**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Parts 201 and 211**

**[Docket No. 2005N–0437]**

## Medical Gas Containers and Closures; Current Good Manufacturing Practice Requirements

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend its current good manufacturing practice (CGMP) regulations to include new requirements for the label, color, dedication, and design of medical gas containers and closures. These requirements are intended to do the following: Make the contents of medical gas containers more readily identifiable, reduce the likelihood that containers of industrial or other gases would be inappropriately connected to medical oxygen supply systems, and reduce the risk of contamination of medical gases. FDA is also proposing to include medical air, oxygen, and nitrogen among, and exclude cyclopropane and ethylene from, those gases intended for drug use that are exempt from certain labeling requirements.

**DATES:** Submit written or electronic comments by July 10, 2006. Submit written comments on the information collection requirements by May 10, 2006. See section VII of this document for the proposed effective date of a final rule based on this document.

**ADDRESSES:** You may submit comments, identified by Docket No. 2005N–0437, by any of the following methods:

*Electronic Submissions*

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

*Written Submissions*

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

*Instructions*: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the ''Request for Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

*Docket*: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Duane Sylvia, Center for Drug Evaluation and Research (HFD–326), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–9040, e-mail: *Duane.Sylvia@FDA.HHS.GOV*.

**SUPPLEMENTARY INFORMATION:**

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### I. Background

*A. Need for Revised Regulations*

FDA is proposing to add requirements to its CGMP regulations to address repeated incidents of medical gasmixups (e.g., the inappropriate administration of an industrial gas to a patient intended to receive a medical gas) and medical gas contamination that have resulted in serious patient injuries and even deaths. As explained in this document, FDA believes that the number of such incidents will be reduced by implementation of the medical gas label, color, design, and dedication requirements proposed in section II.B of this document.

Between 1996 and April 2004, FDA received several reports of medical gas mixups that resulted in at least 8 patient deaths and 16 serious patient injuries. Because nursing homes and hospitals are not required to report adverse events associated with medical gas mixups to FDA, it is likely that the actual number of these events exceeds the number reported. The reports FDA has received involve two major types of containers in which medical gases are currently stored, portable cryogenic containers and high-pressure medical gas cylinders.

1. Incidents Involving Portable Cryogenic Containers

Portable cryogenic containers are used to store gases in liquid form at extremely low temperatures and pressures. These containers are made of stainless steel and are double-walled and vacuum-insulated to minimize the evaporation and venting of their contents. FDA is aware of at least 7 deaths and 12 serious injuries that occurred between 1996 and April 2004

in connection with mixups of gases stored in portable cryogenic containers. Each of these incidents involved the improper connection of a portable cryogenic container holding an industrial gas to a health care facility's oxygen supply system.

Portable cryogenic gas containers have gas-specific use outlet connections that are used to connect the containers to supply systems. Oxygen supply systems are compatible only with gas use outlet connections designed for portable cryogenic containers holding oxygen. In each of the incidents of which FDA is aware, described in more detail in the following paragraphs, the person making the faulty connection to the health care facility's oxygen supply system: (1) Did not check the label on the portable cryogenic container that was inappropriately connected or was not otherwise able to verify the container's contents and (2) was able to readily remove the oxygen-specific gas use outlet connection from an empty medical oxygen container and use it to inappropriately connect the industrial gas container to the supply system.

On December 7, 2000, four patients in a Bellbrook, Ohio, nursing home died and six were injured after being administered industrial nitrogen instead of oxygen. The nursing home had received a shipment of four portable cryogenic medical gas containers. Each was labeled medical oxygen, but one of the containers also bore an industrial nitrogen label that partially obscured the medical oxygen label and was filled with industrial nitrogen instead. When asked to select a new oxygen container, a nursing home employee mistakenly selected the nitrogen container. The employee was initially unable to connect the container to the oxygen supply system because the container's nitrogen-specific gas use outlet connection was incompatible with the connector on the oxygen supply system. However, the employee ultimately made the fatal connection by removing an oxygen-specific gas use outlet connection from an empty portable cryogenic medical oxygen container and by substituting it for the nitrogen-specific connection on the industrial nitrogen container.

On April 22, 1998, a portable cryogenic container of industrial nitrogen was improperly connected to the oxygen supply system for the operating rooms, labor and delivery rooms, and emergency room in an Idaho hospital. The connection was enabled when the supplier's truck driver used a wrench to disconnect the container's existing nitrogen gas use outlet connection, which was incompatible with the hospital's oxygen supply system, and replaced it with a compatible oxygen gas use outlet connection. Two patients died after receiving nitrogen through this misconnection.

On October 14, 1997, a hospital in Nebraska received a shipment of medical oxygen in portable cryogenic containers. The shipment included one portable cryogenic container of industrial argon. The hospital was running low on oxygen and sent a maintenance employee to connect an oxygen container to the oxygen supply system. Although it was properly labeled, the employee selected the argon container without examining its label. When he was unable to connect the container to the oxygen supply system, the employee removed an oxygen gas use outlet connection from an empty portable cryogenic medical gas container, installed it in place of the argon gas use outlet connection on the industrial argon container, and connected the argon container to the oxygen supply system. Argon was administered to a patient undergoing minor surgery who died as a result of this mixup.

On December 2, 1996, nine patients in a children's home in New York experienced adverse reactions after inhaling carbon dioxide in a medical gas mixup. Two of the patients were injured critically and four patients experienced varying stages of respiratory distress following this mixup. The mixup resulted when an employee of the home mistakenly attached a carbon dioxide container to the home's oxygen supply system.After noting that the gas use outlet connection on the carbon dioxide container was not compatible with the connector on the oxygen supply system, the employee removed a gas use outlet connection from an empty medical oxygen container, installed it on the carbon dioxide container, and attached the carbon dioxide container to the home's oxygen supply system.

In addition to the deaths and serious injuries described earlier in this preamble, FDA is aware of other serious cases of medical gas mixups involving portable cryogenic containers. For example, on December 19, 2000, a mixup occurred in a hospital in Arizona. A ventilator alarm sounded during a surgical procedure, and the anesthesiologist quickly removed the ventilator after noticing that the patient's oxygen saturation level was decreasing. An investigation revealed that a portable cryogenic container of industrial nitrogen had been mistakenly connected to the hospital's oxygen supply system. To make the connection, the nitrogen tank's original gas use outlet connection was removed and replaced with an oxygen-specific gas use outlet connection. Although the anesthesiologist's quick response avoided patient injury in this instance, the mixup was caused by events that have resulted in death and serious injury in other cases, such as the ones previously discussed.

FDA anticipates that mixups like those described earlier in this document will be largely averted if: (1) Users can more readily identify portable cryogenic containers that contain medical gases and (2) the gas use outlet connections on these containers cannot be readily removed by persons other than the manufacturers responsible for filling them. As detailed in section II.B of this document, FDA is proposing requirements to achieve these effects. As further discussed in section I.B of this document, the proposed requirements are intended to supplement existing CGMP requirements and related agency guidance and industry recommendations regarding the safe use of medical gases. Existing agency requirements and guidance already address appropriate education and training for persons responsible for connecting portable cryogenic containers to medical gas systems (e.g., training such persons to check the containers' labels and to understand that the containers' gas-specific use outlet connections are safeguards against mixups and that they are not to be removed.)[1]

2. Incidents Involving High-Pressure Medical Gas Cylinders

High-pressure medical gas containers are used to store gases at relatively high pressures and ambient temperatures. These containers are tubular in design and are constructed of steel or aluminum. Between 1996 and April 2004, FDA received several reports of serious injury attributable to high-pressure medical gas cylinders that were contaminated with residue of industrial cleaning solvents, most likely as a result of improper cleaning during the cylinders' conversion from industrial to

[1] See 21 CFR 211.25(a). The agency's draft guidance for industry on ''Current Good Manufacturing Practice for Medical Gases'' (66 FR 24005, May 6, 2003) and its ''Guidance for Hospitals, Nursing Homes, and Other Health Care Facilities—FDA Public Health Advisory'' (66 FR 18257, April 6, 2001), both discussed in section I.B. of this document, contain specific recommendations for, among other things, the appropriate education and training of health care facilities' and medical gas manufacturers' employees who are involved in handling medical gases and their containers. These guidances are available on the Internet at *http://www.fda.gov/cder/guidance/index.htm*.

medical use. There have also been incidents in which industrial gases in high-pressure cylinders have been mistakenly identified for medical use and their contents inappropriately administered to patients, resulting in injury and death. Examples of incidents involving high-pressure medical gas cylinders are described in the following paragraphs.

On July 12, 1999, a hospital in California reported the death of a patient after carbon dioxide was mistakenly administered instead of oxygen. Although it had an appropriate carbon dioxide gas use outlet connection and label, the shoulder of the high-pressure cylinder containing the carbon dioxide was improperly color-marked in green. According to voluntary color standards adopted by the Compressed Gas Association (CGA) and largely followed by industry, green is the standard color used to indicate a high-pressure medical oxygen cylinder.

On March 20, 1998, a surgery center in South Dakota reported that a strong chlorine-like odor emanated from a patient's high-pressure medical oxygen cylinder during surgery.An analysis of the cylinder revealed that it contained traces of freon. It is likely that the root cause of the contamination was inadequate cleaning during the cylinder's conversion from industrial to medical use. In this case, the patient experienced burning eyes and respiratory problems.

