DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 4, 16, 201, 210, 211, 213, 230, 314, and 514

[Docket No. FDA–2021–N–1333]

RIN 0910–AH96

Current Good Manufacturing Practice, Certification, Postmarketing Safety Reporting, and Labeling Requirements for Certain Medical Gases

AGENCY: Food and Drug Administration, Department of Health and Human Services (HHS).

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is issuing a final rule revising the requirements concerning current good manufacturing practice (CGMP), postmarketing safety reporting, and labeling that apply to certain medical gases. This final rule also establishes regulations regarding certification of designated medical gases. This final rule satisfies the medical gas rulemaking requirements of the Consolidated Appropriations Act, 2017.

DATES: This rule is effective December 18, 2025, except for the amendments to §§ 4.2 (amendatory instruction 2), 4.3 (amendatory instruction 3), and 4.4 (amendatory instruction 4) (21 CFR 4.2, 4.3, and 4.4), which are effective February 2, 2026. The incorporation by reference of certain material listed in this rule has been approved by the Director of the Federal Register as of February 2, 2026.

ADDRESSES: For access to the docket to read background documents or comments received, go to *https://www.regulations.gov* and insert the docket number found in brackets in the heading of this final rule into the ''Search'' box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

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SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Final Rule

On May 23, 2022, FDA issued a proposed rule to amend requirements concerning CGMP, postmarketing safety reporting, and labeling that apply to certain medical gases, and to establish regulations regarding certification of designated medical gases (87 FR 31302). This rule satisfies the requirement in section 756 of the Consolidated Appropriations Act, 2017 (Pub. L. 115–31) that FDA issue final regulations revising the Federal drug regulations with respect to medical gases by July 15, 2017.

By tailoring certain labeling, CGMP, certification, and postmarketing safety reporting requirements more narrowly to medical gases, FDA intends to better address the unique characteristics of medical gases. Specifically, the final rule is intended to provide clarity and consistency regarding how information is presented in the labeling of certain medical gases, as well as to ensure important safety information is included. The CGMP requirements in this final rule are intended to reflect appropriate requirements for the manufacturing, processing, packing, and holding of such products. The certification requirements in this final rule implement and clarify the certification process for designated medical gases described in section 576 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360ddd–1). Lastly, the new postmarketing safety reporting regulations for designated medical gases address human and animal use and better reflect the development, manufacturing, and distribution of designated medical gases. Independently and collectively, FDA anticipates that these four categories of regulatory changes will promote greater efficiency in the regulation of medical gases while helping to ensure that they adhere to all applicable safety and quality standards.

Following consideration of comments received and further internal deliberation, we are finalizing this rule as described in this document.

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

We received fewer than 25 comments on the proposed rule. The most detailed comments were from industry trade associations and consultants. The other comments were from individuals. Comments addressed many of the labeling, CGMP, certification, and safety reporting provisions, as well as general considerations, including general support, definitions, timing of the rule, and the effective date.

The remainder of this subsection includes a brief description of the four major provisions of this rule.

1. Labeling Provisions

This rule includes several changes to FDA's drug labeling regulations, including the addition of certain operations required to produce a medical gas to the list of operations that are performed by its manufacturer. We are revising the requirements for stating the ingredients in the labeling of a designated medical gas or medically appropriate combination of designated medical gases (referred to hereafter in this preamble as ''medically appropriate combination'').[1] We also specify

[1] Section 576(a)(3)(A)(i) of the FD&C Act provides that ''[a] designated medical gas for which a certification is granted under paragraph (2) is deemed, alone or in combination, as medically appropriate, with another designated medical gas or gases for which a certification or certifications have been granted, to have in effect an approved application under section [505 or 512], subject to all applicable postapproval requirements,'' for certain indications for use. FDA interprets the term

requirements for the declaration of net quantity of contents in the labeling of designated medical gases and medically appropriate combinations.

We are requiring that all designated medical gases—whether certified for human use, animal use, or both—and medically appropriate combinations bear labeling that is in a standardized format.

FDA is revising the requirements for warning statements for certain medical gases including that the labeling of medical air and carbon monoxide bear certain warning statements. We are including different labeling requirements for final use containers and bulk or transport containers. We also are requiring a new oxygen warning statement and graphic warning symbol to alert users of the risks of smoking, vaping, and open flames near an oxygen container.

FDA is revising the medical gas container labeling regulations to clarify that the owner of a designated medical gas container or a container of a medically appropriate combination can be mentioned on the container to facilitate return of the container to the owner, and to ensure that product quality issues are directed to the appropriate entity. This rule also includes clarifying revisions to the definition of ''portable cryogenic medical gas container'' for purposes of FDA's labeling regulations.

2. CGMP Provisions

FDA is issuing new CGMP regulations specific to medical gases. These regulations include many of the same categories of provisions as the general drug CGMP regulations but reflect differences in how medical gases are manufactured, processed, packed, and held. These regulations represent the minimum CGMP for medical gases. Of note, we include different cleaning requirements for medical gases because these gases are generally manufactured in a sealed, closed system, and because cleaning at inappropriate times can introduce contaminants.

