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**Policy for the Temporary Use of
Portable Cryogenic Containers Not
in Compliance With 21 CFR
211.94(e)(1) For Oxygen and
Nitrogen During the COVID-19
Public Health Emergency**

Guidance for Industry

April 2020
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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or the Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <https://www.regulations.gov>. All comments should be identified with the docket number FDA-2020-D-1136 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA web page titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders> and the FDA web page titled "Search for FDA Guidance Documents," *available at* <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. You may also send an e-mail request to druginfo@fda.hhs.gov to receive an additional copy of the guidance. Please include the document number FDA-2020-D-1136 and complete title of the guidance in the request.

Questions

For questions about this document, contact COVID-19-MedicalGases@fda.hhs.gov.

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Policy for the Temporary Use of Portable Cryogenic Containers Not in Compliance With 21 CFR 211.94(e)(1) For Oxygen and Nitrogen During the COVID-19 Public Health Emergency¹

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

As demand for oxygen and nitrogen intended for medical use increases due to the COVID-19 pandemic, FDA has become aware of concerns regarding a low supply of portable cryogenic medical gas containers and has received inquiries regarding the use of gas containers that do not meet certain regulatory requirements for portable cryogenic medical gas containers (e.g., industrial gas containers).

FDA is issuing this guidance to communicate its policy for the temporary use of certain gas containers for oxygen and nitrogen intended for medical use for the duration of the public health emergency declared by the Secretary of Health and Human Services (HHS) on January 31, 2020.

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020 (85 FR 16949), titled “Process for Making Available Guidance Documents Related to Coronavirus Disease 2019,” available at <https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf>, this guidance is being implemented without prior public comment because

¹ This guidance has been prepared by the Center for Drug Evaluation and Research in consultation with the Center for Devices and Radiological Health at the Food and Drug Administration.

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FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

This guidance is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by HHS, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (42 U.S.C. 247d(a)(2)).

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.² In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.³

This emergent situation has resulted in an acute surge in demand for oxygen used for resuscitation and inhalation therapy and nitrogen used in drug development research settings and medical gas manufacturing. Guidance is needed for manufacturers to address the potential shortfall in containers for these medical gases to meet this surge in demand while still preventing mix-ups and assuring product quality. At such time when the public health emergency is over, as declared by the HHS Secretary, FDA intends to discontinue this enforcement discretion policy and withdraw this guidance.

III. Discussion

Medical gases are generally regulated as finished pharmaceuticals and are subject to current good manufacturing practice (CGMP) requirements.⁴ Compliance with applicable CGMP requirements

² Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Jan. 31, 2020), available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx>.

³ Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), available at <https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>.

⁴ See section 201(g)(1) of the FD&C Act for the definition of "drug." See section 575 of the FD&C Act for the definition of "medical gas" and section 576 of the FD&C Act for the definition of a "designated medical gas." A medical gas that meets the definition of a "drug" under section 201(g)(1) of the FD&C Act is deemed to be adulterated under section 501(a)(2)(B) of the FD&C Act if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing

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helps to ensure the safety, identity, strength, quality, and purity of medical gases. Medical gases that are not manufactured, processed, packed, or held according to applicable CGMP requirements can cause serious injury or death.⁵

Medical gas containers, closures, and labeling are integral parts of medical gas drug products and play a critical role in ensuring that the drug product provided to the patient has the appropriate identity, strength, quality, and purity. Medical gas drug products, including their containers, must meet the requirements of the FD&C Act concerning CGMP and labeling.⁶

To prevent serious injury or death due to mix-ups, there is a specific requirement under FDA's CGMP regulations that portable cryogenic medical gas containers that are not manufactured with permanent gas use outlet connections (e.g., those that have been silver-brazed) 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 container's use) except by the manufacturer (§ 211.94 (e)(1) (21 CFR 211.94(e)(1)));⁷ these connections are generally referred to as *tamper-resistant* connections. If the gas-specific-use outlet connection can be readily removed and replaced, a cylinder could be inadvertently connected to a distribution system containing gas that is different from the gas in the cylinder, with the potential to cause serious injury or death. In general, industrial gas and liquid cylinder fittings have a threaded product-specific valve outlet connection with a device that is intended to deter removal of the fitting and provides an indication that removal was attempted or accomplished (also known as a *tamper-evident* connection).

All portable cryogenic medical gas containers, including those used for oxygen and nitrogen, must be § 211.94(e)(1)-compliant.⁸ However, we understand that there may be difficulty in ensuring that a consistent supply of portable cryogenic medical gas containers that have tamper-resistant outlet connections in compliance with § 211.94(e)(1) is available during the COVID-19 outbreak.

