



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 211

[Docket No. FDA-2005-N-0343]

RIN 0910-AC53

Medical Gas Containers and Closures; Current Good Manufacturing Practice Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is amending its current good manufacturing practice (CGMP) and labeling regulations regarding medical gases. FDA is requiring that portable cryogenic medical gas containers not manufactured with permanent gas use outlet connections have gas-specific use outlet connections that cannot be readily removed or replaced except by the manufacturer. FDA is also requiring that portable cryogenic medical gas containers and high-pressure medical gas cylinders meet certain labeling, naming, and color requirements. These requirements are intended to increase the likelihood that the contents of medical gas containers are accurately identified and reduce the likelihood of the wrong gas being connected to a gas supply system or container. FDA is also revising an existing regulation that conditionally exempts certain medical gases from certain otherwise-applicable labeling requirements in order to add oxygen and nitrogen to the list of gases subject to the exemption, and to remove cyclopropane and ethylene from the list.

DATES: This rule is effective [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. See section V of this document for the compliance date of this final rule.

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## I. Executive Summary

### A. Purpose of the Final Rule

On April 10, 2006, FDA issued a proposed rule to amend our regulations on CGMP to include new or revised requirements for the labeling, color, dedication, and design of medical gas containers and closures (71 FR 18039). The chief impetus for the proposed rule was a number of incidents in which a medical gas container holding a gas other than oxygen was erroneously connected to a health care facility's oxygen supply system, leading to serious injuries and deaths. In addition, FDA recognized that the regulation that conditionally exempts certain medical gases from certain otherwise-applicable prescription drug labeling regulations did not reflect either industry best practices or FDA's current regulatory expectations.

Following consideration of comments received and further internal deliberation, we are finalizing this rule as described in this document. The final rule is intended to increase the likelihood that the contents of medical gas containers are accurately identified and reduce the likelihood of the wrong gas being connected to a gas supply system or container. The final rule also modifies the medical gas conditional labeling exemption regulation such that it now largely reflects existing industry best practices and FDA's current regulatory expectations regarding the labeling of medical gases.

### B. Summary of the Major Provisions of the Final Rule

We received approximately 50 comments on the proposed rule. The most detailed comments were from industry trade associations. The other comments were largely from individual medical gas firms, consultants, or other industry stakeholders, and they generally expressed agreement with the trade associations' comments. We discuss all significant comments in section IV.

The final rule requires that portable cryogenic medical gas containers not manufactured with permanent gas use outlet connections have gas-specific use outlet connections that cannot be readily removed or replaced except by the manufacturer. The rule further requires that portable cryogenic medical gas containers and high-pressure medical gas cylinders meet certain labeling, naming, and color requirements. Principally, portable cryogenic medical gas containers are required to bear a 360° wraparound label identifying the contents of the container, and high-pressure medical gas cylinders are required to be colored on the shoulder of the container in the FDA-designated color or colors associated with the gas or gases held in the container. These requirements are intended to increase the likelihood that the contents of medical gas containers are accurately identified and reduce the likelihood of the wrong gas being connected to a gas supply system or container.

The final rule also revises the medical gas conditional labeling exemption regulation to add oxygen and nitrogen to the list of medical gases subject to the exemption, and to remove cyclopropane and ethylene from the list. The final rule further revises this regulation by adding new warning statement content to be included in oxygen labeling and by expanding the scope of the regulation to include medically appropriate mixtures of medical gases.

### C. Legal Authority

Medical gases are generally regulated as prescription drugs under sections 201(g)(1) and 503(b)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321(g)(1) and 353(b)(1)) (though oxygen may be dispensed without a prescription for certain uses specified at section 576(b)(2) of the FD&C Act (21 U.S.C. 360ddd-1(b)(2)), and are subject to regulation under section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)). Sections 575 and 576 of the FD&C Act (21 U.S.C. 360ddd and 360ddd-1) address the regulation of medical gases and designated medical gases. FDA is invoking its authority under sections 501(a)(2)(B), 502(f) (21 U.S.C. 352(f)), 576(a), and 701(a) (21 U.S.C. 371(a)) of the FD&C Act to create or modify CGMP and labeling regulations applicable to medical gases to ensure that they meet the requirements of the FD&C Act as to safety and have the identity and strength, and meet the quality and purity characteristics, that they purport or are represented to possess, and are labeled with adequate warnings and instructions for use.

#### D. Costs and Benefits

The rule is expected to provide a modest net social benefit (estimated benefits minus estimated costs) to society. Costs are attributed to coloring medical gas containers, complying with the 360° wraparound label requirement for portable cryogenic containers, and requiring gas-specific use outlet connections on portable cryogenic containers to be permanently attached to the valve body (e.g., by silver brazing) or attached to the valve body using a locking mechanism or other appropriate device so that only the manufacturer can readily remove or replace them. Using a standard 10 year time period, we estimate annualized costs to range between \$180,000 and \$1.5 million using a 3 percent discount rate and between \$210,000 and \$1.8 million using a 7 percent discount rate. Benefits are attributed to reducing the probability that medical personnel accidentally administer the wrong gas to patients, resulting in serious injury or death. We

estimate annualized benefits to range between \$800,000 and \$2.8 million using a 3 percent discount rate, and between \$2.5 million and \$8.3 million using a 7 percent discount rate.

Together we estimate annualized net benefits to range between \$620,000 and \$1.3 million using a 3 percent discount rate, and between \$2.3 million and \$6.5 million using a 7 percent discount rate.

## II. Background

### A. History of the Rulemaking

In the Federal Register of April 10, 2006, FDA issued a proposed rule to amend our regulations on CGMP to include new requirements for the labeling, color, dedication, and design of medical gas containers and closures. The chief impetus for issuance of the proposed rule was a number of incidents in which a medical gas container holding a gas other than oxygen was erroneously connected to a health care facility's oxygen supply system, leading to serious injuries and deaths. FDA was also concerned with reports of serious injuries attributable to contamination of high-pressure medical gas cylinders with residue of industrial cleaning solvents, likely as a result of inadequate cleaning during conversion of the cylinder from industrial to medical use. For a detailed account of these incidents, please refer to the proposed rule (71 FR 18039 at 18040-18041).

Accordingly, FDA proposed certain regulatory requirements intended to (1) reduce the likelihood of the wrong gas being attached to a gas supply system or container (and in particular to reduce the likelihood of a gas other than oxygen being connected to an oxygen supply system), (2) make the contents of medical gas containers more easily and accurately identifiable, and (3) reduce the risk of contamination of medical gases. Additionally, FDA proposed including medical air, oxygen, and nitrogen among, and excluding cyclopropane and ethylene

from, the list of gases that are conditionally exempt from certain labeling requirements as described in § 201.161 (21 CFR 201.161). FDA solicited written comments on the proposed rule.