FDA is including requirements for medical gas containers and closures that are similar to the general drug CGMP regulations, with an additional requirement that portable cryogenic medical gas containers and small cryogenic gas containers for use by individual patients have a working gauge to assist the user in determining whether the container contains an adequate supply of medical gas for continued use (minor revisions were made to the version of this provision in the proposed rule). This will help users determine when a container must be refilled or replaced and when a leaking or venting container is empty. We are not including time limitations on production because medical gases are generally not expected to expire or degrade. Additionally, unlike the salvaging requirements under the general drug CGMP regulations, medical gases that have been stored improperly may be salvaged unless their containers have been subjected to adverse conditions that negatively impact the identity, strength, quality, or purity of the product or the integrity of the product's container closure.

3. Certification Provisions

FDA is issuing new regulations regarding the certification process for designated medical gases that are intended to codify the certification process and provide additional clarity where necessary. These requirements govern the process for applicants to file a certification request and supplements as well as the contents of such a request. The regulations also set forth requirements concerning the transfer of ownership of a certification from one entity to another.

We are requiring the submission of a streamlined annual report, to include certain required contents and submission timing. Changes to the proposed rule include requiring submission on a calendar year basis, rather than based on the anniversary of the date the certification request was deemed granted, and clarifying revisions to the list of facilities to be included in the annual report.

These regulations set forth requirements that are similar to the recommendations described in the November 2015 draft guidance for industry ''Certification Process for Designated Medical Gases'' (November 25, 2015, 80 FR 73771) (Ref. 1).

4. Postmarketing Quality and Safety Reporting Provisions

FDA is issuing new postmarketing quality and safety reporting requirements for designated medical gases.

We are including requirements for submitting field alert reports (FARs), including revised submission timelines to allow applicants time to compile sufficient information to complete their FAR.

We are including adverse event reporting requirements related to the use of designated medical gases in humans and animals. For designated medical gases that are certified for human use and deemed to have in effect an approved application under section 505 of the FD&C Act (21 U.S.C. 355), we are requiring that applicants and nonapplicants report serious adverse events within 15 calendar days from when the applicant or nonapplicant has met certain reporting criteria and acquired certain minimum data.

We are issuing requirements for the contents and format of submissions, including an electronic submission requirement, the process for requesting a waiver of the electronic submission requirement, recordkeeping requirements, written procedures requirements, and patient privacy provisions.

For designated medical gases that are certified for animal use and deemed to have in effect an approved application under section 512 of the FD&C Act (21 U.S.C. 360b), we are requiring that applicants and nonapplicants submit serious adverse event reports to FDA within 15 calendar days from when the applicant or nonapplicant has met certain reporting criteria and that recordkeeping requirements related to adverse events are maintained.

C. Legal Authority

Sections 501, 502, 505, 512, 575, 576, and 704 of the FD&C Act (21 U.S.C. 351, 352, 355, 360b, 360ddd, 360ddd–1, and 374), in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serve as our principal legal authority for this final rule.

D. Costs and Benefits

This final rule establishes CGMP regulations specific to medical gases. These regulations include many of the same categories of requirements as the general drug product CGMP regulations but are tailored to reflect differences in how medical gases are manufactured, packaged, labeled, stored, and distributed. We quantify benefits to industry from removing CGMP requirements that would not apply to medical gases, such as removing certain building and facility requirements, including more limited equipment maintenance and cleaning requirements, and codifying some existing practices, which may streamline inspections. Additional benefits will include a potentially small reduction in fires from

''combination'' in this section to mean two or more distinct designated medical gases that are mixed together. For example, a mixture of oxygen and nitrous oxide that each meet the standards set forth in an official compendium could constitute a medically appropriate combination of designated medical gases. However, the addition of oxygen to a container that already contains oxygen would not result in a medically appropriate combination of designated medical gases because only one kind of designated medical gas would be present in the container.

graphic warning labels on oxygen containers, and clarification that adverse events generally are not required to be submitted for reports of the death of a patient or animal who was administered oxygen, nor when fires associated with the administration of oxygen occur but do not include an adverse event experienced by the patient or animal.

We quantify costs to industry from new labeling requirements, regulatory clarification leading to firms becoming compliant with existing requirements, and added CGMP requirements including a requirement for portable cryogenic containers to have a working gauge. Additional costs will include maintaining resumes for consultants, and potential cost of relabeling medical air containers. We estimate that the annualized benefits over 10 years will range from $0.00 million to $7.02 million at a 7 percent discount rate, with a primary estimate of $3.51 million, and from $0.00 million to $7.43 million at a 3 percent discount rate, with a primary estimate of $3.72 million. The annualized costs will range from $1.52 million to $5.30 million at a 7 percent discount rate, with a primary estimate of $3.24 million, and from $1.36 million to $5.11 million at a 3 percent discount rate, with a primary estimate of $3.07 million.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/acronym	What it means
ANDA	Abbreviated New Drug Application.
CDER	Center for Drug Evaluation and Research.
CFR	Code of Federal Regulations.
CGMP	Current Good Manufacturing Practice.
COA	Certificate of Analysis.
CVM	Center for Veterinary Medicine.
FAR	Field Alert Report.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
FDA or Agency	Food and Drug Administration.
FR	Federal Register.
ICSR	Individual Case Safety Report.
NADA	New Animal Drug Application.
NDA	New Drug Application.
NDC	National Drug Code.
OMB	Office of Management and Budget.
PET	Positron Emission Tomography.
PRIA	Preliminary Regulatory Impact Analysis.
USP	United States Pharmacopeia.