On March 27, 1996, a surgical center in Florida detected a chlorine/bleach-like odor emanating from its oxygen supply system, which was comprised of several high-pressure medical gas cylinders. An analysis of the high-pressure cylinders revealed contaminating traces of benzene and xylene that were likely attributable to improper cleaning of the cylinders during their conversion from industrial to medical use. Several patients experienced minor respiratory problems as a result of the contamination.

FDA anticipates that incidents like those described in this subsection can be avoided if, as proposed in this document, all high-pressure medical gas cylinders are painted in the standard colors for identifying gases adopted by the CGA and if, as also proposed, high-pressure cylinders used to hold industrial gases are not converted to medical use. As discussed in section II.B of this document, FDA does not intend to prohibit the continued medical use of high-pressure gas cylinders that have been appropriately converted from industrial to medical use before the date that the requirements proposed in section II.B are finalized and take effect, as long as such cylinders remain dedicated solely to medical use on and after that date.

*B. Current Regulatory Requirements and Recommendations for Medical Gas Containers and Closures*

As detailed in this subsection, medical gas containers and closures are currently addressed by many regulations, guidances, voluntary standards, and recommendations that promote the safe and effective use of medical gases. The proposals in section II.B of this document are intended to supplement, rather than supercede, existing regulations and guidance by adding requirements, based largely on current industry practices, to minimize the incidence of adverse events like those previously described.

All medical gases,[2] including those produced by the air liquefaction process[3] or processed, purified, or refined from a raw material, are prescription drugs under sections 201(g)(1)and 503(b)(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(g)(1) and 353(b)(1)). As such, medical gases are subject to regulation under, among others, section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)) and parts 210 and 211 (21 CFR parts 210 and 211).

Medical gas containers and closures, such as portable cryogenic containers and high-pressure cylinders, are integral parts of the drug product. These containers and closures play a critical role in ensuring that the drug product provided to a patient has the appropriate identity, strength, quality, and purity. Under parts 210 and 211, medical gas manufacturers and distributors must comply with specific CGMP requirements applicable to medical gas containers and closures. Medical gas manufacturers include any individual or firm that fills high-pressure medical gas cylinders or cryogenic medical gas containers by any of the following methods: Liquid to liquid, liquid to gas, or gas to gas. This term includes any third-party company (not the original manufacturer or end user) that acquires liquid medical gas and delivers or fills it into a storage tank. In industry vernacular, a manufacturer is more commonly referred to as a filler, a repackager, or a transfiller. Medical gas distributors include any individual or firm that receives and holds, but does not manipulate, compressed or liquid medical gas in labeled high-pressure cylinders or cryogenic containers.

FDA CGMP regulations that currently address the safety of medical gas containers and closures are extensive and include the following:

- Section 211.80(a), which requires manufacturers of medical gases to establish and follow written procedures for the testing and approval or rejection of containers and closures;
- Section 211.82(a), which requires that medical gas containers and closures be inspected visually for appropriate labeling content, container damage or broken seals, and contamination;
- Section 211.84(a), which requires that medical gas containers and closures be withheld from use until they are examined and released by the quality control unit;
- Section 211.84(d)(3), which requires that medical gas containers and closures be tested for conformance with all written procedures; and
- Section 211.94(b), which requires that medical gas container and closure systems provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of a stored drug product.

Additionally, under § 211.100(a) and (b), manufacturers of medical gases must establish and follow written procedures for production and process control to ensure that medical gases meet applicable specifications for identity, strength, quality, and purity. Also, medical gases are subject to the labeling requirements in §§ 211.122 through 211.137 to ensure that they are correctly labeled with respect to their identity and bear appropriate lot numbers and expiration dating. Further, under § 211.42(b), buildings used by manufacturers and distributors of medical gases must have adequate space for the orderly placement of medical gas containers to prevent mixups or contamination. Under § 211.42(c), operations must be performed within specifically defined areas of adequate size to avoid mixups or contamination of gases during manufacturing, packaging, and labeling operations, as well as during the storage of medical gases after release.

As mandated by § 211.25, individuals involved in the manufacture, processing, packing, or holding of medical gases must have the appropriate combination of education, training, and experience to perform their job functions. Further, before release for

[2] Medical gases include: oxygen, Unites States Pharmacopeia (USP), nitrogen, National Formulary, nitric oxide, nitrous oxide USP, carbon dioxide USP, helium USP, medical air USP, and any mixture of these gases or other gas products approved under a new drug application (NDA).

[3] This process involves extracting atmospheric air and separating it into constituent gases (i.e., nitrogen, oxygen, and argon).

distribution, finished product testing must be conducted on medical gases in accordance with § 211.165 to ensure that they conform to final specifications. Medical gas manufacturers are also subject to several recordkeeping and reporting requirements in §§ 211.180 through § 211.198. As earlier noted, the requirements in this subsection will be supplemented by the additional safety measures FDA is proposing for codification in section II.B of this document.

FDA can take several courses of action in response to identified CGMP violations, including the following:

- Issuing a written warning or notice;
- Seizing affected products, including storage tanks, high-pressure medical gas cylinders, portable cryogenic medical gas containers, cryogenic medical gas containers for home use[4] on the company's premises, cryogenic medical gas containers mounted to trucks and vehicles, as well as tankers;
- Seeking an injunction against the manufacturer and/or distributor; and
- Initiating prosecution.

FDA has issued numerous warning letters and initiated numerous seizure actions, injunctions, prosecutions and civil contempt actions to enforce the CGMP regulations as they apply to medical gases and will continue to take such actions where appropriate.

To supplement existing regulations, FDA has issued guidances and other recommendations for the safe use of medical gases. As further discussed in section II.B of this document, several of the provisions FDA is currently proposing would codify as requirements current recommendations to ensure that they are adopted. In the **Federal Register** of May 6, 2003 (68 FR 24005), FDA announced the availability of a draft guidance for industry entitled ''Current Good Manufacturing Practice for Medical Gases'' (May 6, 2003, draft guidance). This draft guidance provides recommendations for CGMP compliance in the manufacture of compressed and cryogenic medical gases. When finalized, it is expected to help manufacturers and distributors comply with CGMP requirements to ensure the identity, strength, quality, and purity of medical gases. Among other things, the draft guidance includes recommendations that are intended to prevent medical gas mixups and are proposed for codification in section II.B of this document (e.g., using standard colors to identify medical gas cylinders and 360° wraparound labels to identify medical gases in portable cryogenic containers). When these proposals are finalized, the guidance will be amended to reflect their codification.

The May 6, 2003, draft guidance referenced in the previous paragraph follows FDA's February 1989 ''Compressed Medical Gases Guideline,'' which addresses the use of medical gases in the home care setting, including the delivery of oxygen to patients at home, as well as FDA's ''Guidance for Hospitals, Nursing Homes, and Other Health Care Facilities—FDA Public Health Advisory'' (66 FR 18257, April 6, 2001). This public health advisory describes incidents of medical gas mixups and provides recommendations for avoiding these types of incidents, including training facility employees to check the labels of medical gases and to avoid removing the gas-specific fittings (i.e., gas use outlet connections) on portable cryogenic medical gas containers. In July 2001, FDA issued a public health advisory that also discusses medical gas mixups and actions recommended to avoid them.[5] This advisory reiterates the importance of checking labels and not changing the fittings or connectors on cryogenic medical gas containers.

In addition to agency efforts, the medical gas industry and other bodies have taken steps to help prevent medical gas mixups and ensure the safe use of medical gases. For example, since 1973, the CGA has issued a color-marking pamphlet recommending that certain standard colors be used to identify the contents of medical gas containers. The current (fourth) edition of this standard, entitled ''CGA C–9--2004 Standard Color Marking of Compressed Gas Containers Intended for Medical Use,'' was issued on March 10, 2004. Most medical gas manufacturers presently use the colors recommended in the CGA standard to mark high-pressure medical gas cylinders so that their contents can be readily identified. Although the stainless steel composition of portable cryogenic containers renders paint more difficult to apply and maintain, manufacturers that fill these containers have also sought to ease the identification of gases held within them by other methods. As further discussed in sections II.B and IV.B of this document, in recent years, a large majority of these manufacturers have used 360° wraparound labels to identify the contents of portable cryogenic containers used for medical gases. The CGA recommended the use of these labels in a safety bulletin issued in 2001.[6]

Manufacturers have also voluntarily designed the gas use outlet connections on portable cryogenic medical gas containers using varying thread dimensions so that these outlet connections are specific to a particular type of gas and compatible only with connectors to supply systems used to deliver the particular gas. For these reasons, gas-specific use outlet connections on portable cryogenic medical gas containers provide a barrier against the misuse of these gases, provided they are not removed and replaced with, or substituted for, outlet connections specific to a different type of gas. To help ensure that gas use outlet connections on portable cryogenic medical gas containers will not be removed, the CGA has issued a safety bulletin that recommends that these connections be silver brazed or attached by another method to the valve body in a manner that prevents removal or that would render the connection or valve body outlet unusable if removal were attempted or accomplished.[7]

Furthering the safety initiatives discussed in the previous paragraphs, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has encouraged industry's adherence to recommendations provided in FDA's March 2001 ''Guidance for Hospitals, Nursing Homes, and Other Health Care Facilities--FDA Public Health Advisory'' regarding the training of health care employees who handle medical gas containers and the proper storage and handling of these containers.[8] As previously explained, this guidance recommends, among other things, that employees who handle medical gases be trained to carefully check container labels and to avoid changing the gas use outlet connections on cryogenic medical gas containers. In 2002 the JCAHO also added to its Comprehensive Accreditation Manual for Hospitals a description of a hospital medical gas management and training program that emphasized several of the safety measures recommended in FDA's March 2001 guidance. The JCAHO cited this program as an example of how its accreditation standard for utilities

[4] Containers designed to hold liquid oxygen at a patient's home under low pressure and at a very low temperature.