Following publication of the proposed rule, the Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted (Pub. L. 112-144 (July 9, 2012)). Title XI, Subtitle B of FDASIA, “Medical Gas Product Regulation,” added new sections 575, 576, and 577 to the FD&C Act (21 U.S.C. 360ddd, 360ddd-1, and 360ddd-2), creating a new certification process for certain “designated” medical gases, including all of the gases listed at § 201.161 as amended by this rule. Section 575 of the FD&C Act defines the term “designated medical gas” to include oxygen, nitrogen, nitrous oxide, carbon dioxide, helium, carbon monoxide, and medical air that meet the standards set forth in an official compendium. Section 576 of the FD&C Act permits any person to file a request for certification of a medical gas as a designated medical gas for certain specified indications. A designated medical gas for which a certification is granted is deemed to have in effect an approved application under section 505 (New Drug Application) or 512 (New Animal Drug Application) of the FD&C Act (21 U.S.C. 355 or 360b) (see FD&C Act section 576(a)(3)(A)(i)). This approval applies to the designated medical gas alone or in combination, as medically appropriate, with one or more other designated medical gases for which certifications have been granted (Id.).

Section 576 of the FD&C Act also addresses the labeling and prescription drug status of designated medical gases. Section 576(a)(3)(A)(ii) of the FD&C Act, similar to the conditional labeling exemption at § 201.161(a), specifies how the labeling of designated medical gases may meet certain generally applicable statutory labeling requirements. Specifically, section 576(a)(3)(A)(ii) of the FD&C Act provides that the requirements of sections 503(b)(4) of the

FD&C Act (regarding labeling of a drug as a prescription drug) and 502(f) of the FD&C Act (regarding inclusion of adequate directions for use and adequate warnings in drug labeling) are deemed to have been met for a designated medical gas if the labeling on the final use container for the medical gas bears: (1) The information required by section 503(b)(4); (2) a warning statement concerning the use of the medical gas as determined by the Secretary by regulation; and (3) appropriate directions and warnings concerning storage and handling. Section 576(b)(2)(B) of the FD&C Act further provides that, in the case of oxygen provided for certain uses specified at section 576(b)(2)(A), the requirements of section 503(b)(4) of the FD&C Act are deemed to have been met if the labeling bears a warning that the oxygen can be used for emergency use only and for all other medical applications a prescription is required. Finally, section 576(b) of the FD&C Act provides that designated medical gases shall generally be subject to the requirements of section 503(b)(1) of the FD&C Act (requiring that drugs meeting certain specified conditions be dispensed only upon prescription), while also providing that oxygen may be dispensed without a prescription for certain specified uses.

#### B. Summary of Comments to the Proposed Rule

FDA received approximately 50 written comments on the proposed rule. Comments were submitted by trade associations representing the medical gas and home health care industries, medical gas firms, medical gas industry consultants and other industry stakeholders, and one State regulatory body.

The comments addressed the following topics, among others:

- The appropriate warning statements to be included in oxygen and medical air labeling.

- Safety issues associated with converting a gas container from industrial to medical use and how best to address them.
- The utility and appropriateness of coloring medical gas containers in whole or in part.
- The appropriate content and configuration of wraparound labeling on portable cryogenic medical gas containers.
- Estimated costs to comply with the proposed rule and whether such costs are justified under a cost-benefit analysis.

### C. General Overview of the Final Rule

This final rule includes many of the provisions of the April 2006 proposed rule, with certain modifications described in section IV.C of this document. In particular, the final rule adds oxygen and nitrogen to, and removes cyclopropane and ethylene from, the list of medical gases in § 201.161(a) that are conditionally exempt from the labeling requirements of § 201.100(b)(2) and (3), and (c)(1). The final rule also requires that portable cryogenic medical gas containers and high-pressure medical gas cylinders meet certain labeling, naming, and coloring requirements as provided in new § 201.328. The final rule further requires that portable cryogenic medical gas containers not manufactured with permanent gas use outlet connections have gas-specific use outlet connections that cannot be readily removed or replaced except by the manufacturer by amending § 211.94 (21 CFR 211.94) through the addition of new paragraph (e).

This final rule also reflects revisions FDA is making to the April 2006 proposed rule in light of comments received. In addition to other changes discussed in section IV.C of this document, FDA is making the following significant changes to the proposed rule:

- Revisions to Conditional Labeling Exemptions for Medical Gases

FDA is making additional revisions to § 201.161 in response to concerns raised by comments. First, in response to a comment questioning § 201.161(b)'s exclusion of gas mixtures from the scope of the § 201.161(a) conditional labeling exemptions applicable to certain medical gases, FDA is removing this exclusion. Second, in response to comments that oxygen labeling should bear a different warning statement from other medical gases listed at § 201.161, paragraph (a) of § 201.161 now includes new warning statement requirements specific to oxygen. Third, in response to comments that medical air labeling should bear a different warning statement from other medical gases listed at § 201.161, FDA has determined that medical air should be removed from the scope of the final rule, for the reasons discussed in section IV.C of this document. Fourth, FDA is also revising the regulation such that the warning statement that must be included on labeling to qualify for the labeling exemption must contain certain specified information, but need not consist of the exact words used in the regulation.

If the labeling on a final use container of a designated medical gas (or medically appropriate mixture of designated medical gases) includes the information required by section 503(b)(4) of the FD&C Act as well as the information required to obtain the conditional labeling exemptions provided at § 201.161(a) as revised by this rule, FDA will consider such labeling to meet the conditions set forth at section 576(a)(3)(A)(ii) of the FD&C Act, and, therefore, to have met the requirements of sections 503(b)(4) and 502(f) of the FD& C Act.

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

In § 211.94(e)(1) of the proposed rule, FDA proposed generally prohibiting cryogenic containers and high-pressure cylinders used to hold industrial gases from being converted to medical use to minimize the risk of contamination of medical gases by industrial contaminants or

cleaning solvents. As discussed further in section IV.C of this document, FDA agrees with comments stating that such a prohibition would be unnecessarily costly, as these types of contamination incidents appear to be rare and existing regulations regarding cleaning and inspection of drug containers and closures are sufficient to address this issue. Accordingly, FDA is not finalizing this proposed requirement.

### III. Legal Authority

Medical gases are generally regulated as prescription drugs under sections 201(g)(1) and 503(b)(1) of the FD&C Act (though oxygen may be dispensed without a prescription for certain uses specified at section 576(b)(2) of the FD&C Act, and are subject to regulation under section 501(a)(2)(B) of the FD&C Act. Sections 575 and 576 of the FD&C Act address the regulation of medical gases and designated medical gases. Under sections 501(a)(2)(B), 502(f), and 701(a) of the FD&C Act, FDA has the authority to create and modify CGMP and labeling regulations to ensure that drugs meet the requirements of the FD&C Act as to safety and have the identity and strength, and meet the quality and purity characteristics, that they purport or are represented to possess, and are labeled with adequate warnings and instructions for use. Medical gas containers, closures, and labeling 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. Medical gas mix-ups have caused deaths and serious injuries. These incidents have occurred despite current regulations and guidance addressing the safe handling of medical gases. FDA is therefore invoking the authority granted by sections 701(a), 501(a)(2)(B), 502(f), and 576(a) of the FD&C Act to issue CGMP and labeling regulations designed to facilitate the safe use of medical gases and to ensure that medical gases are labeled

with adequate warnings and instructions for use. The specific requirements in these regulations will help to ensure the safety of these products.