III. Background

A. Need for the Regulation/History of the Rulemaking

Medical gases have historically been manufactured, labeled, and distributed in a manner different than most other drugs. Under section 576 of the FD&C Act, the process for obtaining marketing authorization for a designated medical gas also differs from the process for obtaining marketing authorization for other human and animal drugs. Moreover, because of these differences, FDA believes that the likelihood of identifying new safety issues for medical gases is low. Thus, some existing regulations are not well-tailored to addressing designated medical gases and other medical gases. FDA undertook this rulemaking to address these differences, and to decrease regulatory burden where appropriate. On May 23, 2022, FDA issued a proposed rule to amend requirements concerning CGMP, postmarketing safety reporting, and labeling that apply to certain medical gases, and to establish regulations regarding certification of designated medical gases.

Although we believe that these four categories of regulatory changes will best help to address the unique characteristics of medical gases when implemented collectively, each provision independently improves the clarity of the regulations and requirements applicable to medical gases. In the event of a stay or invalidation of any major provision(s), those that remain in effect would continue to function sensibly [2] to advance the statutory requirements applicable to medical gases and provide useful, clear standards for firms to meet their existing statutory obligations. For example, invalidation of the major provisions related to certification of a designated medical gas would have no effect on those addressing CGMP for medical gases. Likewise, in the absence of new provisions specific to postmarketing safety reporting for medical gases, each of the other major provisions would continue to contribute to greater clarity and efficiency for the medical gas industry, while helping to maintain a high standard of safety and quality. Finally, because medical gases have historically been regulated as drugs rather than as a specialized subset thereof, were any major provision in this regulation invalidated, medical gases would continue to be regulated under the existing general regulatory regime corresponding to that provision (*e.g.,* if medical gas CGMP requirements are invalidated, medical gases would remain subject to the general drug CGMP requirements in parts 210 and 211 (21 CFR parts 210 and 211)). Therefore, it is FDA's intent to preserve each of the rule's four major provisions to the fullest possible extent, to help address the unique aspects of medical gases that set them apart from most other drugs.

[2] See, *e.g., Belmont Mun. Light Dep't* v. *FERC,* 38 F.4th 173, 188 (D.C. Cir. 2022) (finding severability of a portion of an administrative action, applying the principle that severability is appropriate where ''the agency prefers severability to overturning the entire regulation'' and where the remainder of the regulation ''could function sensibly without the stricken provision'') (citations omitted).

B. Summary of Comments to the Proposed Rule

We received fewer than 25 comments on the proposed rule. The most detailed comments were from industry trade associations and consultants. The other comments were from individuals. Comments covered many aspects of the proposed rule, including:

- General considerations, including general support, definitions, timing of the rule, and the effective date;
- Labeling requirements, including labeling statements and the applicability of labeling provisions to different types of containers;

• CGMP requirements, including buildings and facilities, equipment, control of incoming products, packaging and labeling control, holding and distribution, laboratory controls, records, and returned medical gases;
• Certification requirements, including annual reporting, withdrawal, and the applicability of current requirements in part 314 (21 CFR part 314); and
• Postmarketing quality and safety reporting requirements, including submitting FARs, reporting of individual case safety reports (ICSRs) related to human use, and reporting of adverse events related to animal use.

IV. Legal Authority

We are issuing this final rule under sections 501, 502, 505, 512, 575, 576, 701, and 704 of the FD&C Act. Medical gases are generally regulated as prescription drugs under sections 201(g)(1) and 503(b)(1) of the FD&C Act (21 U.S.C. 321(g)(1) and 353(b)(1)) (although oxygen may be provided without a prescription for certain uses specified at section 576(b)(2) of the FD&C Act).

Section 501 of the FD&C Act describes the circumstances under which a drug is deemed to be adulterated. Under section 501(a)(2)(B) of the FD&C Act, a drug is deemed to be adulterated 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 practice. For purposes of section 501(a)(2)(B), ''current good manufacturing practice'' includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

Section 502 of the FD&C Act describes the circumstances under which a drug is deemed to be misbranded. Under section 502(f) of the FD&C Act, a drug is deemed to be misbranded unless its labeling bears adequate directions for use and such adequate warnings against use where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration, in such manner and form, as are necessary for the protection of users. Under section 704 of the FD&C Act, FDA is authorized to inspect, among other things, records in any establishment in which prescription drugs or nonprescription drugs intended for human use are manufactured, processed, packed, or held bearing on whether such products are in violation of the FD&C Act.