[5] See ''FDA Public Health Advisory: Potential for Injury from Medical Gas Misconnections of Cryogenic Vessels'' (July 20, 2001). This advisory may be accessed on the Internet at *http://www.fda.gov/cdrh/safety/medical-gas-misconnect.html*. Additional information on this subject may be accessed on the Internet at *http://www.fda.gov/cder/consumerinfo/medgas.htm*.

[6] See CGA Safety Bulletin SB-26, 2d edition (November 26, 2001).

[7] See *id*.

[8] See JCAHO Sentinel Event Alert, issue 21 (July 2001).

management (EC.1.7), which addresses in part the reduction of nosocomial (or hospital-related) illnesses and injuries, may be implemented.

Additionally, the National Fire Protection Association (NFPA) recently revised its Standard for Health Care Facilities to include various measures to prevent medical gas mixups.[9] Many State and local governments require health care facilities to comply with NFPA standards. Certain measures adopted by the NFPA, such as wraparound labeling for cryogenic liquid cylinders and the use of gas-specific use outlet connections on such cylinders that are difficult to remove, are similar to requirements that FDA is proposing in section II.B of this document. When followed, existing regulations, guidances, and standards have helped to enhance the safe use of medical gases. However, as previously noted, despite these requirements and recommendations, instances of death and serious injury attributable to medical gas mixups and contamination have continued to occur. The requirements proposed in section II.B of this document will supplement existing requirements and increase the adoption of certain presently voluntary recommendations that help enhance medical gas safety.

## II. Description of Proposed Requirements

### *A. Revisions to Labeling Exemptions*

Section 201.100 (21 CFR 201.100) lists various conditions, which if all are met, exempt prescription drug products from the act's requirement that their labeling bear adequate directions for use. Among others, these conditions include the following:

- The label of the drug bears its recommended or usual dosage (§ 201.100(b)(2)),
- For a drug not intended for oral use, the label bears the drug's route of administration (§ 201.100(b)(3)),
- Labeling on or within the drug's packaging bears adequate information for its use and any relevant hazards, contraindications, side effects, and precautions under which licensed practitioners can use the drug safely and for the purposes for which it is intended (§ 201.100(c)(1)).

Current § 201.161(a) (21 CFR 201.161(a)) states that carbon dioxide, cyclopropane, ethylene, helium, and nitrous oxide gases intended for drug use are exempted from the requirements of § 201.100(b)(2), (b)(3), and (c)(1), provided that their labeling bears, in addition to any other information required by the act: (1) The specific warning set forth in § 201.161(a)(1) regarding use of these gases by experienced and licensed practitioners only, (2) any needed directions concerning the gases' conditions of storage, and (3) warnings against dangers inherent in their handling. FDA is proposing that medical air, oxygen, and nitrogen be added to § 201.161(a)'s list of exempted gases. These drugs were, for various reasons, excluded when § 201.161(a) was originally issued in 1970. However, based on its years of regulatory experience with medical air, oxygen, and nitrogen, FDA believes that compliance with the requirements of § 201.100(b)(2), (b)(3), and (c)(1) is unnecessary for these gases if the warning and direction requirements in § 201.161(a), as well as the labeling and coloring requirements proposed in § 211.94(e)(4) and described in the following paragraphs, are met. In addition, FDA proposes to delete cyclopropane and ethylene from § 201.161(a). These gases are no longer used in medical procedures because they are flammable and pose a risk of explosion or fire.

### *B. Revised Requirements for Medical Gas Containers and Closures*

The proposed rule would add a new paragraph (e) under § 211.94 to provide requirements for medical gas containers and closures. The following proposed requirements would enhance the safe use of medical gases by: (1) Diminishing the likelihood that cryogenic containers or high-pressure cylinders used to store medical gases will be tainted with industrial contaminants, (2) decreasing the likelihood of medical gas mixups attributable to the removal and replacement of gas-specific use outlet connections on portable cryogenic containers, and (3) increasing the likelihood that the contents of high-pressure cylinders and portable cryogenic containers will be easily and accurately identified by persons selecting medical gases for administration to patients. The elements of proposed § 211.94(e) are explained in the following paragraphs.

#### 1. Prohibition on Conversion of Cryogenic Containers and High-Pressure Cylinders From Industrial to Medical Use

Proposed § 211.94(e)(1) would prohibit cryogenic containers and high-pressure cylinders that are used to hold industrial gases from being converted to medical use after the final rule becomes effective. The proposed rule would not prohibit the continued medical use of cryogenic containers or high-pressure cylinders previously used to hold industrial gases if such containers have been appropriately converted to medical use (according to standard industry practice) by the time the final rule takes effect and are used solely for medical purposes thereafter. See proposed § 211.94(e)(2). When finalized, proposed § 211.94(e) would supersede and codify an existing recommendation in FDA's draft guidance for industry on ''Current Good Manufacturing Practice for Medical Gases,'' (68 FR 24005) which recommends, among other things, that high-pressure cylinders and cryogenic containers used for medical gases be dedicated to medical use only.

FDA believes that proposed § 211.94(e)(1) is necessary to minimize the risk of contamination of medical gases by industrial contaminants (e.g., chlorine, hydrocarbons, arsenic compounds, industrial cleaning solvents, or foreign gas residue) and to ensure the safety, quality, and purity of medical gases. After the effective date of the final rule, by prohibiting the conversion of high-pressure cylinders or portable cryogenic containers from industrial to medical use, proposed § 211.94(e)(1) would eliminate any potential uncertainty that might otherwise exist as to whether such a container, if converted to medical use, would have been properly cleaned and purged of industrial gas and contaminants.

#### 2. Requirements for Secure Gas Use Outlet Connections on Portable Cryogenic Medical Gas Containers

Proposed § 211.94(e)(3) would require portable cryogenic medical gas containers that are not manufactured with permanent gas use outlet connections to have gas-specific use outlet connections that are attached to the valve body in such a way that they cannot be readily removed or replaced except by the medical gas manufacturer. This proposed requirement would not apply to high-pressure medical gas cylinders because FDA is not aware of any incidents of gas use outlet connection replacement or removal involving such cylinders or of a likelihood of such incidents.

Proposed § 211.94(e)(3) is designed to prevent the types of incidents (described in section I.B of this document) that have occurred when gas-specific use outlet connections on portable cryogenic containers have been removed and replaced with other outlet connections that permit containers of inappropriate gases to be connected to oxygen supply systems. It has been possible for gas use outlet connections

[9] See NFPA 99; *Standard for Health Care Facilities* (2005 edition).

to be readily removed in cases where the connection is attached by a pipe thread outlet and tape. The proposed rule would require that gas use outlet connections on portable cryogenic medical gas containers be permanently attached to the valve body (e.g., by silver brazing) or otherwise attached to the valve body using a locking mechanism or other appropriate device that precludes the easy removal of the connections by parties other than the manufacturer. As earlier noted in section I.B of this document, the CGA has recommended in part that gas use outlet connections be permanently attached to cryogenic medical gas containers by silver brazing or another method that would prevent the connections' removal. Moreover, as discussed in section IV.B of this document, FDA estimates that approximately 90 percent of the containers that would be subject to this requirement already comply with its terms. Thus, this proposed requirement is consistent with current industry recommendations and practice.

For the purposes of proposed § 211.94(e)(3) and (e)(4) (discussed in the following paragraphs), portable cryogenic medical gas containers include all cryogenic medical gas containers that are both capable of being transported and 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, except small cryogenic containers for use by individual patients in their homes and portable liquid oxygen units that are intended to be distributed empty (i.e., unfilled), as described by § 868.5655 (21 CFR 868.5655). The agency is primarily concerned with situations in which medical gas mixups have most often occurred (i.e., where a portable cryogenic container holding a gas other than oxygen is delivered, and an employee of the gas manufacturer or the receiving facility misidentifies the container and is able (by substituting a gas-specific use outlet connection removed from an oxygen container) to connect the inappropriate container to an oxygen supply system for medical use). Proposed § 211.94(e)(3) and (e)(4) would not apply to cryogenic containers that are too large (e.g., a tank truck or trailer) to be connected to a medical gas supply system.