#### IV. Comments on the Proposed Rule and FDA Response

##### A. Introduction

We describe and respond to comments on the proposed rule in this section. We respond to certain comments on the Preliminary Regulatory Impact Analysis (PRIA) in the Final Regulatory Impact Analysis (see Section VI). For ease of identification, the word “Comment,” in parentheses, will appear before the comment’s description, and the word “Response,” in parentheses, will appear before our response. The number assigned to each comment is purely for organizational purposes and does not signify the comment’s value or importance or the order in which it was received. Many of the comments voiced the same or highly similar concerns and made the same or highly similar recommendations; these comments have been consolidated where possible.

##### B. Description of General Comments and FDA Response

(Comment 1) Many comments contend that FDA’s proposal does not reflect the risk-based principles that have historically been enunciated in connection with recent CGMP policy. These comments state that risk-based principles focus regulation on critical areas that are likely to achieve the greatest public health impact. Thus, these comments state that because the impact of FDA’s proposed rule is disproportionate to and beyond the scope of any public health risk associated with medical gases, it is inconsistent with the Agency’s risk-based approach for CGMP. The comments further contend that the incidents cited in the preamble of the proposed rule do not support the number of requirements proposed, and that a single requirement in the

proposed rule--requirement for secure connections on portable containers--would have prevented all but one of the fatalities cited in the preamble.

(Response 1) FDA agrees in part with these comments and has, following reanalysis of expected costs and benefits, declined to adopt certain provisions in the proposed rule and has revised other proposed provisions to more efficiently achieve public health objectives. Many of the requirements in the final rule are consistent with what we understand to be industry practices (Refs. 1-3). We continue to believe that medical gas containers and closures, such as portable cryogenic containers and high-pressure cylinders, are integral parts of the drug product and play a critical role in ensuring that the drug provided to the patient has the appropriate identity, strength, quality, and purity. Accordingly, we believe that this rule, as finalized, is fully consistent with FDA's risk-based approach to CGMP regulation.

(Comment 2) Many comments contend that FDA significantly underestimated the costs to industry imposed by the rule as proposed. These comments estimate these potential costs to be in the range of \$855 million to \$1.3 billion, as opposed to FDA's estimate of \$950,000 to \$1.2 million. These comments request that the cost assumptions and conclusions contained in the preamble to the proposed rule be critically reexamined by the Department of Health and Human Services and the Office of Management and Budget (OMB).

(Response 2) We considered these concerns, as appropriate, in preparing the Final Regulatory Impact Analysis (see Section VI).

### C. Specific Comments and FDA Response

- Revisions to Labeling Exemptions for Certain Medical Gases (§ 201.161)

FDA proposed adding medical air, oxygen, and nitrogen to the list of gases conditionally exempted by § 201.161(a) from the labeling requirements of § 201.100(b)(2) and (3), and (c)(1).

FDA proposed these changes because, based on its years of regulatory experience with these gases, FDA believed that compliance with § 201.100(b)(2) and (3), and (c)(1) would be unnecessary if the warning statement and storage and handling directions required to obtain the conditional § 201.161(a) labeling exemptions were included in the labeling of such gases and the labeling and coloring requirements found in proposed § 211.94(e)(4) were met. FDA also proposed removing cyclopropane and ethylene from § 201.161(a), as these gases are no longer used in medical procedures because they are flammable and pose a risk of explosion or fire.

Comments support these proposed changes to the list of exempted gases. Many comments expressed concern, however, over how these proposed changes would affect the labeling of oxygen and medical air. These concerns are set forth in comments 3 and 4, followed by FDA's response.

(Comment 3) Many comments express significant concerns with FDA's proposal to add oxygen to the list of gases at § 201.161(a) without providing a warning statement specific to oxygen. The warning statement at § 201.161(a)(1) previously provided that the gas may only be used by or under the supervision of a licensed practitioner. These comments argue that requiring this statement for oxygen could eliminate the ability of first responders to administer oxygen without a prescription. These comments also note that the labeling on oxygen containers that has long been in use by the industry, which provides for use without a prescription in certain situations when administered by properly trained personnel, would no longer be acceptable and would need to be changed. These comments state that further changes are needed to address these issues.

(Comment 4) Many comments further note that the warning statement at § 201.161(a) does not include certain warnings currently included on oxygen labels. For instance, widely used

oxygen labeling warns that uninterrupted use of high concentrations of oxygen over a long duration without monitoring its effect on oxygen content of arterial blood may be harmful and that oxygen should not be used on patients who have stopped breathing unless used in conjunction with resuscitative equipment.

(Response to Comments 3 and 4) FDA is further revising § 201.161(a)(1) in response to these comments.

Prior to the revisions finalized in this rule, § 201.161(a) provided that if the labeling of the medical gases listed in the rule--carbon dioxide, cyclopropane, ethylene, helium, and nitrous oxide intended for drug use--bore a specified warning statement and any needed directions concerning the conditions for storage and warnings against the inherent dangers in the handling of the specific compressed gas, those gases would be exempt from certain otherwise-applicable labeling requirements concerning the recommended or usual dosage, the drug's route of administration, and adequate directions for use. Section 201.161(b) provided that the exemption in § 201.161(a) did not apply to any mixture of the gases covered by the regulation with oxygen or with each other. In the 2006 proposed rulemaking FDA proposed adding oxygen, medical air, and nitrogen, and removing cyclopropane and ethylene, from the scope of § 201.161, but proposed no other changes to the rule.

As many comments point out, the warning statement previously specified at § 201.161(a)(1) differs significantly from the warning statement that has long been in use on oxygen labeling. FDA agrees with these comments that this oxygen-specific warning statement is more useful and appropriate for oxygen than the general warning statement previously specified at § 201.161(a)(1).

FDA further agrees with these comments that conditioning the § 201.161(a) labeling exemptions on inclusion of a warning statement limiting oxygen to prescription use would be inconsistent with the longstanding use of oxygen without a prescription in certain situations. It would also be inconsistent with new section 576(b)(2)(B) of the FD&C Act which, as discussed in section II.A of this document, provides that, in the case of oxygen provided without a prescription for certain uses specified at section 576(b)(2)(A), the requirements of section 503(b)(4) of the FD&C Act shall be deemed to have been met if the labeling bears a warning that the oxygen can be used for emergency use only and for all of other medical applications a prescription is required.

Therefore, § 201.161(a)(1)(i) of this final rule provides warning statement requirements specific to oxygen, as well as an additional warning statement requirement for oxygen that may be provided for certain uses without a prescription. FDA believes most oxygen containers currently marketed in the United States bear labeling that satisfies these new requirements (Ref. 1).

(Comment 5) Some comments express concerns with FDA's proposal to add medical air to the list of gases at § 201.161(a) without providing a warning statement specific to medical air. These comments point out that widely used medical air labeling indicates that medical air may be used without a prescription by properly trained personnel for breathing support, while for all other uses a prescription is required. These comments note that such labeling would be inconsistent with the warning statement previously specified at § 201.161(a)(1), which provided that the gas may only be used by or under the supervision of a licensed practitioner.

(Response 5) FDA acknowledges the comments that certain non-prescription uses of medical air are medically appropriate, and, accordingly, that the 'prescription only' warning

statement at § 201.161(a)(1)(i) as finalized by this rule is not appropriate for medical air. FDA is not finalizing the proposal to add medical air to the list of gases at § 201.161, and the question of what constitutes an appropriate warning statement for medical air remains under consideration by FDA.