Section 576 of the FD&C Act describes the certification process for designated medical gases (as defined in section 575 of the FD&C Act) and the effect of certification, the applicability of FDA's prescription requirements, and certain labeling requirements. Under section 576(a)(3)(A)(i) of the FD&C Act, a certified designated medical gas is subject to all applicable postapproval requirements. Under section 505(k) of the FD&C Act, FDA has the authority to establish certain postmarketing safety reporting regulations for human drugs to enable FDA to determine or facilitate a determination as to whether there are or may be grounds to invoke section 505(e) of the FD&C Act, which concerns the withdrawal or suspension of approval of a new drug application (NDA) or abbreviated new drug application (ANDA). Section 512(l) of the FD&C Act authorizes FDA to establish postmarketing safety reporting regulations for new animal drugs to enable FDA to determine or facilitate a determination as to whether there are or may be grounds to withdraw approval of an application pursuant to section 512(e) or 512(m)(4) of the FD&C Act.

Thus, sections 501, 502, 505, 512, 575, 576, and 704 of the FD&C Act, in conjunction with our general authority in section 701(a) of the FD&C Act to issue regulations for the efficient enforcement of the FD&C Act, serve as our principal legal authority for this final rule.

V. Comments on the Proposed Rule and FDA Response

A. Introduction

We received fewer than 25 comment letters on the proposed rule by the close of the comment period, each containing one or more comments on one or more issues. We received comments from individuals, trade organizations, and industry consultants.

We describe and respond to the comments in sections V.B. through V.G. of this document. We have numbered each comment to help distinguish between different comments. We have grouped similar comments together under the same number, and, in some cases, we have separated different issues discussed in the same comment and designated them as distinct comments for purposes of our responses. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received.

Additionally, on its own initiative, FDA is making minor technical and grammatical changes to the rule to improve clarity.

B. Description of General Comments and FDA Response

(Comment 1) Some comments make general remarks supporting the proposed rule without focusing on a particular proposed provision. One comment also notes that the COVID–19 pandemic highlighted the need for updated medical gas regulations.

(Response 1) We appreciate these comments of support and agree that this rulemaking is needed.

(Comment 2) One comment encourages FDA to publish this rule widely to ensure that all affected entities access it.

(Response 2) FDA is publishing this final rule publicly consistent with requirements under the Administrative Procedure Act and Agency practice. We believe this sufficiently addresses the need to make regulatory changes widely accessible to the public.

(Comment 3) One comment discusses when to publish the final rule, urging FDA to issue the final rule swiftly.

(Response 3) FDA acknowledges the public interest in finalizing this rule promptly. The Agency works within its defined processes to draft, clear, and issue regulations. During the rulemaking process, FDA published in the Unified Agenda of Federal Regulatory and Deregulatory Actions (Unified Agenda) its estimated timeline for completion of the final rule.

C. Description of Part 4 Comments and FDA Response

FDA proposed changes to part 4, subpart A (21 CFR part 4, subpart A) to reflect the new CGMP requirements for medical gases proposed in part 213 (21 CFR part 213). FDA proposed definitions of ''medical gas'' and ''medical gas CGMPs'' in § 4.2, and conforming changes to account for combination products that contain a medical gas in § 4.3. FDA also proposed in § 4.4 conforming changes to account for combination products that contain a medical gas, as well as a list of CGMP provisions from part 213 that must be satisfied if the CGMP operating system for a combination product containing a medical gas has been shown to comply with the device quality system regulations. We received one comment on these provisions, which we discuss below.

(Comment 4) One comment notes that some manufacturers of designated medical gases will not know whether their product will ultimately be used as

a drug constituent part of a combination product. As such, the comment asks whether such designated medical gases are subject to the CGMP regulations in part 4.

(Response 4) In the example in the comment, if the entities are manufacturing only the gas, they would not be subject to the CGMP regulations in part 4, which only apply to combination product manufacturers (§ 4.1). Such original manufacturers of designated medical gases only have to comply with part 213. However, for example, a third party manufacturing a combination product that includes such a designated medical gas would be subject to these part 4 CGMP requirements.

D. Part 16

FDA proposed to revise § 16.1(b)(2) (21 CFR 16.1(b)(2)) to broaden the scope of regulatory hearings to include hearings relating to revocation of a grant of a certification for a designated medical gas. We did not receive comments on the proposed revision and are finalizing the provision as proposed with minor technical changes made on our own initiative.

E. Description of Part 201 Comments and FDA Response

1. General Comments

(Comment 5) One comment makes general remarks supporting the proposed revisions to the labeling regulations in part 201 (21 CFR part 201) without focusing on a particular proposed provision.

(Response 5) We appreciate this comment of support.