The proposed rule does not apply to containers of industrial gases because these products are not drugs, and thus would not require manufacturers of such gases to outfit portable cryogenic containers intended for industrial use with gas use outlet connections that are difficult to remove. However, as previously discussed, mixups may result if the gas use outlet connection on a portable cryogenic container holding a particular industrial gas is removed and replaced with a use outlet connection that is specific to a different gas and compatible with a medical gas supply system. Therefore, FDA strongly encourages medical gas manufacturers that handle portable cryogenic containers holding industrial gases, as well as portable cryogenic containers holding medical gases, to make the gas use outlet connections difficult to remove on both their industrial and medical containers. FDA believes that most manufacturers already comply with this recommendation. As noted in the previous paragraphs, the CGA's safety bulletin SB–26 advises, in part, that outlet connections on cryogenic medical gas containers be affixed using silver brazing or another method that prevents their removal. Among other things, this bulletin also advises that outlet connections on cryogenic industrial gas containers be used with a device that deters the connections' removal and provides indication in the case that removal is attempted.[10]

The agency also notes that the delivery, after receipt in interstate commerce, of industrial gas to a medical account in a cryogenic container that is mislabeled as medical gas would be a prohibited act under section 301 of the act (21 U.S.C. 331). Section 201(g)(1)(B) of the act defines drugs as all ''articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man.'' In the circumstances described in this paragraph, the industrial gas delivered to a medical account (such as a hospital or nursing home) and labeled as medical gas would be intended for such a medical use and thus would be a drug. Moreover, because the industrial gas would be unsuitable and improperly labeled for medical use, it would be adulterated and misbranded under sections 501 and 502 of the act (21 U.S.C. 352), respectively. Accordingly, its delivery and sale to a medical facility would violate section 301 of the act. In addition, the responsible individuals from the gas manufacturer and/or distributor could be held liable under the act for the illegal delivery. (See section 303 of the act (21 U.S.C. 333).)

[10] See CGA Safety Bulletin SB–26, 2d edition (November 26, 2001).

3. Requirement for 360° Wraparound Label for Portable Cryogenic Medical Gas Containers

Proposed § 211.94(e)(4)(i) would require each portable cryogenic medical gas container to be conspicuously marked with a 360° wraparound label identifying its contents. (As explained in section II.B.2 of this document, portable cryogenic medical gas containers subject to this requirement would not include small cryogenic containers for use by individual patients in their homes or portable liquid oxygen units intended to be distributed empty, as described in § 868.5655.) This proposed label requirement is intended to make the contents of these containers more readily known to persons responsible for handling and connecting them to medical gas supply systems in hospitals or other health care facilities and thereby reduce the likelihood of medical gas mixups. Unlike high-pressure medical gas cylinders, which, as earlier noted, manufacturers usually voluntarily paint in standard colors to identify their contents, portable cryogenic medical gas containers are rarely colored. Therefore, it is difficult for users to distinguish these containers from portable cryogenic containers holding industrial gases without reading the containers' labels.

As discussed in section I.B of this document, because of their stainless steel construction, it is difficult to apply and maintain paint on portable cryogenic containers. As also noted in section I.B, in recent years most manufacturers have voluntarily identified medical gases stored in these containers using 360° wraparound labels. These labels are currently readily available from several large label manufacturing firms with the specific colors and wording that we are proposing to require. To ensure that all manufacturers use this method to correctly identify medical gas containers, FDA is proposing to require that portable cryogenic medical gas containers be identified using a 360° wraparound label.

Proposed § 211.94(e)(4)(i)(A) would require that each 360° wraparound label bear an FDA-designated standard name for the contained medical gas. Proposed § 211.94(e)(4)(i)(B) would require that the lettering for the standard name appear in either an FDA-designated standard color against a white background, or in white against an FDA-designated color background. Proposed standard names and colors, which are based on those already widely used by industry, are listed in proposed § 211.94(e)(5). All the standard names

proposed in this provision include the word ''medical'' to distinguish containers labeled with these names from those holding industrial gases.

Additionally, because portable cryogenic medical gas containers tend to be fairly large, the agency is proposing in § 211.94(e)(4)(i) (C) that the lettering for the names of medical gases held in these containers be at least 2 3/4 inches high so they can be easily seen. This proposal is based on discussions with industry, which revealed that 2 3/4-inch lettering is the standard size already commonly used by the medical gas industry. FDA is further proposing in § 211.94(e)(4)(i)(D) that the names of the gases be printed continuously on the wraparound label and be capable of being read around the entire container. FDA believes that this proposal, too, reflects existing widespread industry practice. Additionally, proposed § 211.94(e)(4)(i)(E) would require that the label be located on the sidewall near the top of the container but below the top weld seam. FDA understands that placing the label in this location increases its durability and is already common practice. Proposed § 211.94(e)(4)(i)(F) would require that the label be affixed to the container in a manner that ensures that it cannot be easily detached or worn, and that it does not interfere with other labeling.

Although FDA is not proposing to require that portable cryogenic medical gas containers be colored, the agency is aware that, on rare occasions, manufacturers may voluntarily color the shoulders of these containers. To avoid confusion in these cases, manufacturers would be required by proposed § 211.94(e)(4)(i)(G) to use the standard colors designated in proposed § 211.94(e)(5) to identify the gases stored in the containers. If manufacturers choose to color portable cryogenic medical gas containers, the requirement to use the colors designated in proposed § 211.94(e)(5) would be in addition to, and not instead of, the requirement to use the 360° wraparound label in proposed § 211.94(e)(4)(i).

Current § 211.125(c) requires manufacturers to follow procedures to reconcile the quantities of labeling issued, used, and returned, and to evaluate 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. In light of the unique nature of the 360° wraparound labels FDA is proposing for portable cryogenic medical gas containers, the agency has determined that compliance with the reconciliation requirements of § 211.125(c) is not practical for these labels. Compliance would be impractical because the labels are not discrete but, rather, are supplied on a large reel or spool as a continuous string of repeated medical gas names that can be cut into an unfixed number of labels of varying sizes.

4. Requirement to Color High-Pressure Medical Gas Cylinders

Proposed § 211.94(e)(4)(ii) would require that high-pressure medical gas cylinders be identified with a standard color as provided in proposed § 211.94(e)(5). Nonaluminum high-pressure medical gas cylinders would be required to be colored in whole in the applicable standard color. Aluminum high-pressure medical gas cylinders would be required to be colored only on the shoulder portion of the cylinder because the bodies of these cylinders are coated with a thermal indicator that turns a different color when the cylinders have been exposed to fire.

The agency recognizes that hospitals, nursing homes, and other firms or individuals may occasionally purchase high-pressure medical gas cylinders from manufacturers for their own private use. Under proposed § 211.94(e)(4)(ii), manufacturers would be required to color these cylinders in the applicable standard color designated in § 211.94 (e)(5) prior to their sale for private use. FDA understands that private owners may wish to distinguish high-pressure medical gas cylinders they own from those owned by manufacturers and that, in the past, private owners have sometimes distinguished their cylinders by painting them a different color than those owned by manufacturers. To avoid confusion with cylinders painted in the standard colors proposed in § 211.94(e)(5), the agency encourages private owners who wish to distinguish their high-pressure medical gas cylinders to mark those cylinders using a possession sticker or to stencil their name vertically on the body of the cylinders.

The proposed container coloring requirements described in the preceding paragraphs are consistent with present industry practice and should not represent a significant burden for most medical gas manufacturers. Currently, the vast majority of high-pressure medical gas cylinders are voluntarily colored in accordance with the standard colors in proposed § 211.94(e)(5). As discussed in section I.A.2 of this document, at least one death is known to have resulted from an inappropriately colored high-pressure medical gas cylinder. The agency emphasizes that employees responsible for handling medical gases are required to have the training and education necessary to identify a medical gas by reading the container label. However, as past events have demonstrated, individuals responsible for handling medical gases do not always read the labels on these gases carefully. The agency believes that coloring high-pressure medical gas cylinders in standard colors provides an important additional safeguard against the improper use of these cylinders and can be accomplished with minimal burden on industry.

As noted earlier in this document, proposed § 211.94(e)(5) specifies the colors that would be required to be used on the exterior surfaces of high-pressure medical gas cylinders under proposed § 211.94(e)(4)(ii). The colors proposed in § 211.94(e)(5) are the same as those currently recommended by the CGA and voluntarily used by most of the U.S. medical gas industry to identify medical gases. Under proposed § 211.94(e)(4)(ii)(D), high-pressure cylinders holding a mixture or blend of medical gases would be required to be colored with the standard colors representing each component. All colors would be required to be visible when viewed from the top of the cylinder. The portion of the cylinder painted in each color must correspond roughly to the proportion of each gas in the mixture. For example, a mixture of oxygen (95 percent) and carbon dioxide (5 percent) must be represented by a cylinder (or cylinder shoulder, if the cylinder is aluminum) that is predominantly green with a gray band or shoulder.

To ensure that the colors painted on high-pressure medical gas cylinders will endure, under proposed § 211.94(e)(4)(ii)(C), the materials used for coloring would be required to be reasonably resistant to fading and durable when exposed to atmospheric conditions. This provision would further require that the materials not be readily soluble in water after they have been applied and properly dried or cured. The agency declines to specify an exact shade of color or a color specification that must be used under proposed § 211.94(e)(5). However, to avoid confusion, the color shade selected should be such that its hue and intensity, when viewed in normal indoor light, cannot be mistaken for another color by persons having normal color perception.

**III. Legal Authority**

As discussed in section I.B of this document, all medical gases are prescription drugs under sections 201(g)(1) and 503(b)(1) of the act, and

are subject to regulation under section 501(a)(2)(B) of the act and parts 210 and 211. Under sections 701(a) (21 U.S.C. 371(a)) and 501(a)(2)(B) of the act, FDA has the authority to create and modify CGMP regulations to ensure that drugs are safe and have the identity, strength, quality, and purity they are purported or represented to possess. Medical gas containers and closures are integral parts of medical gas drug products and play a critical role in ensuring that these products are safe and have the appropriate identity, strength, quality, and purity. As discussed in section I.B of this document, incidents involving misuse and contamination of medical gases have caused death and serious injury to patients. As also previously discussed, these incidents have occurred despite current regulations and guidances addressing the safe handling of medical gases.