(Comment 6) Many comments note that the proposed rule does not address labeling for medical gas mixtures, but rather leaves in place § 201.161(b)'s exclusion of gas mixtures from the scope of the § 201.161(a) conditional labeling exemptions. These comments recommend for the short term that § 201.161(b) remain as currently published but that FDA nonetheless permit these medical gas mixtures to be labeled consistent with industry practice, which utilizes the warning statement previously specified at § 201.161(a)(1).

(Response 6) FDA notes that, as discussed in section II.A of this document, following publication of the proposed rule new section 576(a)(3)(A)(i) was added to the FD&C Act by FDASIA. This new section provides that designated medical gases for which a certification is granted are deemed alone or in combination, as medically appropriate, with one or more other designated medical gases for which certifications have been granted to have in effect an approved application.

Accordingly, FDA is further revising § 201.161(a)(1) in response to these comments. Specifically, FDA has determined that medically appropriate mixtures of the gases listed at § 201.161(a) should be eligible for the conditional labeling exemptions provided by § 201.161(a). Accordingly, in this final rule FDA is removing the § 201.161(b) exclusion and is specifying that the general warning statement requirements applicable to the gases listed at § 201.161(a) (other than oxygen) are also applicable to medically appropriate mixtures of the listed gases (see § 201.161(a)(1)(ii) of this final rule).

(Comment 7) A comment requests that medical xenon be added to the list of exempted gases in § 201.161(a) as it is used clinically as a general anesthetic and as a diagnostic and test agent.

(Response 7) FDA disagrees that medical xenon should be added to the list of gases for which the § 201.161(a) conditional labeling exemptions are available. Xenon is not a designated medical gas and is not otherwise approved for use as a general anesthetic. Certain xenon gas radioisotopes have been approved as diagnostic agents, but these products have approved prescription drug labeling. Accordingly, it would be inappropriate to add xenon gas to the list of gases at § 201.161(a).

(Comment 8) Many comments contend that the content in proposed § 211.94(e)(4) is misplaced by being located in part 211 (21 CFR part 211, CGMP requirements) rather than part 201 (21 CFR part 201, labeling requirements). These comments recommend that any proposed labeling requirements be included in part 201.

(Response 8) FDA largely agrees with these comments and is reorganizing this content in the final rule. Specifically, the labeling content requirements in proposed § 211.94(e)(4) are being finalized under new § 201.328, while requirements that medical gas labels and coloring materials be resistant to wear and, in the case of labels, not susceptible to inadvertent removal, have been retained in § 211.94(e).

- Requirement for 360° Wraparound Label for Portable Cryogenic Medical Gas Containers (§ 201.328(a)(1))

In § 211.94(e)(4) of the proposed rule (renumbered as § 201.328(a)(1) in this final rule), FDA proposed to require portable cryogenic containers to bear 360° wraparound labeling that meets naming, lettering, and placement specifications.

(Comment 9) Many comments expressed concern about the proposed requirement that the word “Medical” precede the name of the gas on the wraparound label. These comments state that there is a risk that users would focus on the “Medical” designation and ignore the more significant information, i.e., the identity of the gas itself (e.g., oxygen versus nitrogen). Therefore, these comments recommend removing this requirement from the final rule. Some of these comments also state that this naming requirement would be inconsistent with the “established name” of the gas, e.g., Oxygen USP or Nitrogen NF (see definition of “established name” at section 502(e)(3) of the FD&C Act). As an alternative, one comment proposes that the rule refer to the product name and provide that either the word “Medical” may precede, or “USP” or “NF” may follow, the product name.

(Response 9) FDA proposed adding the word “Medical” to the wraparound label to distinguish containers labeled with medical gases from containers holding industrial gases. This proposed requirement was intended to make the contents of the containers more readily and accurately identified by 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 mix-ups. However, FDA agrees with the comments that inclusion of the word “Medical” in the name of the gas would be inconsistent with the established names of medical gases.

Accordingly, as set forth in § 201.328(a)(2), FDA will instead require that the portable cryogenic containers bear a label (either the wraparound label or a separate label) near the top of the container but below the top seam weld that includes the phrase “For Medical Use,” “Medical Gas,” or some similar phrase that indicates the gas is for medical use in conspicuous lettering.

FDA has also reconsidered the proposed requirement that gases be identified on the wraparound label by their “standard names.” Section 502(e) of the FD&C Act provides that a drug product is misbranded unless its label bears the established name of the drug, if there is such a name. All of the gases listed at § 201.328(c) have established names. Thus, the proposed requirement regarding “standard names” is not necessary, and we are removing this concept from the final rule.

(Comment 10) A few of the parties providing comments state that while they agree with the proposed requirement at § 211.94(e)(4)(i)(E) that the label be placed “as close to the top of the container as possible but below the top weld seam”, they object to the following phrase: “...so that it cannot be easily detached or worn” (§ 211.94(e)(4)(i)(F)). These comments express concern that if the label is worn or detached by the user, for whatever reason, the manufacturer may be considered to be not in compliance with the proposed rule requirements, when in fact the firm may have properly placed the label.

(Response 10) FDA agrees that this proposed requirement should be revised. The key issue is that the wraparound label be affixed such that it is not susceptible to wear or to being inadvertently removed during normal use, and FDA is revising this requirement accordingly (see § 211.94(e)(2) of this final rule).

(Comment 11) Many comments note that the minimum lettering height requirement for the name of the gas on the wraparound label in the proposed rule (2 ¾ inches) is inconsistent with the industry practice (minimum letter height of 2 inches). According to these comments, requiring 2 ¾ inch letters will reduce the number of times the name can be fully printed on the label, and will come at a considerable expense to those suppliers that currently comply with the 2-inch industry practice.

(Response 11) FDA is revising the minimum letter height requirement in consideration of these comments. The final rule states that the lettering height for the name of the gas on the label must be at least 2 inches high (see § 201.328(a)(1)(ii) of this final rule).

- Color Requirements for Medical Gas Cylinders (§ 201.328(a)(1)(v) and (b))

(Comment 12) Many comments support color-coding high-pressure cylinders, but are concerned that FDA may be placing undue emphasis on this means of identification. These comments contend that health care personnel should primarily rely on the label to identify the gas or gases in a container, and argue that reliance on color is problematic because of the variability of lighting conditions, color fading, and potential personnel colorblindness. Other comments state that reliance on color coding would appear to contradict training programs that industry and FDA have implemented to prevent mix-ups, as the consistent and fundamental themes of these training programs has been to emphasize that the label should be the primary indicator of a container's contents.

(Response 12) FDA agrees that the wording on the label should be used as the primary means of identifying a drug product. Requiring color coding of high-pressure cylinders, which we understand is already industry practice (Ref. 2), simply provides an additional safeguard to facilitate accurate identification of the drug product and detection of potential errors.

Additionally, § 211.25 addresses the need to train qualified personnel in the manufacture, processing, packing, or holding of a drug product. Proper training should help mitigate against the possibility that users might improperly rely solely on the cylinder's color to identify its contents.