2. Manufacturer Definition (Proposed § 201.1)

FDA proposed revisions to the ''manufacturer'' definition in § 201.1(b), adding proposed paragraph (11) to address medical gas manufacturing activities for purposes of part 201 and section 502(a) and (b)(1) of the FD&C Act. We proposed to specify that, with respect to a medical gas, the manufacturer is the person fabricating the gas by chemical reaction, physical separation, compression of atmospheric air, purification (*e.g.,* reprocessing an industrial gas into a medical gas), by combining two or more distinct medical gases, or by other process.

(Comment 6) One comment recommends that FDA remove the catchall ''other processes'' and include filling a medical gas container in the list of manufacturing operations. The comment expresses that this change would capture operations performed post-fabrication.

(Response 6) FDA does not agree with this recommendation. The operations listed in § 201.1(b)(11) focus on methods of ''fabricating the gas,'' rather than downstream processes. While certain downstream processes will be subject to the CGMP requirements in part 213 when in effect, the purpose of § 201.1(b) is to capture the primary activities conducted to initially produce a drug product.

3. Adequate Directions for Use (§ 201.100)

Although FDA did not propose revisions to § 201.100, the Agency received comments proposing revisions to the current text.

(Comment 7) One comment proposes a new § 201.100(a)(1)(iv) to specify that a designated medical gas used to clean or purge medical gas containers, including medical gas pipelines, is exempt from the requirement in section 502(f)(1) of the FD&C Act that its labeling bear adequate directions for use. The comment adds that this would allow individuals to obtain designated medical gases for such use (for example, nitrogen for purging medical pipelines).

(Response 7) FDA does not agree with this comment. Revisions to § 201.100(a)(1) are not necessary because gases used for the purposes described in the comment do not meet the definition of a drug under section 201(g)(1) of the FD&C Act. Therefore FDA's drug labeling requirements, including the requirement to bear adequate directions for use, would not apply to a gas intended only for these uses.

(Comment 8) One comment proposes revisions to § 201.100(b) exempting designated medical gases in compliance with § 201.161 from the labeling requirements in § 201.100(b) because § 201.161 as revised by this rulemaking includes specific requirements for designated medical gas labeling.

(Response 8) FDA does not believe these revisions are needed. The purpose of § 201.100 is to exempt prescription drugs from the requirements in section 502(f)(1) of the FD&C Act if certain requirements are met. For designated medical gases, section 576(a)(3)(A)(ii) of the FD&C Act already addresses this requirement by stating that, for such gases, the requirements of sections 503(b)(4) and 502(f) of the FD&C Act are deemed to have been met for a designated medical gas if the labeling on its final use container bears the information required by section 503(b)(4), a warning statement concerning the use of the medical gas (as determined by the Secretary by regulation), and appropriate directions and warnings concerning storage and handling.

The revisions to § 201.161 in this rulemaking further satisfy this requirement, as sections 503(b)(4) and 502(f) of the FD&C Act are deemed to have been met for a designated medical gas if the final use container bears the information required in § 201.161(a).

4. Medical Gas Labeling Statements (Proposed § 201.161)

FDA proposed several changes to the medical gas labeling requirements in § 201.161. We proposed moving the warning statement requirements for oxygen in § 201.161(a)(1)(i) to § 201.161(a)(1), without proposing any changes to the requirements. We also proposed moving the warning statement requirements for nitrogen, carbon dioxide, helium, nitrous oxide, and medically appropriate combinations of oxygen, nitrogen, carbon dioxide, helium, and nitrous oxide in § 201.161(a)(1)(ii) to § 201.161(a)(2) and proposed expanding their scope to all designated medical gases other than oxygen as well as medically appropriate combinations of any medical gases. We also proposed adding a requirement that the final use container bears the symbol ''Rx only.'' In proposed § 201.161(a)(3), we proposed requiring that the final use container bears appropriate directions and warnings concerning storage and handling.

In proposed § 201.161(b), we proposed requirements that a designated medical gas or medically appropriate combination of designated medical gases in a bulk or transport container be identified with the name of the product contained therein and accompanied by documentation identifying the product as meeting applicable compendial standards.

Lastly, proposed § 201.161(c) included several definitions. We received no comments on the proposed definitions of ''designated medical gas'' (proposed § 201.161(c)(1)) or ''bulk or transport container'' (proposed § 201.161(c)(3)) and are finalizing these definitions as proposed with minor technical changes made on our own initiative. We proposed to define ''final use container'' as a container that is for direct use or access by a patient or healthcare provider to administer a designated medical gas or medically appropriate combination of designated medical gases, not including bulk or transport containers or containers that are described in § 868.5655 (21 CFR 868.5655).

We respond to the comments on proposed § 201.161 in the following paragraphs.

(Comment 9) One comment recommends that the oxygen warning statement in proposed § 201.161(a)(1)(i) include additional instances in which oxygen may be provided without a prescription aside from depressurization or environmental oxygen deficiency, or emergency resuscitation. As an example of such an additional use, the comment suggests the emergency use of oxygen for hyperbaric oxygen therapy for decompression sickness.

(Response 9) FDA disagrees. The uses described in § 201.161(a)(1)(i) of the proposed rule are consistent with the circumstances described in section 576(b)(2)(A) of the FD&C Act under which oxygen may be provided without a prescription. FDA does not believe it would be appropriate to include additional uses in this provision.