FDA is therefore invoking the authority granted by sections 701(a) and 501(a)(2)(B) of the act to propose CGMP regulations that are designed to prevent the misuse and contamination of medical gases. The specific requirements in these proposed regulations would be an integral part of the manufacturing, processing, packing, and holding of medical gases and help to ensure the safety of these products. These requirements constitute current good manufacturing practice under section 501(a)(2)(B) of the act. In addition to this CGMP statutory authority, the labeling requirements in the proposed regulations (i.e., the use of wraparound labels and standard colors and names) are also authorized under section 502 of the act.

## IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4)). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not an economically significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because, as explained in the following sections of this document, FDA estimates that the proposed rule would result in an annualized cost to small businesses equivalent to 0.1 percent of their revenues or less, the agency believes that the rule is unlikely to have a significant economic impact on a substantial number of small entities. However, since we cannot exclude the possibility of a significant economic impact because of the large number of small businesses that could be affected and the limited amount of data on which the estimate in the previous sentence is based, a regulatory flexibility analysis is included.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

FDA is proposing to amend § 211.94 to require the use of certain safeguards in the production, storage, and use of medical gases. These changes to the CGMP regulations would include new requirements for the label, color, dedication, and design of medical gas containers and closures. Specifically, the amended regulations would require the following: (1) Gas use outlet connections on portable cryogenic medical gas containers be permanently attached or otherwise locked to the valve body so they cannot be readily removed except by the manufacturer, (2) a 360° wraparound label clearly identifying the container's contents be affixed near the top of portable cryogenic medical gas containers, and (3) high-pressure medical gas cylinders be painted an FDA-designated standard color. Additionally, the proposal would prohibit the medical use of high-pressure cylinders or cryogenic containers that have previously been used to hold industrial gases if such containers have not been appropriately converted to medical use by the final rule's effective date and are not solely dedicated to medical use on and after this date.

### *A. Benefits*

This proposal is expected to reduce the risk of accidents involving the improper handling of medical gases and therefore the number of accidental injuries and deaths from these accidents.

As discussed in section I.A of this document, FDA has received reports from nursing homes and hospitals of accidents involving the improper handling of portable cryogenic containers and high-pressure medical gas cylinders that resulted in 8 deaths and 16 injuries between 1996 and April 2004. Because there is no requirement that nursing homes and hospitals report such incidents to us, we assume that these figures underestimate the number of deaths and injuries over this time period. On average, this equates to approximately one death and two injuries per year. As noted earlier in this document, these deaths and injuries have been associated with portable cryogenic containers and high-pressure cylinders that were misidentified or contaminated, or whose gas-specific use outlet connections were inappropriately removed and replaced. FDA believes that this proposal, when finalized, will drastically reduce, if not completely eliminate, the foregoing errors and the human deaths and injuries that might otherwise occur. We estimate that this proposed rule could eliminate, on average, one death per year.

There are different methodologies for valuing the avoidance of mortalities because of regulatory action. One approach is based on society's willingness-to-pay to avoid incremental risks of a statistical death. A widely cited study calculates this value based on occupational wage premiums necessary to accept increased work-place fatality risks.[11] This study implies a societal value of about $5 million per statistical death avoided. A more recent study by Viscusi that compares worldwide estimates of the value of a statistical life (VSL) concludes that a more appropriate VSL estimate for the United States is about $7 million.[12] Because we estimate that this proposed rule could prevent, on average, one death per year, we estimate the benefit of the rule in the first year alone at about $7 million. The avoidance of the increased medical costs, lost productivity, and investigation or

[11] See Viscusi, W.K., *Fatal Tradeoffs, Public and Private Responsibilities for Risk*, Oxford University Press, 1992.

[12] See Viscusi, W.K., and J.E. Aldy, ''The Value of a Statistical Life: A Critical Review of Market Estimates Throughout the World,'' *The Journal of Risk and Uncertainty*, volume 27, no. 1, p. 63, 2003.

litigation costs associated with up to two additional medical gas-related injuries per year, although positive, would not be expected to add substantially to this total. Because of the small number of medical gas-related incidents that occur on average each year, there is some uncertainty surrounding the benefit of this proposed rule in any individual year.

*B. Costs*

Depending on their current level of compliance, medical gas manufacturers would be expected to incur compliance costs for the following:

- Silver brazing or locking gas use outlet connections on portable cryogenic medical gas containers,
- Purchasing and attaching 360° wraparound labels on portable cryogenic medical gas containers,
- Painting high-pressure medical gas cylinders in the appropriate FDA-designated color(s), and
- Forgoing the use of portable cryogenic containers and high-pressure cylinders for both industrial and medical use. Additionally, manufacturers may be expected to incur a very slight increase in record maintenance costs for container closures subject to this proposed rule.

The agency used the best available data from industry contacts and FDA personnel to generate cost estimates for this proposal, and we are inviting public comment and additional data on the methods used to make these estimates.

1. Brazing or Locking of Gas Use Outlet Connections on Portable Cryogenic Medical Gas Containers

Under proposed § 211.94(e)(3), portable cryogenic containers that hold medical gases would be required to have gas use outlet connections that are either permanently attached to the valve body or attached to the valve body in a manner that does not permit them to be readily removed except by the manufacturer. There are at least two methods of compliance: (1) Silver brazing the gas use outlet connection to permanently attach it to the valve body or (2) using any of several locking devices to lock the outlet connection to the valve body. Currently manufactured cryogenic containers incorporate brazed gas use outlet connections or locking devices, but some older containers that are still in use may not.

Although FDA does not presently have a broader sample of company data to draw upon, data from several of the large industrial gas producers show that they have, on average, about 4,375 portable cryogenic medical gas containers each. Further, contacts at these firms suggested that industrial gas producers (seven in total) supply about 10 percent of all portable cryogenic containers in medical use. Based on this information, FDA estimates that approximately 306,000 portable cryogenic medical gas containers would be subject to this proposed rule (4,375 x 7 x 10 = 306,250). FDA anticipates that cryogenic medical gas containers used by home care firms would not be subject to the proposed brazing or locking requirement. To the agency's knowledge, the only cryogenic medical gas containers such firms would fill would be small cryogenic containers for use at home by individual patients. These containers would be exempt from proposed § 211.94(e)(3).

The cost of materials and labor for the silver brazing process is expected to range from $50 to $150 per cryogenic container.[13] This range reflects estimated costs for companies that are capable of performing brazing operations in-house, as well as for those that would need to contract this work to an outside company. An informal industry estimate of current compliance with silver brazing is between 90 percent and 100 percent for larger distributors.[14] Very few small firms, which may have lower compliance rates, are expected to operate portable cryogenic container facilities that would be subject to this proposed rule. FDA conservatively estimates, therefore, that about 90 percent of all portable cryogenic medical gas containers (approximately 276,000 containers [306,250 x .9 = 275,625]) currently comply with proposed § 211.94(e)(3). The compliance cost of silver brazing all other cryogenic containers that would be subject to this provision is estimated to range from approximately $1,531,000 (30,625 x $50) to approximately $4,594,000 (30,625 x $150).

An alternative to silver brazing that would also comply with the proposed requirement would be locking gas use outlet connections on portable cryogenic medical gas containers to the valve bodies on such containers using any of several locking valves or devices. These locking valves or devices are priced at about $10 to $15 each. FDA estimates that, at most, another $2 to $3 would be required in labor costs to attach each locking valve or device. Accordingly, FDA estimates that the total cost of complying with proposed § 211.94(e)(3) through the use of locking valves or devices would range from $12 to $18 per cryogenic container. Again assuming a current compliance rate with the proposed provision of 90 percent (275,625 containers), the total cost of this option for industry would be expected to be no more than approximately $551,000 ([306,250–275,625] x $18).

Because locking valves or devices are less costly than silver brazing and have become more widely used by industry, FDA expects that firms that do not currently comply with proposed § 211.94(e)(3) will choose to use these devices to achieve compliance with the proposed requirement. Accordingly, the cost estimate for the proposed rule includes the locking device option and excludes the silver brazing option.

2. 360° Wraparound Label for Portable Cryogenic Medical Gas Containers

Proposed § 211.94(e)(4)(i) would require that portable cryogenic containers used to hold medical gases be identified with a 360° wraparound label specifying their contents. FDA received a cost estimate of the wraparound label from only one manufacturer. Although the manufacturer reported this cost at about $1 per label, the size of the shipment ordered may affect the average price for all manufacturers. Taking this into account, as well as the lack of estimates from other manufacturers that could result in a higher estimate, FDA assumes that the average cost is $1.50 per label for this analysis. FDA estimates that an additional labor cost of about $3 would be required to attach each label to a portable cryogenic container. As noted previously in this document, FDA estimates that approximately 306,000 cryogenic containers would be subject to this proposed rule when finalized. The current compliance rate for proposed § 211.94(e)(4)(i) is not known with certainty but is conservatively estimated at 90 percent (approximately 276,000 containers).[15] Based on this estimate, total industry compliance costs for proposed § 211.94(e)(4)(i) would amount to approximately $135,000 ([306,000 - 276,000] x $4.50).