(Comment 13) Many comments recommend removing the requirement of "colored in whole" for non-aluminum high-pressure cylinders. These comments state that the current industry practice is to paint the shoulder to match the designated color for that medical gas. This

is based on manufacturer recommendations that some non-aluminum high-pressure cylinders should not be painted in whole due to concerns about concealing defects.

(Response 13) FDA agrees with these comments. Thus, the final rule requires only that high-pressure medical gas cylinders be colored on the shoulder portion of the cylinder (see § 201.328(b)), which is consistent with what FDA understands to be industry practice (Ref. 2).

(Comment 14) Many comments dispute FDA's assumption that a large majority of high-pressure medical gas cylinders are already in compliance with the proposed coloring requirements. These comments note that portions of the shoulders of many cylinders are painted white to make retest information more visible, and that the upper neck portion of many cylinders are not painted a color based on the contents of the cylinder.

(Response 14) The cylinder coloring requirement in the final rule (see § 201.328(b)) would not require recoloring of cylinders colored in the manner described in the comments. As long as the cylinder shoulder is colored in the FDA-designated color or colors, the upper neck portion of the cylinder need not be that same color and use of white to make retesting information on a portion of the shoulder of the cylinder more visible is acceptable.

(Comment 15) Many comments recommend removal of the requirement that high-pressure medical gas cylinders containing mixtures of gases be painted in rough proportion to the fractions of gases contained in the mixture. These comments express concern that this method may cause the end user to ignore the label and rely on color proportions to identify the contents of a mixture. Additionally, these comments recommend that the following language be incorporated in the regulation: "when color marking consists of 2 or more colors, the pattern shall permit a portion of the colors to be seen together when viewed from the top," which is consistent with industry practice.

(Response 15) FDA agrees with these comments. Therefore, FDA is revising the rule to require that the color for every constituent gas be visible when the cylinder is viewed from the top, and to remove the proportionality requirement.

(Comment 16) Many comments recommend removing the proposed requirement (at § 211.94(e)(4)(i)(G) in the proposed rule) that if the shoulder portion of a portable cryogenic medical gas container is colored, the color used must be the FDA-designated color of the gas held in the container. These comments point out that painting cryogenic containers with dark colors causes increased heat absorption, accelerating the rate of product venting, which could lead to unsafe conditions. These comments also note that large cryogenic containers made from carbon steel are painted in whole (including on the shoulder) in a light-reflective color, which would not necessarily correspond to the FDA-designated color or colors of the gas or gases held in the container.

(Response 16) FDA agrees with these concerns and is revising the proposed coloring requirement for portable cryogenic medical gas containers. As set forth in § 201.328(a)(1)(v) of the final rule, a portable cryogenic medical gas container may only be colored, in whole or in part, in the color or colors designated at § 201.328(c) if the gas or gases held in the container correspond to that color or those colors. The container may still be colored in a light-reflective color such as white (or some other color that is not an FDA-designated gas color), or simply not colored at all.

Finally, FDA is revising color requirements for the wraparound label such that they only apply to portable cryogenic medical gas containers that hold a single gas (see § 201.328(a)(1)(i) of this final rule). FDA believes that multiple colors on a single wraparound label--either in the lettering or in the background--may be impractical. Firms may still choose to follow the color

scheme at § 201.328(a)(1)(i) for portable cryogenic medical gas containers that hold gas mixtures or blends, but will not be required to do so.

- Proposed Prohibition on Conversion of Cryogenic Containers and High-Pressure Cylinders From Industrial to Medical Use (proposed § 211.94(e)(1))

In § 211.94(e)(1) of the proposed rule, FDA proposed prohibiting cryogenic containers and high-pressure cylinders used to hold industrial gases from being converted to medical use, subject to limited exceptions.

(Comment 17) Many comments oppose any requirements to dedicate high-pressure cylinders and cryogenic containers to solely one use--industrial or medical. These comments contend that the root cause of the contamination incidents involving high-pressure cylinders discussed in the preamble to the proposed rule was the improper cleaning of cylinders, regardless of whether the cylinders previously held gases intended for medical or industrial use. These comments argue that the costs that would be associated with implementing this rule are not justified considering that the preamble to the proposed rule identified only two contamination incidents leading to injuries. According to these comments, these costs would include procuring additional containers (and associated assets), tracking individual containers over their useful life, marking containers for industrial or medical use, and increased distribution expenses. These comments further argue that FDA significantly underestimated the costs associated with this requirement in the economic analysis provided in the preamble to the proposed rule.

Many comments state that the proposed prohibition on conversion of medical gas containers from industrial to medical use is unwarranted because existing CGMP requirements, particularly § 211.94(c) (requiring cleaning of containers and closures to assure they are suitable for their intended use) and § 211.100(a) (requiring written procedures for process and production

control designed to assure drug products have the identity, strength, quality, and purity they purport or are represented to possess), are adequate to prevent contamination associated with such conversion. These comments further argue that the proposed rule is inconsistent with FDA's past advice that medical gas assets can be converted from industrial to medical use and need not be dedicated to industrial use provided the items in question undergo validated cleaning procedures when converted to medical use.

(Response 17) FDA has reevaluated this proposed requirement in light of these concerns. FDA has determined that the risk of contamination associated with converting gas containers from industrial to medical use is relatively low, and can be fully addressed if the manufacturer, in compliance with §§ 211.84(a), 211.94(c), 211.100, and other applicable CGMP regulations, employs adequate, validated cleaning and production control strategies when performing such conversion. FDA also agrees with the comments that the proposed requirement to dedicate containers to either industrial or medical use would be quite expensive to implement, and, in light of our assessment that existing regulations are adequate to address this concern, not cost-justified. Accordingly, we are removing this requirement from the final rule.

(Comment 18) One comment states that the incidents dated March 20, 1998, and March 27, 1996, attributed in the proposed rule to contamination likely associated with conversion of high-pressure cylinders from industrial to medical use, could have been ignition events involving polytetraethylene seals or sealing tape. The comment suggests that a more detailed description of these events should be provided in order to make clear that the odors and compounds detected were from improper cleaning and not from ignition events.

(Response 18) As stated, FDA has reevaluated the necessity of the proposed non-conversion requirement and is removing it from the final rule.

- Requirement for Secure Gas-Specific Use Outlet Connections on Portable Cryogenic Medical Gas Containers (§ 211.94(e)(1))

In § 211.94(e)(3) of the proposed rule, FDA proposed to require that portable cryogenic medical gas containers not manufactured with permanent gas use outlet connections have gas-specific use outlet connections that cannot be readily removed or replaced except by the manufacturer. FDA is finalizing this provision (renumbered as § 211.94(e)(1)) with certain minor modifications explained in this document.

(Comment 19) Many comments support this requirement, as it would have a positive impact on patient safety by making medical gas mix-ups less likely. In fact, these comments recommend that the rule be extended to other outlets typically found on portable cryogenic medical gas containers, namely, the vent outlet and liquid fill/withdrawal outlet.

(Response 19) FDA is not aware of mix-up incidents involving the vent outlet valves or with liquid fill/withdrawal outlets, and such hypothetical mix-ups do not seem likely, given that the gas use outlet connection should be the only connection used to connect a portable cryogenic container to a health care facility's gas supply system. Accordingly, FDA believes that it is not necessary to extend the secure gas-specific use outlet connection requirement to vent outlets or liquid fill/withdrawal outlets.