(Comment 10) Regarding FDA's proposed requirement in § 201.161(a)(1)(ii) that final use containers bear a ''No Smoking'' and ''No Vaping'' warning statement and a graphic symbol conveying that smoking, vaping, and open flames near oxygen are dangerous, one comment notes that industry may need time to develop graphic symbols and text.

(Response 10) FDA recognizes the concerns expressed in this comment, and we note, as stated in section VI of this document, that firms will have 18 months to develop the required warning statement and graphic symbol. The Agency is happy to discuss the matter further with industry as firms develop graphics to address this requirement.

(Comment 11) One comment proposes adding a new § 201.161(a)(1)(iii) to state that, if oxygen is provided as a designated medical gas in the form of a cryogenic liquid in a cryogenic final use container meeting the definition of a device, the warning statements in § 201.161 are not required. The comment conditions this on the device label providing adequate directions for use in accordance with the device approval. The comment notes that this would reflect the current labeling appearing on home oxygen units.

(Response 11) FDA does not agree that this revision is needed. The definition of ''final use container'' in § 201.161(c)(2) already makes clear that the term does not include containers meeting the definition of a medical device and classified under § 868.5655. As devices, these containers have separate labeling requirements. Therefore, further clarification in § 201.161 is not necessary.

(Comment 12) In response to FDA's request for feedback regarding the inclusion in § 201.161(a)(2) of medical air in the proposed labeling requirements for designated medical gases other than oxygen and medically appropriate combinations of designated medical gases, one comment responds that they do not oppose this.

(Response 12) FDA appreciates the feedback on this request.

(Comment 13) One comment requests that FDA add language to § 201.161(a)(2) explaining that the required statements in § 201.161 are not required for cryogenic nitrogen in an open top dewar. The comment notes that certain uses of cryogenic nitrogen, such as dermatological use, are device uses rather than drug uses.

(Response 13) While FDA agrees that cryogenic nitrogen being used for certain dermatological purposes is a device use, and therefore not subject to § 201.161, the Agency declines to add the requested language. As revised by this rule, § 201.161(a) states that section 503(b)(4) of the FD&C Act, which only applies to drugs, is deemed to have been met if a designated medical gas is in compliance with § 201.161(a). Therefore, it is clear that the requirements in § 201.161 only apply to medical gases that are drugs, and that if a gas is a device, it is subject to applicable device labeling requirements. This position is consistent with FDA's draft guidance for industry entitled ''Certification Process for Designated Medical Gases'' [3] (Ref. 1).

(Comment 14) One comment requests that FDA revise § 201.161(b) to require that a designated medical gas or medically appropriate combination of designated medical gases in a bulk or transport container must be ''provided with'' documentation identifying the product as meeting applicable compendial standards, rather than ''accompanied by'' such documentation. This comment is intended to allow for current industry practices of electronic delivery of such documentation.

(Response 14) FDA believes that this change is unnecessary. Information promptly transmitted electronically would be considered to accompany a drug. Therefore, revisions are not necessary to address the concern expressed in this comment.

(Comment 15) One comment recommends that the definition of ''final use container'' in § 201.161(c)(2) be revised to mean a container that is ''labeled'' for direct use, rather than a container that is ''for'' direct use. The comment notes that the proposed definition of ''bulk or transport container'' includes cylinders that are connected to a medical gas supply system, such as a hospital's oxygen system. However, the comment asserts that cylinder banks may contain individual labeled cylinders.

(Response 15) FDA disagrees with the proposed revision. First, specifying that a container is a final use container if it is ''labeled'' for direct use would be circular, and a firm could avoid being regulated as a final use container simply by not labeling its containers accordingly. Second, FDA believes that the purpose of the container should determine the appropriate labeling. If the container is intended to be used as a final use container, it must be labeled in compliance with § 201.161(a), and if a container is intended to be used as a bulk or transport container, it must be labeled in compliance with § 201.161(b).

5. Labeling of Medical Gas Containers (Proposed § 201.328)

FDA proposed changes to § 201.328(a)(1) to reference § 213.94(e)(3) instead of § 211.94(e)(2). We also proposed to add § 201.328(d) to clarify that a container filled with a designated medical gas or medically appropriate combination of designated medical gases may bear a statement identifying the name of the owner of the container or the address to which the container should be returned after use, noting that this statement may appear on a separate sticker or decal. We further proposed that if the owner of the container is not the manufacturer, packer, or distributor of the designated medical gas or medically appropriate combination of designated medical gases, that shall be clearly stated on the container. Proposed § 201.328(d) further notes that the addition of such statement shall not cause the owner of the cylinder to be a ''relabeler'' for purposes of FDA's registration and listing requirements.