3. Painting of High-Pressure Medical Gas Cylinders

Proposed § 211.94(e)(4)(ii) would require that high-pressure cylinders holding medical gases identified in proposed § 211.94(e)(5) be painted in the standard colors also identified in § 211.94(e)(5). As discussed previously

[13] Lower estimate made by medical gas manufacturer during a site visit by FDA on June 28, 2001. Upper estimate projected by FDA.

[14] Estimate provided to FDA by a major consulting firm for medical gas companies.

[15] Estimate provided to FDA by a major consulting firm for medical gas companies.

in this document, the coloring standards identified in proposed § 211.94(e)(5) have been widely used throughout the industry for many years. Consequently, the current compliance rate with this proposed provision is expected to be extremely high, and only a very small percentage of customer-owned cylinders are expected to be out of compliance. Although the current compliance rate cannot be predicted with certainty, FDA believes that it is at least 99 percent.[16] The compliance costs for proposed § 211.94(e)(4)(ii) have been calculated based on an estimated compliance rate of 99.5 percent.

FDA does not have a complete set of data upon which to confidently estimate the number of high-pressure cylinders used for medical gases. Data from several industrial gas producers that also supply medical gases show that the number of cylinders per establishment varies greatly, even among this subset of medical gas suppliers.[17] Using this data, FDA estimates that the average industrial gas establishment has about 3,000 high-pressure cylinders for use with medical gases. There are 3,400 establishments that are known to supply medical gases. The total number of high-pressure medical gas cylinders that would be subject to proposed § 211.94(e)(4)(ii) is therefore estimated at about 10.3 million (3,000 x 3,400). This estimate likely exceeds the actual number of high-pressure cylinders that would be affected by this proposed rule because certain firms that supply medical gases in these cylinders are not expected to operate establishments as large as those of industrial gas manufacturers and, consequently, are not expected to have as many high-pressure medical gas cylinders. As noted earlier in this document, FDA estimates that 99.5 percent of the high-pressure medical gas cylinders that would be subject to this proposed rule are currently in compliance with the proposed coloring requirements (approximately 10,249,000 cylinders [10,300,000 x .995]). Thus, even if each affected establishment handled the estimated average of 3,000 high-pressure medical gas cylinders, only approximately 51,000 such cylinders (10,300,000–10,249,000) would need to be colored to come into compliance with proposed § 211.94(e)(5). Painting costs for these cylinders are estimated to range from $5 to $10 each, including both labor and materials. The total cost of this provision is therefore estimated at between $255,000 (51,000 x 5) and $510,000 (51,000 x 10).

4. Prohibition of Container Use for Both Industrial and Medical Purposes

Proposed § 211.94(e)(1) and (e)(2) would prohibit high-pressure cylinders and portable cryogenic containers from being used to store medical gases if they were previously used to hold liquid or compressed industrial gases and were not converted to medical use by the effective date of the final rule. FDA has anecdotal information that the practice of converting these containers back and forth from industrial to medical use is very rare, although it does occur. To the extent that such conversion occurs, FDA expects this provision to cause a small percentage of firms to purchase additional high-pressure cylinders or portable cryogenic containers to maintain their current supplies of these products for both medical and industrial uses. The agency does not have enough data or information to predict the number of additional containers that the average firm would purchase. The number should be very low, however, and the majority of firms should not be affected by this provision. Additionally, some off-setting savings would be expected if proposed § 211.94(e)(1) and (e)(2) are implemented because certain costs associated with converting high-pressure cylinders or portable cryogenic containers from industrial to medical use would be eliminated, including the costs of cleaning, purging, relabeling, and changing the gas use outlet connections on containers being converted. FDA invites public comment and data on the prevalence and public health risk of container conversion across the medical gas industry and estimated costs of compliance with proposed § 211.94(e)(1).

5. Records Maintenance

As mentioned previously in this document, proposed § 211.94(e)(3) would require that gas use outlet connections on portable cryogenic medical gas containers be permanently attached to the valve body or otherwise attached so that they cannot be readily removed, except by the manufacturer. As explained earlier in this document, FDA is aware of at least two methods by which industry could comply with this proposed requirement: (1) Silver brazing the gas use outlet connection to the valve body so that the outlet connection is permanently attached, or (2) using a locking valve or device to secure the gas use outlet connection to the valve body. Locking valves and devices would be considered part of a medical gas' container closure.

Under existing § 211.184, manufacturers are required to maintain certain records for medical gas container closures because they are considered part of the finished drug product. Specifically, under § 211.184(a), the following information must be maintained:

- Records regarding the identity and quantity of each shipment of container closures;
- The name of the supplier;
- The supplier's lot number or numbers, if known;
- The receiving code; and
- The date of receipt.

Under § 211.184(b), records of the results of any test or examination conducted on a container closure under § 211.182(a) must be maintained. Under § 211.184(c), an individual inventory record must be maintained for each container closure. Under § 211.184(e), records of the disposition of any rejected container closure must be maintained.

In light of the requirements described in this subsection of the rule, proposed § 211.94(e)(3) could result in a slight increase in the medical gas industry's record maintenance activities if, after this provision is finalized, industry chooses to use locking valves or devices on portable cryogenic medical gas containers that do not already comply with the proposed provision. As noted earlier in this document, such valves or devices would be considered part of the medical gas' container closure. FDA would not, however, expect the costs of establishing and keeping the records required by § 211.184 for locking valves or devices to be substantial. Additionally, FDA anticipates that, in the vast majority of cases, records for locking valves or devices would not be required to be updated after the valves or devices have been inspected upon their receipt by medical gas manufacturers, or would only very rarely be required to be updated, under § 211.184.

To account for the records maintenance costs potentially associated with proposed § 211.94(e)(3), including the possibility that some small percentage of maintenance records for locking valves or devices could require periodic updating, FDA estimates that manufacturers would be required to expend approximately 2 minutes (mins.) on record maintenance activities per locking device per year. This estimate includes time that would be associated with the initial inspection of the locking valve or device by the manufacturer. As previously discussed

[16] Based on experience of The Center for Drug Evaluation and Research personnel involved in medical gas issues.

[17] Based on phone contacts between FDA personnel and medical gas suppliers in June 2002.

in section IV.B.1 of this document, FDA estimates that 306,250 portable cryogenic medical gas containers are currently in use and that about 90 percent of these (approximately 275,625 containers) already comply with proposed § 211.94(e)(3). FDA expects that, with respect to the remaining estimated 30,625 containers, industry would opt to comply with proposed § 211.94(e)(3), when finalized, through the use of locking valves or devices, which are less costly than silver brazing. As explained earlier in this document, records maintenance costs would be associated with these valves and devices and, thus, would be costs of compliance associated with proposed § 211.94(e)(3). At an industrial manager's wage rate of approximately $53 per hour (including a 35 percent increase for benefits), FDA estimates that this proposed provision would result in a records maintenance compliance cost of approximately $54,000 per year for the entire industry (30,625 x 2 mins. x [$53/60 mins.]).

6. Total Costs

Individual cost elements of this proposed rule as well as total costs are shown in table 1 of this document.

TABLE 1.—PROPOSED RULE COSTS

| Cost Component | One-Time Cost | Annualized Cost[1] |
|---|---|---|
| Brazing/locking of gas use outlet connections for portable cryogenic medical gas containers | $551,000 | $78,000 |
| 360° Wraparound labels for portable cryogenic medical gas containers | $138,000 | $20,000 |
| Painting high-pressure medical gas cylinders the standard industry color | $255,000 to $510,000 | $36,000 to $73,000 |
| Records maintenance | N/A | $54,000 |
| Total costs | $944,000 to $1,199,000 | $188,000 to $225,000 |

[1]Over 10 years at 7 percent discount rate.

*C. Comparison of Costs and Benefits*

The estimated benefits of this proposed rule compare favorably to the estimated costs. The medical gas accident data noted earlier in this analysis show that these accidents have been claiming more than one life and two additional injuries per year. On average, the benefit of avoiding one statistical death per year is estimated at about $7 million. The one-time costs of this proposed rule are expected to total from about $950,000 to $1.2 million. These costs (not including the records maintenance costs), when annualized over a 10-year period at 7 percent, are estimated to range from about $134,000 to $171,000 per year. With the addition of annual records maintenance costs of approximately $54,000, the total annualized cost is estimated to be between $188,000 and $225,000. Average one-time establishment and firm costs would be expected to range from about $300 to $400 and $900 to $1,200, respectively. Even at an effectiveness rate of only about 10 percent (or one death avoided every 10 years), the benefits of the proposed rule would still compare favorably with its costs.

*D. Regulatory Flexibility Analysis*

The following analysis, along with other sections of this preamble, constitutes the regulatory flexibility analysis as required under the Regulatory Flexibility Act.

1. Need for and Objectives of the Rule

The agency is proposing this rule to help prevent deaths and injuries from the improper use of medical gases. The rule is intended to dramatically lower the incidence of the types of potentially fatal medical gas mixups that have occurred in the past.

2. Description and Estimate of Small Entities

This proposed rule would affect manufacturers and distributors of medical gases. The Small Business Administration (SBA) sets size limits for small businesses according to the North American Industrial Classification System (NAICS) business categories. Medical gas suppliers fall into the following categories:

- Small industrial gas manufacturers (NAICS code 325120) are those with less than 1,000 employees,
- Small home health care service companies (NAICS code 621610) are those with less than $11.5 million in revenue,
- Small chemical and allied product wholesalers (NAICS code 422690) are those with less than 100 employees, and
- Small home health equipment rental companies are those with less than $6 million in revenue.