Compliance with the requirement in § 211.94(e)(1) to use portable cryogenic medical gas containers with either permanent gas use outlet connections or gas-specific use outlet connections that are attached to the valve body as described in the regulation plays an important role in

practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." See 21 CFR parts 210 and 211.

⁵ A number of injuries and deaths have resulted from medical gases not being produced or handled properly. For example, there have been 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. For further details regarding several of these incidents, see proposed rule "Medical Gas Containers and Closures; Current Good Manufacturing Practice Requirements" (71 FR 18039, April 10, 2006).

⁶ See 21 CFR parts 201, 210, and 211.

⁷ For purposes of § 211.94(e)(1), the term "manufacturer" includes any individual or firm that fills high-pressure medical gas cylinders or cryogenic medical gas containers.

For purposes of § 211.94(e)(1), 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 21 CFR § 868.5655).

⁸ See *id.*

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protecting patients by making medical gas mix-ups less likely, and the preamble to the 2016 final rule that codified § 211.94(e)(1) indicates that many commenters supported the requirement for this reason. However, in light of the anticipated low supply of § 211.94(e)(1)-compliant containers during the COVID-19 public health emergency, there may be circumstances where § 211.94(e)(1)-compliant containers are not available and patients would benefit from the use of oxygen and nitrogen in portable cryogenic medical gas containers that are not in compliance with § 211.94(e)(1), provided certain additional steps are taken that would, under the circumstances, adequately mitigate the likelihood of incorrect connections of the wrong cryogenic oxygen or nitrogen tank.⁹

Therefore, because of the public health emergency posed by COVID-19, when § 211.94(e)(1)-compliant portable cryogenic medical gas containers are not available, FDA does not intend to take enforcement action against firms that fill and distribute oxygen and nitrogen intended for medical use in portable cryogenic medical gas containers that are not in compliance with § 211.94(e)(1) for the duration of the public health emergency declared by the Secretary of HHS on January 31, 2020, provided the following circumstances are present:

- The gas manufacturing and labeling is in compliance with all other applicable requirements, including CGMP and labeling requirements.¹⁰ For example:
 - Components, drug product containers, and closures are tested and approved or rejected, pursuant to 21 CFR 211.84.
 - Containers and closures are cleaned to assure they are suitable for their intended use, pursuant to 21 CFR 211.94(c).
 - Written procedures for production and process control, designed to assure drug products have the identity, strength, quality, and purity they purport or are represented to possess, are established and followed, pursuant to 21 CFR 211.100.
 - Any existing labeling on the container is consistent with the required drug labeling and does not otherwise misbrand the product or violate applicable drug labeling requirements in 21 CFR part 201.¹¹

⁹ See Medical Gas Containers and Closures; Current Good Manufacturing Practice Requirements (81 FR 81685, November 18, 2016).

¹⁰ FDA has issued a draft guidance for industry, *Current Good Manufacturing Practice for Medical Gases* (June 2017). When finalized, this draft guidance will provide recommendations regarding the application of certain CGMP requirements to medical gases. The draft guidance is intended, when finalized, to reduce the regulatory compliance burden for the medical gas industry by providing clear, up-to-date, detailed recommendations regarding CGMP issues that have been the subject of industry questions. Subject to the policy described in this guidance, the June 2017 draft guidance for industry will, when finalized, reflect FDA's most current thinking regarding the application of CGMP requirements to medical gases.

¹¹ In general, it is the responsibility of the manufacturer to ensure that any existing labeling on the container does not violate applicable requirements (see 21 CFR part 211 subpart G). FDA expects that in most instances removal of inconsistent or violative labeling would be preferable to covering or obliteration and is the most common practice in industry.

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- The valve has an additional, prominent tag or label on or near the valve, directing users not to tamper with or remove the connection in order to prevent mix-ups.
- Manufacturers only distribute containers that are not in compliance with § 211.94(e)(1) if there are no § 211.94(e)(1)-compliant portable cryogenic medical gas containers available at the time of filling or distribution.
 - For the containers not in compliance with § 211.94(e)(1), the container is fitted with a *tamper-evident* connection that is suitable for its intended use.
- Manufacturers remove the cylinders that are not compliant with § 211.94(e)(1) from medical use as soon as practicable, during or at the end of the public health emergency.
- The manufacturer provides training to individuals responsible for the delivery and filling of such containers on the appropriate inspection of tamper-evident connections, including the instruction not to tamper with, or remove, the connection.¹²
- The connection is made by a trained individual, and such individual makes the connection without tampering.
- Records are maintained to identify, reconcile, and retrieve containers that are not in compliance with § 211.94(e)(1) at the end of the public health emergency.

¹² The manufacturer's staff should also provide training to the end users (e.g., healthcare facilities) of the containers on the importance of not removing or changing the gas-specific valve outlet connection.