(Comment 16) Although FDA did not propose changes to the definition of ''portable cryogenic medical gas container'' in § 201.328(a), one comment did suggest changes. This provision refers to a container 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, including portable liquid oxygen units as defined in § 868.5655. First, the comment requests to remove the term ''base unit''

[3] ''Gases not intended for human or animal drug use . . . do not fall within the definition of 'medical gas' provided in section 575(2) of the FD&C Act, and are not subject to the certification process described in this guidance.''

because the term is commonly used to refer to the device maintained at a patient's home that is filled with oxygen. The comment notes that these containers are not typically moved. Second, the comment suggests removing ''small'' before ''cryogenic gas containers'' in the exclusionary language, as well as including language clarifying that cryogenic gas containers utilize proprietary connections. Third, the comment suggests removing from the exclusionary language the reference to devices defined in § 868.5655.

(Response 16) FDA agrees that the term ''base unit'' should be removed from the definition. Because there may be confusion over what a ''base unit'' includes, we believe it is more appropriate to focus on the purpose of the container. As such, we are revising the definition to include, among other things, a container that ''is used to fill small cryogenic gas containers for use by individual patients.''

However, we disagree with the other requested changes. Because portable cryogenic medical gas containers can be in patients' homes, we believe that it is critical that they include proper labeling. Removing ''small'' before ''cryogenic gas containers'' would unnecessarily expand the exclusionary language and limit the scope of products subject to the labeling requirements described in part 201. We also do not believe adding the qualifier that cryogenic gas containers utilize proprietary connections to the exclusionary language is appropriate, as it is not clear why the exclusion should depend on the type of connections used. We also note that these requested revisions are not consistent with similar revisions proposed for § 213.94(e)(1) (concerning requirements for medical gas containers and closures) (see response 30).

We do not believe it is appropriate to remove the reference to § 868.5655 from the exclusionary language. It is unclear why the comment suggests removing this language while also noting that base units are considered devices; if the reference to § 868.5655 were removed from the exclusionary language, the definition might arguably be read to consider such devices to be portable cryogenic medical gas containers subject to the wraparound labeling requirement. This distinction between containers that are devices, and those that are not, is important, and FDA believes that the definition as revised makes clear which containers are devices subject to applicable device requirements, and which are portable cryogenic medical gas containers subject to applicable drug requirements.

Lastly, we are revising ''does not include'' to ''exclude,'' consistent with the revisions discussed in response 31 below. As finalized, the term ''portable cryogenic medical gas containers'' excludes cryogenic containers that are not designed to be connected to a medical gas supply system.

(Comment 17) One comment requests that § 201.328(d) be revised to clarify that, if information identifying the name of the owner of the container or the address to which the container should be returned after use appears on a separate sticker or decal, such sticker or decal should not cover up other language on the label.

(Response 17) FDA appreciates the concern that labeling information should be clearly displayed and not covered up, but the Agency does not believe the proposed revisions are necessary because other provisions address this issue. In particular, section 502(c) of the FD&C Act states that a drug shall be misbranded if any word, statement, or other information required by or under authority of the FD&C Act to appear on the label or labeling is not prominently placed thereon with such conspicuousness and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

Additionally, § 201.15(a)(6) of FDA's labeling regulations makes clear that ''obscuring designs or vignettes'' may cause required information to lack the prominence and conspicuousness required by section 502(c) of the FD&C Act.

F. Part 210

FDA proposed conforming edits to the general provisions concerning drug CGMP requirements in part 210 to reflect the proposed establishment of medical gas CGMP requirements in part 213. We did not receive comments on the proposed revisions and are finalizing the provisions as proposed with minor technical changes made on our own initiative.

G. Part 211

FDA proposed conforming edits to the drug CGMP requirements in part 211 to reflect that medical gases would no longer be subject to this part. We did not receive comments on the proposed revisions and are finalizing the provisions as proposed.

H. Description of Part 213 Comments and FDA Response

1. General Comments

(Comment 18) Some comments make general remarks supporting the proposed CGMP regulations without focusing on a particular proposed provision.

(Response 18) We appreciate these comments of support.

2. Definitions (Proposed § 213.3)

FDA proposed definitions of several terms used in part 213. We received comments on several of those proposed definitions, as discussed below. We are finalizing as proposed (with minor technical and grammatical changes made on our own initiative) those definitions for which we received no comments.

a. Acceptance Criteria (Proposed § 213.3(b)(1))

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

(Comment 19) One comment requests that the ''acceptance criteria'' definition in proposed § 213.3(b)(1) be consistent not only with the acceptance criteria definition in part 210, but also the corresponding definitions in other regulations and guidance. For example, the comment notes that the ''acceptance criteria'' definition in part 212 (21 CFR part 212) concerning positron emission tomography (PET) drugs differs from the proposed definition for medical gases.

(Response 19) FDA does not believe that revisions are necessary. The proposed ''acceptance criteria'' definition in § 213.3(b)(1) is identical to the current ''acceptance criteria'' definition in § 210.3(b)(20), and FDA further believes that it is generally consistent with the ''acceptance criteria'' definition in § 212.1. In any case, PET drugs are outside the scope of this rulemaking, as FDA did not propose any revisions to part 212 in the proposed rule.

b. Batch (Proposed § 213.3(b)(2))

We proposed to define ''batch'' as a specific quantity of a medical gas or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(Comment 20) One comment suggests that batches, as defined in proposed § 213.3(b)(2), and lot numbers, as defined in § 213.3(b)(10), be defined per day. The comment argues that this

would provide sufficient information for downstream tracking and reporting.