It can be difficult to assign a company to a single or primary NAICS code because of the similarities between NAICS categories and because companies often have product sales or service sales in more than one category. For example, home health care service firms and home health equipment rental firms are very similar and often have sales that fall into both categories. For purposes of this rulemaking, they have been assigned to one category, a combined home health care service and equipment rental companies category, with a small business limit of $11.5 million. This limit reflects the higher of the two applicable limits under the NAICS for home health care service firms and home health equipment rental firms, respectively.

The 3,400 establishments on FDA's list of medical gas suppliers are operated by about 1,020 individual companies. A sample of the establishments run by these companies was taken to generate data to estimate the economic impacts on small businesses that would be imposed by this proposed rule. This sampling of the firms and their corresponding establishments shows the following: (1) Approximately 80 percent of the firms (about 800) and 32 percent of the establishments (about 1,100) would be in the home health care service and equipment rental industry, (2) approximately 13 percent of the firms (about 130) and 67 percent of the establishments (about 2,300) would be in the industrial gas industry, and (3) approximately 6 percent of the firms (about 70) and 2 percent of the establishments (about 70) would be in

the chemical and allied products wholesale industry. Because of the small sample size, the true size of these categories may vary. In particular, the last category, which would include welding supply companies, may be substantially larger than the 6 percent of firms reported. A separate counting of welding firms in the database shows that they may represent over 15 percent of all registered medical gas firms.

The 1997 Economic Census (the Census) (the last census for which detailed data are available) reports 118 industrial gas manufacturers with 643 establishments. About 10 of these manufacturers are reported to have more than 1,000 employees. Therefore, FDA estimates that about 108 industrial gas manufacturers are small businesses according to the SBA criteria. For the chemical and allied products wholesale industry, the 1997 data show that the average establishment has less than 15 employees. The data also show that none of these companies has more than 100 employees. FDA assumes, therefore, that all the companies in this category are small businesses according to the SBA criteria. The Census data show that only about 4 percent of the combined home health care equipment rental companies and home health care service companies would exceed the NAICS revenue criteria for small business inclusion. Therefore, FDA estimates that about 768 firms (800 firms x 96 percent) in this category are small businesses. In total, FDA estimates that about 950 of the 1,020 companies in the medical gas supply industry are small businesses according to the SBA criteria. If welding supply companies in fact do represent a significantly higher percentage of all firms than shown by our sample, FDA would expect that more than 950 of the 1,020 medical gas distributors would be small businesses. In either case, over 93 percent of the firms providing medical gases would be considered small businesses according to the SBA criteria.

3. Reporting, Recordkeeping, and Compliance Requirements

The size of the compliance burden, as described previously in this document, would probably be smaller on a per establishment basis for those firms that are not categorized as industrial gas manufacturers or welding supply companies. Home health care service and equipment rental companies do not fill or distribute portable cryogenic medical gas containers to hospitals or nursing homes. To the agency's knowledge, the only cryogenic medical gas containers these firms would fill would be small cryogenic containers for use at home by individual patients. As discussed earlier in this document, these containers would not be subject to the requirements proposed for portable cryogenic medical gas containers in this rule. These proposed requirements comprise the majority of the estimated total compliance cost burden. While most industrial gas manufacturers were classified as small according to the SBA criteria, it is believed that all, or almost all, of these manufacturers would provide cryogenic gas filling services and would therefore incur a larger share of the compliance burden.

The one-time compliance costs for all firms were previously reported to range, on average, from about $900 to $1,200 per firm. Average firm costs for small businesses would be expected to be slightly less than this average. However, even at the level described here, one-time compliance costs would represent the following: (1) Less than 0.01 percent of revenues for the average small industrial gas manufacturer, (2) about 0.03 percent of revenues for the average small chemical and allied product wholesaler, and (3) about 0.1 percent of revenues for the average small home health care service and equipment rental company. It is not likely that these amounts would create a significant impact on these small businesses. However, because we estimated average impacts across fewer than 1,000 small businesses, we cannot state with confidence that a substantial number of affected firms would not have impacts significantly higher than the average costs estimated. We request public comment and data on the industry sectors and impacts as discussed in this analysis.

4. Other Federal Rules

FDA is not aware of any other Federal rules that overlap, duplicate, or conflict with the proposed rule.

5. Alternative Policies

Alternative policies were considered during the development of this proposed rule. One alternative would have been to require that all high-pressure medical gas cylinders and portable cryogenic medical gas containers be physically separated on delivery trucks according to the specific medical gas each contained. The purpose of this requirement would have been to further reduce the risk of accidental mixups between containers containing different industrial and medical gases. This alternative would, however, be expected to greatly reduce delivery truck capacity and productivity. To promote efficiency, medical gas cylinders and containers are currently loaded onto delivery trucks in the order they are received from customers along the trucks' delivery routes, without regard to the type of gas being loaded. Further, requiring the physical separation of gas containers on delivery trucks would necessitate additional container handling by personnel during the delivery process, thereby potentially increasing the risk of human handling errors, such as errors in medical gas identification. FDA believes that, on the whole, this alternative would impose greater annual compliance costs without significantly reducing the risk of accidents beyond those reductions provided by the provisions of the proposed rule. Therefore, it was not included in this proposal.

Another option would have been to delete the general warning statement that is currently required to appear on the labeling of certain medical gases under § 201.161(a)(1)[18] and require instead that each such gas be labeled with a gas-specific statement of warnings. However, the agency could not identify any accidents or other problems that could be directly traced to a misunderstanding of the general warning statement currently in effect. Additionally, the current warning statement has the advantage of being familiar and well-established. Allowing manufacturers to create differing warning statements specific to each medical gas could cause identical gases from different manufacturers to have different warnings and result in unnecessary confusion for medical gas users. For both of these reasons, this option was not included in the proposed rule.

A third option would have been to require that the shoulders of portable cryogenic medical gas containers be painted the appropriate standard color designated in proposed § 211.94(e)(5). This alternative was not adopted because the proposed alternative of requiring a 360° wraparound label was deemed appropriate to ensure the easy identification of medical gases stored in portable cryogenic containers. Further, as discussed earlier in this document, these containers are currently rarely painted. Rather, most of industry has been identifying medical gases stored in these containers using 360° wraparound

[18] This warning statement reads: ''Warning—Administration of (name of gas) may be hazardous or contraindicated. For use only by or under the supervision of a licensed practitioner who is experienced in the use and administration of (name of gas) 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.''

labels instead. Accordingly, compliance costs would be expected to be relatively greater if FDA pursued the alternative of requiring that portable cryogenic medical gas containers be colored.

The final alternative would have been to exempt small businesses from this proposed rule. However, this option would present greater risks to the public health and nullify most of the rule's expected effects. As noted previously in this document, using the SBA criteria for identifying small businesses in the relevant industry categories, FDA estimates that about 950 of the 1,020 firms that would be subject to this rule, or about 93 percent, would be considered small businesses. Accordingly, if small businesses were exempted from the rule, it would be too limited in scope to effectively reduce the risk of medical gas mixups. Moreover, FDA believes that the expected costs of compliance with the proposed rule, discussed earlier in this document, are low and not sufficient to warrant a small business exemption. Therefore, no such exemption was adopted as part of the proposed rule.

## V. Paperwork Reduction Act of 1995

This proposed rule contains collection of information requirements that are subject to review by OMB under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). Collections of information include any request or requirement that persons obtain, maintain, retain, or report information to the agency, or disclose information to a third party or to the public (44 U.S.C. 3502(3) and 5 CFR 1320.3(c)). The information collection requirements included in this proposed rule are described in this section of the preamble with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on the following topics: (1) Whether the collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden created by the collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

*Title*: Medical Gas Containers and Closures; Current Good Manufacturing Practice Requirements.

*Description*: FDA is proposing requirements for medical gases to help prevent deaths and serious injuries that can result from the improper use of such products. The proposed rule would revise FDA's CGMP regulations and other regulations to include new requirements for the label, color, dedication, and design of medical gas containers and closures. Among other proposed requirements, § 211.94(e)(4)(i) would require that portable cryogenic containers used to hold medical gases be conspicuously marked with a 360° wraparound label. Additionally, proposed § 211.94(e)(3) would require that portable cryogenic medical gas containers that are not manufactured with permanent gas use outlet connections be equipped with connections that are secured to the container using a locking device or other method that ensures that the connection cannot be readily removed or replaced except by the manufacturer.

*Description of Respondents*: Persons and businesses, including small businesses and manufacturers.

*Burden Estimates*: The total annual reporting and recordkeeping burden is estimated to be 4,070 hours. Table 2 of this document provides estimates of the annual reporting burden under the proposed rule. Table 3 of this document provides estimates of the annual recordkeeping burden.

Proposed § 211.94(e)(4)(i) would require that each portable cryogenic container used to hold medical gases be marked with a 360° wraparound label identifying the container's contents. FDA's database of establishments that manufacture medical gases includes about 3,400 such establishments. As discussed in section IV.B.1 of this document, we estimate that there are approximately 306,000 portable cryogenic containers in distribution that would be subject to the proposed 360° wraparound label requirement. FDA estimates that approximately 90 percent of these containers have already been marked with such a label. Thus, on average, each manufacturer would need to put labels on approximately nine containers ([306,000 ÷ 3,400] - [.9 x (306,000 ÷ 3,400]). FDA estimates that approximately 6 minutes would be required to attach a label to each container. Thus, the total burden hours associated with proposed § 211.94(e)(4)(i) would be approximately 3,060 hours (3,400 x 9 x .10 hours).