(Comment 20) Some comments propose that the Agency slightly modify the exemption for "small cryogenic gas containers for use by individual patients" from the proposed definition of "portable cryogenic medical gas containers." These comments note that some liquid oxygen home units designed for use by individual patients are, in fact, also used in certain situations to fill other containers for use by patients. These comments are concerned that if the exemption is not clarified, these liquid oxygen home units may be subject to the secure gas use outlet

connection rule if they are used to fill other containers. Accordingly, these comments propose that the exemption be revised to include “small cryogenic gas containers designed for use by individual patients at their residence, including health care facilities” (emphasis added).

(Comment 21) Many comments propose that FDA clarify in the rule that the requirement for secure gas-specific use outlet connections is inapplicable to cryogenic containers that are too large (e.g., tank trucks, trailers, rail cars) to be connected to a medical gas supply system.

(Response to Comments 20 and 21) FDA agrees that the definition of “portable cryogenic medical gas container” as used in the rule should be clarified. As such, we are clarifying in the final rule that cryogenic gas containers not designed to be connected to a medical gas supply system, including tank trucks, trailers, rail cars, and liquid oxygen home units, are exempt from the secure gas-specific use outlet connection requirement.

(Comment 22) A comment recommends that base units used to fill portable containers for use by patients in hospitals and other health care facilities, and large cryogenic containers that may be placed on trailers along with vaporizers and that are used as emergency backup when repairs are performed on the health care facility’s permanent storage system, also be excluded from the rule. The comment states that because these base units and containers remain within the control of the medical gas manufacturer, and not the consumer, the risk of an improper connection is substantially reduced.

(Response 22) FDA does not agree that base units used to fill portable containers for use by patients in hospitals and other health care facilities and large cryogenic containers that may be placed on trailers along with vaporizers and that are used as emergency backup when repairs are performed on the health care facility’s permanent storage system should be excluded from the rule. We believe that requiring such containers (which are designed to be connected to a medical

gas supply system) to have secure gas-specific use outlet connections will help minimize the likelihood that an incorrect gas is connected to a gas distribution system or container.

(Comment 23) Many comments express concern with the discussion of records maintenance in the proposed rule. The PRIA indicated that there could be a slight increase in the medical gas industry's container closure records maintenance activities under § 211.184 if the industry chooses to use locking valves or devices to bring portable cryogenic containers into compliance with the secure gas-specific use outlet connection requirement. The proposed rule stated that under existing § 211.184(b), records of the results of any test or examination of a container closure under § 211.82(a) must be maintained, and that under existing § 211.184(c), an individual inventory record must be maintained for each container closure. FDA estimated that about 10 percent of the existing inventory of portable cryogenic containers would need to be modified to comply with the secure gas-specific use outlet connection requirement, that the industry would choose to comply through use of locking valves or devices (rather than silver brazing, which is more expensive), and that the records maintenance activities associated with this work would amount to about 2 minutes per locking device per year, resulting in an annualized records maintenance cost of about \$54,000 dollars per year. The estimate of 2 minutes per locking device per year includes time associated with the initial inspection of the locking valve or device by the manufacturer (71 FR 18039 at 18048-18049).

The comments express concern that the proposed rule's reference to § 211.184(c) in particular entails a change of policy from FDA's historic application of records maintenance regulations to the medical gas industry and amounts to a new records maintenance expectation for medical gas containers and closures that would cost the industry between \$376 and \$665 million dollars to meet. The comments appear to reach this much higher number by assuming

that it would be necessary to serialize valves and/or permanently mark all valves and connections on portable cryogenic containers to meet what they contend are FDA's new records maintenance expectations.

(Response 23) FDA does not believe that serializing or permanently marking all valves and connections on portable cryogenic containers is necessary to satisfy the requirements of § 211.184. FDA did not intend to announce new or heightened records maintenance expectations for medical gas container closures in the proposed rule. While FDA believes that the records maintenance activities used to arrive at the estimate in the PRIA section for the records maintenance costs associated with the secure gas-specific use outlet connection requirement are appropriate, medical gas manufacturers may employ alternative records maintenance procedures to document any work performed to bring container closures into compliance with the secure gas-specific use outlet connection requirement.

As discussed in the Final Regulatory Impact Analysis (see Section VI), the estimated records maintenance costs associated with the secure gas use outlet connections requirements have been revised to range between \$70 and \$3,500. This reduction in estimated costs is largely driven by updated information showing that the number of portable cryogenic containers in the market is much lower than was thought at the time the proposed rule was issued.

- Miscellaneous Comment

(Comment 24) A comment requests that the final rule include a requirement that all personnel handling medical gases have documented competency training. This comment states that medical gases are USP listed and should be delivered by qualified personnel, such as respiratory therapists (who, according to this comment, are the only health care professionals specifically educated and competency-tested in all aspects of oxygen therapy).

(Response 24) In § 211.25 individuals engaged in the manufacture, processing, packing, or holding of a drug product (which would include a medical gas manufacturer's delivery personnel) are required to have the education, training, and experience necessary to perform assigned functions. Further, we are not aware that actual administration of medical gases to patients is part of the function of medical gas delivery personnel, so it is not clear why such personnel would need to be trained to administer gases to patients. We believe the existing regulation (§ 211.25) is sufficient to address any issues that may arise regarding the qualifications of a medical gas manufacturer's delivery personnel.

#### V. Compliance Date

This rule is effective [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Affected firms and persons are encouraged to comply as soon as possible after the effective date. We recognize, however, that while most of the requirements of this final rule are already industry practices (Refs. 1-3), such practices are not ubiquitous. Accordingly, the compliance date is [INSERT DATE 180 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. We believe it would be reasonable for affected firms and persons to fully implement this final rule in that amount of time.

(Comment 25) FDA received several comments that the 60-day time period proposed for implementation of the proposed rule is insufficient. These comments state that the proposal will impact every portable cryogenic container and request that FDA provide a reasonable transition period consistent with FDA precedents.

(Response 25) FDA agrees, and is establishing a compliance date that is 180 days after publication of the final rule in the Federal Register, as noted previously. The Agency believes that it would be reasonable for affected firms and persons to fully implement the final rule in this

amount of time. Furthermore, to avoid any contradiction with this compliance date, and for purposes of clarity, FDA is removing paragraph (c) of § 201.161, which states that regulatory action may be initiated with respect to any article shipped within the jurisdiction of the FD&C Act contrary to the provisions of this section after 60 days following publication of this section in the Federal Register.

## VI. Economic Analysis of Impacts

### A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us 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). We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule imposes new burdens on small entities, we cannot certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing “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 1 year.” The current threshold after adjustment for inflation is \$146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in an expenditure in any year that meets or exceeds this amount.

### B. Summary of Costs and Benefits

This final rule amends the CGMP and labeling regulations for medical gases. These amendments include the following: (1) Portable cryogenic medical gas containers not manufactured with permanent gas use outlet connections must have gas-specific use outlet connections that cannot be readily removed or replaced except by the manufacturer; (2) portable cryogenic medical gas containers must have a 360° wraparound label that clearly identifies the container’s contents and conforms to certain placement, lettering, and other requirements; (3) high-pressure medical gas cylinders (and portable cryogenic medical gas containers, if colored) must be colored using an FDA-designated standard color (or colors in the case of gas mixtures); (4) the list of medical gases that are conditionally exempt from certain otherwise-applicable labeling requirements has been revised; and (5) the warning statements required to be on final use containers to qualify for the conditional exemption from certain otherwise-applicable labeling requirements have been modified for oxygen and medical air.

