulation modified to be appropriate for medical gases

These records shall include the following:

(a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in § 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known. Designated medical gases or combinations thereof are not required to identify and quantify each lot of drug product containers and closures. Designated medical gases are not required to quantify each lot of components.

(b) 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.

(c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure. Designated medical gases or combinations thereof are not required to have an individual inventory record of components, drug product containers and closures.

(d) Documentation of the examination and review of labels and labeling for conformity with established specifications in accord with §§ 211.122(c) and 211.130(c).

(e) The disposition of rejected components, drug product containers, closure, and labeling.

Rationale for modification

For subparagraphs (a) and (c): These requirements do not apply to designated medical gas containers and closures as they are inspected immediately prior to use in the manufacturing operations. Drug product containers and closures for designated medical gases or combinations thereof are reused multiple times and are not associated with a particular lot.

§ 211.186 Master production and control records.

Regulation modified to be appropriate for medical gases

(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of

master production and control records shall be described in a written procedure and such written procedure shall be followed.

(b) Master production and control records other than for designated medical gases or combinations thereof shall include:

(1) The name and strength of the product and a description of the dosage form;

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;

(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;

(5) A statement concerning any calculated excess of component;

(6) A statement of theoretical weight or measure at appropriate phases of processing;

(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to § 211.192 is required;

(8) A description of the drug product containers, 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;

(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

(c) Master production and control records for designated medical gases are the firms Standard Operating Procedures (SOPS) or quality manual. Designated medical gas manufacturers shall develop procedures for the manufacturing, labeling, testing, packing, holding, distributing, documentation, and quality control activities that include the dated signature of the individual(s) responsible for these procedures and the dated signature of a second quality control individual that independently approved these procedures.

Rationale for modification

Section (c) identifies industry's long-standing practice and is consistent with industry standards.

§ 211.188 Batch production and control records.

Regulation modified to be appropriate for medical gases

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:

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

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

(1) Dates;

(2) Identity of individual major equipment and lines used;

(3) Specific identification of each batch of component or in-process material used;

(4) Weights and measures of components used in the course of processing;

(5) In-process and laboratory control results;

(6) Inspection of the packaging and labeling area before and after use;

(7) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

(8) Complete labeling control records, including specimens or copies of all labeling used;

(9) Description of drug product containers and closures;

(10) Any sampling performed;

(11) Identification of the persons performing and directly supervising or checking each significant step in the operation;

(12) Any investigation made according to § 211.192.

(13) Results of examinations made in accordance with § 211.134.

(c) Designated medical gases or combinations thereof shall be exempt from the requirements of this section.

Rationale for modification

Appropriate production and control records for designated medical gases or combinations thereof have been added to the new proposed section 211.189.

An Air Separation Unit (ASU) typically runs continuously, 24 hours a day, 365 days a year. Performing a batch analysis on a tank where the product is continually monitored as it enters the bulk storage tank provides no value nor does it improve the safety of the product. The product is not only tested continuously but then each trailer of medical product is also tested. This provides assurance the product meets specifications. The ASU has been validated with an emphasis around the make to tank analyzers and product trip functions to ensure the integrity of the storage tank is always maintained. This regulation, as written, has been interpreted to require medical gas product be diverted and vented while the bulk tank "batch" analysis is being performed or tanks be emptied prior to creating a new "batch" which is wasteful and unnecessary.

In addition, 211.188(b)(7) & (8) are not appropriate for designated medical gases as calculation of yield is not logical as described in section 211.103.

Finally, applying an actual cylinder label to the batch record is not logical because of the following reasons:

- *the manual application of a sample label to the batch record provides no additional safety assurance that it matches the manual application on the cylinder as would be the case in traditional pharmaceutical automated applications;*
- *labels are reused; and*
- *therefore a 100% inspection of cylinder labels is performed during the production process.*

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51933, Sept. 8, 2008]

§ 211.189 Production and control records for designated medical gases.

Current regulation

§ 211.189 does not currently exist.

Regulation modified to be appropriate for medical gases

(a) For designated medical gases manufactured by continuous operation

(1) Documentation that significant events in the manufacture, processing or holding of the drug product produced during the continuous operation was accomplished, including:

(i) Dates and times of significant events including in-process and laboratory control results as applicable;

(ii) Identification of drug product container (bulk storage tank);

(iii) Final product testing results as applicable (i.e after plant upset);

(iv) Dated signature or initials of the persons completing the operation log; and

(v) Batch traceability is maintained by the testing and release of each bulk trailer.

(b) For designated medical gases manufactured by batch process

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

(i) Dates;

(ii) Identification of individual storage tanks being batched;

(iii) Specific identification of each component or in-process material used as applicable;

(iv) Measures of components used in the course of processing as applicable;

(v) Results of laboratory tests for finished medical gas;

(vi) Dated signature or initials of the persons performing laboratory tests, and the individual assigned to perform QCU functions;

(vii) Any investigation made according to § 211.192;

(viii) Results of examinations made in accordance with § 211.134;

(c) For designated medical gases manufactured by filling containers by lot;

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

(i) Dates;

(ii) Identification of the source supply(s);

(iii) Specific identification of each component;

(iv) Measures of components used in the course of processing as applicable;

(v) Label application and reconciliation record as appropriate, including identification of the labeling used if multiple product labels are used for the same medical gas;

(A) A specimen or photocopy of the product label applied does not need to be attached to the batch production record.