Under proposed § 211.94(e)(3), medical gas manufacturers that use portable cryogenic medical gas containers that are not manufactured with permanent gas use outlet connections would be required to use a locking device or other method to ensure that the gas use outlet connection on the container cannot be readily removed or replaced except by the manufacturer. As noted earlier in this document, the locking device or other method used would be considered part of the container closure, and manufacturers would be required to maintain records in accordance with § 211.184 for such articles. This would result in a slight increase in the recordkeeping burden under § 211.184 for medical gas manufacturers.

The burdens for maintaining records under § 211.184 have previously been estimated by FDA, and this collection of information was approved by OMB until August 31, 2005, under OMB control number 0910–0139. FDA is not re-estimating approved burdens in this rulemaking. Only the additional recordkeeping burdens on medical gas manufacturers under § 211.184 that are associated with proposed § 211.94(e)(3) are estimated in table 3 of this document.

As discussed in section IV.B.1 of this document, FDA estimates that 90 percent of the roughly 306,000 portable cryogenic medical gas containers that would be subject to proposed § 211.94(e)(3) (.9 x 306,000 = 275,400) already comply with this proposed provision. The agency therefore expects that approximately 30,600 portable cryogenic containers (306,000–275,400) would need to be brought into compliance with the provision when it is finalized. As explained earlier in this document, with respect to these 30,600 containers, FDA expects that manufacturers will elect to use locking devices or other articles that would be considered drug product container closures to achieve compliance with proposed § 211.94(e)(3). Accordingly, these 30,600 portable cryogenic medical gas containers would be subject to additional records maintenance requirements under § 211.184. As discussed previously in this document, FDA estimates additional time of approximately 2 minutes (2 mins. ÷ 60 mins. per hour = .033 hours) per container per year will be needed to maintain records under § 211.184 for portable cryogenic medical gas containers as a result of proposed § 211.94(e)(3). Therefore, the total additional recordkeeping burden resulting from proposed § 211.94(e)(3) would be approximately 1,010 hours

(30,600 containers x .033 hours) per year.

FDA estimates the burden for the collection of information as follows:

TABLE 2.—ESTIMATED ANNUAL REPORTING BURDEN

| 21 CFR Section | No. of Respondents | Annual Frequency of Response | Total Annual Responses | Hours per Response | Total Hours |
|---|---|---|---|---|---|
| 211.94(e) (4)(i)(labeling--third party disclosure) | 3,400 | 9 | 30,600 | .10 | 3,060 |
| Total | | | | | 3,060 |

TABLE 3.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

| 21 CFR Section | No. of Recordkeepers | Annual Frequency of Recordkeeping | Total Annual Records | Hours Per Record | Total Hours |
|---|---|---|---|---|---|
| 211.184 | 3,400 | 9 | 30,600 | .033 | 1,010 |
| Total | | | | | 1,010 |

[1]Capital, operating, and/or maintenance costs associated with this proposed rulemaking are estimated in section IV of this document.

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding this information collection to the Office of Information and Regulatory Affairs, OMB.

The Office of Management and Budget (OMB) is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the proposed information collection requirements are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Fumie Yokota, Desk Officer for FDA, FAX: 202–395–6974.

## VI. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## VII. Effective Date

FDA proposes that any final rule based on this proposal become effective 60 days after publication in the **Federal Register**. Because the proposed requirements have largely already been adopted as standard industry practice, the agency believes that it would be reasonable to implement the final rule as rapidly as possible.

## VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

## IX Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit written comments regarding information collection to OMB (see **ADDRESSES**). Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

## List of Subjects

*21 CFR 201*

Drugs, Labeling, Reporting and recordkeeping requirements.

*21 CFR 211*

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

Therefore, under the Federal Food, Drug, and Cosmetic Act and authority delegated to the Commissioner of Food and Drugs, FDA proposes to amend 21 CFR parts 201 and 211 as follows:

## PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Section 201.161 is amended by revising the section heading and the introductory text of paragraph (a) to read as follows:

### § 201.161 Medical gases.

(a) Medical air, oxygen, nitrogen, carbon dioxide, helium, and nitrous oxide gases intended for drug use are exempted from the requirements of § 201.100(b)(2), (b)(3), and (c)(1), provided that, where applicable, the requirements of § 211.94(e)(4) 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:

* * * * *

## PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

3. The authority citation for 21 CFR part 211 continues to read as follows:

**Authority:** 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374 42 U.S.C. 216, 262, 263a, 264.

4. Section 211.94 is amended by adding paragraph (e) to read as follows:

**§ 211.94 Drug product containers and closures.**

* * * * *

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

(1) Except as provided in paragraph (e)(2) of this section, cryogenic containers or high-pressure cylinders used at any time to hold a liquid or compressed industrial gas may not be subsequently used to hold any type of liquid or compressed medical gas.

(2) The prohibition in paragraph (e)(1) of this section does not apply to any cryogenic container or high-pressure cylinder that was once used to hold a liquid or compressed industrial gas if the container or cylinder:

(i) Was converted to use for holding a liquid or compressed medical gas in accordance with standard industry practice before [effective date of final regulation]; and

(ii) Is used solely to hold a liquid or compressed medical gas on and after [effective date of final regulation] and is in compliance with all other applicable requirements.

(3) 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 by any of the following methods: Liquid to liquid, liquid to gas, or gas to gas. For the purposes of paragraphs (e)(3) and (e)(4) 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. The term does not include small cryogenic gas containers for use by individual patients or portable liquid oxygen units when distributed empty, as defined at § 868.5655 of this chapter.

(4) *Label and color requirements.* (i) Each portable cryogenic medical gas container must be conspicuously marked with a 360° wraparound label identifying its contents.

(A) The label must identify the medical gas held in the container by the gas' standard name, as designated in paragraph (e)(5) of this section.

(B) The standard name must be printed on the label in one of the following ways:

(*1*) Using lettering that appears in the standard color designated for the gas in paragraph (e)(5) of this section and that is printed against a white background, or

(*2*) Using lettering that appears in white against a background that is painted in the standard color for the gas as designated in paragraph (e)(5) of this section.

(C) The lettering for the name of the gas on the label must be at least 2 3/4 inches high.

(D) The name of the gas must be printed continuously around the label and be capable of being read around the entire container.

(E) 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.

(F) The label must be affixed to the container so that it cannot be easily detached or worn, and in a manner that does not interfere with other labeling.

(G) If the shoulder portion of a portable cryogenic medical gas container is colored, the color used must be that designated in paragraph (e)(5) of this section for the gas held within the container.

(ii) High-pressure medical gas cylinders must be identified with FDA-designated standard colors according to the following:

(A) Non-aluminum high-pressure medical gas cylinders must be colored in whole in the standard color designated in paragraph (e)(5) of this section for the gas contained in the cylinder.

(B) Aluminum high-pressure medical gas cylinders must be colored on the shoulder portion of the cylinder in the standard color designated in paragraph (e)(5) of this section for the gas contained in the cylinder.

(C) The materials used for coloring must be reasonably resistant to fading, durable when exposed to atmospheric conditions, and not readily soluble in water after they have been applied and properly dried or cured.

(D) High-pressure medical gas cylinders containing a blend or combination of medical gases must be colored with the standard colors of each component gas, as designated in paragraph (e)(5) of this section. Each such color must be visible when viewed from the top of the cylinder and must appear in rough proportion to the fraction of the gas it represents in the combination or mixture.

(5) The standard names and colors required to identify medical gases under paragraph (e)(4) of this section are:

| Standard Name | Standard Color |
|---|---|
| Medical Air | Yellow |
| Medical Carbon Dioxide | Gray |
| Medical Helium | Brown |
| Medical Nitrogen | Black |
| Medical Nitrous Oxide | Blue |
| Medical Oxygen | Green |
| Mixture or Blend of Medical Gases | Standard colors for each component |

5. Section 211.125 is amended by adding a sentence to the end of paragraph (c) to read as follows:

**§ 211.125 Labeling issuance.**

* * * * *

(c) * * * Labeling reconciliation is also waived for 360° wraparound labels on portable cryogenic medical gas containers.

Dated: November 21, 2005.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

[FR Doc. 06–3370 Filed 4–7–06; 8:45 am]

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## DEPARTMENT OF THE TREASURY

## Internal Revenue Service

## 26 CFR Part 1

**[REG–146384–05]**

**RIN 1545–BF02**

## Application of Section 338 to Insurance Companies

**AGENCY:** Internal Revenue Service (IRS), Treasury.

**ACTION:** Notice of proposed rulemaking by cross-reference to temporary regulation.

**SUMMARY:** In the Rules and Regulations section of this issue of the **Federal Register**, the IRS is issuing temporary regulations that provide guidance under section 197 that apply to the treatment of certain insurance contracts assumed in an assumption reinsurance transaction and section 338 that apply to a deemed sale or acquisition of an insurance company's assets pursuant to an election under section 338 of the Internal Revenue Code, to a sale or acquisition of an insurance trade or