The rule is expected to provide a modest net social benefit (estimated benefits minus estimated costs) to society. Costs are attributed to coloring medical gas containers, complying with the 360° wraparound label requirement for portable cryogenic containers, and requiring gas-specific use outlet connections on portable cryogenic containers to be permanently attached to the valve body (e.g., by silver brazing) or attached to the valve body using a locking mechanism or other appropriate device so that only the manufacturer can readily remove or replace them.

Using a standard 10 year time period, we estimate annualized costs to range between \$0.18 million to \$1.5 million using a 3 percent discount rate and \$0.21 million to \$1.8 million using a 7 percent discount rate. Benefits are attributed to reducing the probability that medical personnel accidentally administer the wrong gas to patients, resulting in serious injury or death. We estimate annualized benefits to approximately range between \$0.8 million to \$2.8 million using a 3 percent discount rate, and \$2.5 million to \$8.3 million using a 7 percent discount rate. Together we estimate annualized net benefits to range between \$0.62 million to \$1.3 million using a 3 percent discount rate, and \$2.3 million to \$6.5 million using a 7 percent discount rate.

FDA also examined the economic implications of the rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires us to analyze regulatory options that would lessen the economic effect of the rule on small entities. The rule imposes new costs to small entities. We estimate the rule's one-time costs to roughly range between 0.0001 percent and 0.13 percent of average annual revenues.

The full analysis of economic impacts is available in the docket for this final rule (Ref. 4) and at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

#### VII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(j) and (k) 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.

#### VIII. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the OMB under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection provisions are shown in this section with an estimate of the third-party disclosure and recordkeeping burdens. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

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

Description: The final rule revises FDA's labeling and CGMP regulations to include new requirements for the label, color, and design of medical gas containers and closures. These requirements are intended to make the contents of medical gas containers more readily identifiable and to reduce the likelihood that the wrong gas will be connected to a medical gas supply system.

Description of Respondents: Persons and businesses, including small businesses and manufacturers, involved in the processing, manufacturing, transportation, handling, and administration of designated medical gases. FDA's database of establishments that manufacture medical gases includes about 2,500 such establishments.

We estimate the burden for the collection of information as follows:

Third-party disclosure: Table 1 shows the estimated one-time third-party disclosure burden. Upon implementation of the requirements under the final rule, we expect respondents will have realized the associated burden. In our subsequent PRA evaluation conducted in connection with requesting a renewal of OMB's approval of the information collection

associated with this rule (assuming that initial approval occurs), we will adjust our estimate accordingly.

Table 1.--Estimated One-Time Third-Party Disclosure Burden<sup>1</sup>

21 CFR Sections	No. of Respondents	No. of Disclosures per Respondent	Total Disclosures	Average Burden per Disclosure	Total Hours
201.328(a)(1) and (2) and 211.94(e)(2) Portable Cryogenic Medical Gas Container Labels and Colors	2,500	14	35,000	0.10 (6 minutes)	3,500
201.328(b) and 211.94(e)(2) High-Pressure Medical Gas Cylinder Colors	2,500	984	2,460,000	0.10 (6 minutes)	246,000
Total	2,500	998	2,495,000	0.10 (6 minutes)	249,500

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

A gas listed at § 201.161(a) is exempt from certain labeling requirements if its labeling bears, among other things, a warning statement that conforms to § 201.161(a)(1). Section 201.161(a)(1)(i) specifies the content to be included in a warning statement for oxygen and § 201.161(a)(1)(ii) specifies the content to be included in a warning statement for nitrogen, carbon dioxide, helium, nitrous oxide, and any medically appropriate combinations of any of the gases listed in § 201.161(a). FDA believes most medical gases are already labeled in a manner that complies with § 201.161(a) as finalized. Furthermore, because § 201.161(a) provides the warning statement content to be included in medical gas labeling, the inclusion of these warning statements on medical gas labeling is not considered a “collection of information” subject to review under the PRA. See 5 CFR 1320.3(c)(2) (providing that “the public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public is not included” within the definition of “collection of information”).

Under § 201.328(a)(1), each portable cryogenic medical gas container must be conspicuously marked with a 360° wraparound label identifying its contents. The identity of the medical gas held in the container must be printed on the label in one of the following ways: Using lettering that appears in the standard color designated for the gas in § 201.328(c) and that is printed against a white background, or using lettering that appears in white against a background that is painted in the standard color for the gas as designated in § 201.328(c). The lettering for the name of the gas on the label must be at least 2 inches high; the name of the gas must be printed continuously around the label and be capable of being read around the entire container; 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; and, if the shoulder portion of a portable cryogenic gas container is colored, the color used must be the standard color or colors designated in § 201.328(c) for the gas or gases held within the container.

Under § 201.328(a)(2), the 360° wraparound label required in § 201.328(a)(1), or a separate label, must include in conspicuous lettering the phrase “For Medical Use,” “Medical Gas,” or some similar phrase that indicates the gas is for medical use. Finally, under § 211.94(e)(2), the wraparound label must be affixed to the container in a manner that does not interfere with other labeling and such that it is not susceptible to becoming worn or inadvertently detached during normal use, and the wraparound label must be reasonably resistant to fading, durable when exposed to atmospheric conditions, and not readily soluble in water.

We estimate that there are approximately 35,000 portable cryogenic containers in medical gas service that are subject to the labeling requirements at § 201.328(a). As discussed in the Economic Analysis of Impacts, FDA conservatively estimates that all manufacturers will

choose to comply with § 201.328(a) by removing any existing wraparound labels from all portable cryogenic containers and replacing them with wraparound labels that meet all of the requirements at § 201.328(a). Thus, on average, each manufacturer would need to add labels to (or re-label) approximately 14 containers ( $35,000 \div 2,500$ ). FDA estimates that approximately 6 minutes would be required to remove any existing wraparound label and attach a new wraparound label to each container. Thus, the total burden third-party disclosure burden hours associated with § 201.328(a)(1) and (2) is approximately 3,500 hours ( $2,500 \times 14 \times 0.10$  hours).

Section 201.328(a)(1)(v) also provides that a portable cryogenic cylinder may only be colored in the color or colors designated in § 201.328(c) if the gas or gases held within the container correspond to that color or those colors. Alternatively, the container may be colored in a light-reflective color such as white (or some other color which is not an FDA-designated gas color), or simply not colored at all. Based on discussions with subject matter experts, we believe that few to no cryogenic containers will require recoloring as a result of this requirement, and therefore we estimate no third-party disclosure burden associated with this requirement.