(vi) Results of laboratory tests for finished medical gas;

(vii) Dated signature or initials of the filler, analyst, and the individual assigned to perform quality control unit (QCU) functions;

(viii) As appropriate results of examinations made in accordance with § 211.134;

Rationale for modification

Section 211.189 was developed to address the uniqueness of the following processes:

- *The air separation unit is a continuous process and does not meet the traditional batch model;*
- *Defines the manufacturing of designated medical gases using a more traditional batch model; and*
- *Defines the filling of designated medical gases into high pressure and liquefied containers using the lot process.*

§ 211.192 Production record review.

All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation, where appropriate, shall be made and shall include the conclusions and followup. For designated medical gases or combinations thereof, investigations are not required for prefill or in-process container non-conformance which does not impact the identity or strength of the drug product.

Rationale for modification

Containers and closure non-conformance discovered during prefill or in-process inspections are not traceable to a root cause and do not impact final product quality therefore, investigations into these non-conformances is not required.

§ 211.194 Laboratory records.

Regulation modified to be appropriate for medical gases

(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

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

(2) A statement of each method used in the testing of the sample. The statement shall indicate the location of 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. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods,{2} or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use.

(3) A statement of the weight or measure of sample used for each test, where appropriate.

(4) 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 component, drug

product container, closure, in-process material, or drug product, and lot tested. Only visual observation and subsequent manual recording is required for analytical equipment that provides a direct reading or requires a simple math calculation using a direct reading.

(5) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors. It is not necessary to provide the actual calculation where the result is evident through use of simple addition and subtraction (for example 100 – 0.1 = 99.9).

(6) A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.

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

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

(b) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall 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.

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

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

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

Rationale for modification

Certain common analytical equipment only provides a visual indication of the analysis. It is not necessary to provide the actual calculation where the result is evident through use of simple addition and subtraction (for example 100 – 0.1 = 99.9).

[43 FR 45077, Sept. 29, 1978, as amended at 55 FR 11577, Mar. 29, 1990; 65 FR 18889, Apr. 10, 2000; 70 FR 40880, July 15, 2005; 70 FR 67651, Nov. 8, 2005]

§ 211.196 Distribution records.

Regulation modified to be appropriate for medical gases

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For ~~compressed~~ designated medical gases or combinations thereof ~~products~~, distribution records are not required to contain a description of dosage form, lot or control numbers.

Rationale for modification

Designated medical gas distribution records do not require a description of the dosage form as it is uniquely prescribed by a licensed practitioner. These changes align with FDASIA.

[49 FR 9865, Mar. 16, 1984]

§ 211.198 Complaint files.

Regulation modified to be appropriate for medical gases

(a) Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with § 211.192. Such procedures shall 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 § 310.305 of this chapter.

(b) A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products and designated medical gases or combinations thereof lacking expiration dating because they meet the criteria for exemption under § 211.137, such written records shall be maintained for 3 years after distribution of the drug product.

(1) The written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant.

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

(3) Where an investigation under § 211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

Rationale for modification

To be consistent with 211.137 and to define record retention for designated medical gases or combinations thereof.

[43 FR 45077, Sept. 29, 1978, as amended at 51 FR 24479, July 3, 1986; 68 FR 15364, Mar. 31, 2003]

Subpart K—Returned and Salvaged Drug Products

§ 211.204 Returned drug products.

Regulation modified to be appropriate for medical gases

Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of § 211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed. Designated medical gases in cryogenic medical gas containers containing residual product are not considered returned drug products.

Rationale for modification

Cryogenic medical gas containers typically contain residual product upon their return to the manufacturer. These containers are not considered returned drug product and can be refilled per a firm's procedure.

§ 211.208 Drug product salvaging.

Regulation modified to be appropriate for medical gases

Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition shall be maintained for drug products subject to this section.

Designated medical gases or combinations thereof may be salvaged unless their containers have been subjected to adverse conditions that impact the identity, strength, quality, and purity of the product. Procedures for the holding, testing, and reprocessing of salvaged designated medical gases or combinations thereof shall be in writing and shall be followed.

Rationale for modification

The identity, strength, quality, and purity of the designated medical gases or combinations thereof are not impacted when in containers that are subjected to adverse conditions identified in the existing regulations such as extremes in temperature, humidity, smoke, fumes, pressure, and age.

References

Unless otherwise specified, the latest edition shall apply.

[1] *Food and Drug Administration Safety and Innovation Act,* Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20401. www.gpo.gov

[2] *Code of Federal Regulations*, Title 21 CFR (Food and Drugs), Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20401. www.gpo.gov

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