Under § 201.328(b), high-pressure medical gas cylinders must be colored on the shoulder with the colors designated in § 201.328(c) for the gas contained in the cylinder, and such colors must be visible when viewed from the top of the cylinder. Under § 211.94(e)(2), the materials used for coloring medical gas containers must be reasonably resistant to fading, durable when exposed to atmospheric conditions, and not readily soluble in water. Based on information contained in the Economic Analysis of Impacts (see Section VI), we estimate that as many as 10 percent of the estimated 24.6 million high-pressure cylinders in medical service will require coloring or recoloring to comply with § 201.328(b). Thus, on average, each manufacturer

would need to color 984 containers (2.46 million ÷ 2,500). We conservatively estimate that it will take an average of 6 minutes to color a cylinder. Thus, the total third-party disclosure burden hours associated with § 201.328(b) is approximately 246,000 hours (2,500 x 984 x 0.10 hours).

Recordkeeping: Table 2 shows the estimated annual recordkeeping burden associated with the information collection

Table 2.--Estimated Annual Recordkeeping Burden<sup>1</sup>

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
211.184 and 211.94(e)(1) Records Maintenance of Secure Gas Use Outlet Connection Requirement	2,500	0.7	1,750	0.033 (2 minutes)	58

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

Section 211.94(e)(1) requires that portable cryogenic medical gas containers that are not manufactured with permanent gas use outlet connections must have gas-specific use outlet connections that are attached to the valve body so that they cannot be readily removed or replaced except by the manufacturer. A small portion of the existing inventory of portable cryogenic containers would need to be modified to comply with this requirement, and manufacturers must maintain records in accordance with § 211.184 for drug product containers. As discussed in the Economic Analysis of Impacts (see Section VI), FDA conservatively estimates that manufacturers will need to secure the gas use outlets of as many as 1,750 portable cryogenic containers to bring them into compliance with the final rule. As a result each manufacturer would incur annual recordkeeping under § 211.184 incident to bringing, on average, 0.7 containers into compliance with the secure gas use outlet connection requirement (1,750 ÷ 2,500). Consistent with our estimate in the proposed rule, this should require an

average of 2 minutes (0.033 hours) per container. This results in an annual burden of 58 hours (2,500 x 0.7 x 0.033 hours) for 1,750 records.

The information collection provisions of this final rule have been submitted to OMB for review, as required by section 3507(d) of the PRA. Before the effective date of this final rule, FDA will publish a notice in the Federal Register announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

#### IX. Federalism

We have analyzed this final 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, we conclude 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.

#### X. References

The following reference is on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at <http://www.regulations.gov>. FDA has verified the Web site address, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. CGA M-15, Standard for Appropriate and Effective Regulations for Medical Gases within 21 CFR Parts 201, 2015, and 210/211 (Compressed Gas Association 2014, 1st ed), at pages 1, 14-15, 35.

2. CGA C-9, Standard Color Marking of Compressed Gas Containers for Medical Use (Compressed Gas Association 2013, 5th ed).

3. CGA Safety Bulletin SB-26, Cylinder Connections on Portable Liquid Cryogenic Cylinders (Compressed Gas Association 2014, 4th ed).

4. Medical Gas Containers and Closures; Current Good Manufacturing Practice Requirements, Final Regulatory Impact Analysis, Final Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis, Docket No. FDA-2005-N-0343, available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 211

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

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

PART 201--LABELING

1. The authority citation for 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. Revise § 201.161 to read as follows:

§ 201.161 Medical gases.

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

(1)(i) In the case of oxygen, a warning statement providing that uninterrupted use of high concentrations of oxygen over a long duration, without monitoring its effect on oxygen content of arterial blood, may be harmful; that oxygen should not be used on patients who have stopped breathing unless used in conjunction with resuscitative equipment; and, in the case of oxygen that may be provided without a prescription for use in the event of depressurization or other environmental oxygen deficiency, or for oxygen deficiency or for use in emergency resuscitation when administered by properly trained personnel, a warning statement providing that oxygen may be used for emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation, and that for all other medical applications a prescription is required.

(ii) In the case of nitrogen, carbon dioxide, helium, nitrous oxide, and medically appropriate combinations of any of the gases listed in paragraph (a) of this section, a warning statement providing that the administration of the gas or gas combination (as applicable) may be

hazardous or contraindicated; and that the gas or gas combination (as applicable) should be used only by or under the supervision of a licensed practitioner who is experienced in the use and administration of the gas or gas combination (as applicable) and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications, and side effects and the precautions to be taken.

(2) Any needed directions concerning the conditions for storage and warnings against the inherent dangers in the handling of the specific compressed gas.

(b) [Reserved]

3. Add new § 201.328 to read as follows:

§ 201.328 Labeling of medical gas containers.

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

(1) Each portable cryogenic medical gas container must be conspicuously marked with a 360° wraparound label identifying its contents. Such label must meet the requirements of § 211.94(e)(2) of this chapter and the following additional requirements.

(i) If the container holds a single gas, the name of the gas held in the container must be printed on the label in one of the following ways:

(A) Using lettering that appears in the color designated for the gas in paragraph (c) of this section and that is printed against a white background, or

(B) Using lettering that appears in white against a background that is painted in the color for the gas designated in paragraph (c) of this section.

(ii) The lettering for the name of the gas on the label must be at least 2 inches high.

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

(iv) The label must be on the sidewall of the container, as close to the top of the container as possible but below the top weld seam.

(v) A portable cryogenic medical gas container may only be colored in the color or colors designated in paragraph (c) of this section if the gas or gases held within the container correspond to that color or those colors.

(2) A label on the container (either the 360° wraparound label required in paragraph (a)(1) of this section or a separate label) must include, in conspicuous lettering, the phrase “For Medical Use”, “Medical Gas,” or some similar phrase that indicates the gas is for medical use.

(b) High-pressure medical gas cylinders. Each high-pressure medical gas cylinder must be colored on the shoulder portion of the cylinder in the color or colors designated in paragraph (c) of this section. The color or colors must be visible when viewed from the top of cylinder.

(c) Medical gas colors. The colors required to identify medical gases under paragraph (a) and (b) of this section are:

Medical Gas	Color
Medical Air	Yellow
Carbon Dioxide	Gray
Helium	Brown
Nitrogen	Black
Nitrous Oxide	Blue

Oxygen	Green
Mixture or Blend	Colors corresponding to each component gas

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4. The authority citation for 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.

5. Amend § 211.94 by adding new 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) Gas-specific use outlet connections. Portable cryogenic medical gas containers that are not manufactured with permanent gas use outlet connections (e.g., those that have been silver-brazed) must have gas-specific use outlet connections that are attached to the valve body so that they cannot be readily removed or replaced (without making the valve inoperable and preventing the containers' use) except by the manufacturer. For the purposes of this paragraph, the term "manufacturer" includes any individual or firm that fills high-pressure medical gas cylinders or cryogenic medical gas containers. For the purposes of this section, a "portable cryogenic medical gas container" is one that is capable of being transported and is intended to be attached to a medical gas supply system within a hospital, health care entity, nursing home, other facility, or home health care setting, or is a base unit used to fill small cryogenic gas containers for use by individual patients. The term does not include cryogenic containers that are not designed to be connected to a medical gas supply system, e.g., tank trucks, trailers, rail cars, or small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined at § 868.5655 of this chapter).

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

6. Amend § 211.125 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 15, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016-27838 Filed: 11/17/2016 8:45 am; Publication Date: 11/18/2016]