(Response 20) FDA disagrees. As discussed in the proposed rule, we believe the proposed ''batch'' definition allows for significant flexibility in defining a batch to address considerations raised by different types of firms and different manufacturing, processing, packing, and holding activities (87 FR 31302 at 31310). We do not believe the term should restrict batches to a quantity produced in a single day. As such, we also do not believe that any revisions to the definition in § 213.3(b)(10) for ''lot number, control number, or batch number'' are necessary.

c. Commingling or Commingled (Proposed § 213.3(b)(3))

We proposed to define ''commingling or commingled'' as the act of combining one lot of designated medical gas or component with another lot or lots of the same designated medical gas or component.

(Comment 21) One comment concurs with the definition of ''commingling or commingled'' in proposed § 213.3(b)(3), but notes that, in the event lots are combined, firms should maintain tracking information at the container level to record which lots are included in the combined product and when they were added.

(Response 21) We believe that the tracking requirements established in this final rule sufficiently address any risks associated with the receipt of gases from multiple suppliers. Specifically, § 213.82 contains requirements for the receipt of incoming designated medical gases, including that either a signed certificate of analysis (COA) must accompany the gas or that the receiving firm must conduct full compendial testing (all tests necessary to ensure compliance with an official compendium), and that an identity test must be performed (see response 26 below for more information regarding revisions to § 213.82). Additionally, § 213.101(b) requires that in-process and final product containers of components and incoming designated medical gases shall identify the name of the component or designated medical gas or the name and percentage of each component or designated medical gas if they contain multiple components or designated medical gases, and the unique lot number assigned.

d. Original Manufacturer (Proposed § 213.3(b)(13))

We proposed to define ''original manufacturer'' as the person or entity that initially produces a designated medical gas by chemical reaction, physical separation, compression of atmospheric air, purification (*e.g.,* re-processing an industrial gas into a medical gas), or other means.

(Comment 22) One comment suggests that the ''original manufacturer'' definition in § 213.3(b)(13) be revised to exclude processing agents such as nitrogen used in bottle purging and product overlay because these gases are not a part of the drug product and are not considered medical gases.

(Response 22) FDA does not believe that revisions are necessary to address this concern. We agree that gases used in the production of drugs that are not medical gases are not subject to part 213. Such gases may be subject to part 211 if the drug product is subject to those regulations depending on the use of the gas, but that is outside the scope of this rulemaking. We also note that, as discussed below in response 45, we do not believe it is necessary for the definition to include ''or entity'' because the word ''person'' captures all relevant entities. As such, we have revised the definition to remove ''or entity.''

(Comment 23) One comment proposes adding a definition of ''subsequent manufacturer'' in § 213.3(b) to resolve regulatory uncertainty that may exist without distinguishing between subsequent manufacturers and original manufacturers.

(Response 23) FDA does not believe that this definition is necessary. We understand ''subsequent manufacturer'' to refer to a person that performs manufacturing operations after the initial production of a designated medical gas, such as transfilling and curbside filling. We agree that subsequent manufacturers that are not engaged in the activities described in § 213.3(b)(13) are not original manufacturers. However, the proposed rule preamble clarified what kinds of entities would not be considered an original manufacturer (87 FR 31302 at 31311). If a provision does not specify that it applies only to original manufacturers, then subsequent manufacturers subject to part 213 would need to comply as applicable. Moreover, part 213 does not use the term ''subsequent manufacturer,'' and the comment's proposed revisions would only use the term in the definition section.

3. Buildings and Facilities (Proposed Part 213, Subpart C)

FDA proposed to establish requirements for the design and construction features of buildings and facilities for the manufacture, processing, packing, or holding of medical gases (proposed § 213.42). We received one comment on these provisions, which we discuss below.

(Comment 24) One comment asks for clarification regarding what FDA considers to be ''adequate space'' in proposed § 213.42(a), which would require that buildings and facilities used in the manufacture, processing, packing, or holding of a medical gas be of adequate design, including adequate space, for the orderly placement of equipment and materials to prevent mix-ups and allow for adequate cleaning, maintenance, and proper operations. The comment asserts that the term is ambiguous and proper equipment, operations, and labeling should allow firms to mitigate the risk of mix-ups.

(Response 24) The use of the term ''adequate space'' is intended to allow for flexibility in designing a manufacturing facility that prevents mix-ups and allows for adequate cleaning, maintenance, and proper operations. We agree that there are not necessarily size restrictions and that using proper equipment and processes are key to ensuring that the space is appropriate for the operations. We do not believe that revisions to § 213.42(a) are necessary.

4. Equipment (Proposed Part 213, Subpart D)

FDA proposed to establish several requirements concerning equipment used in the manufacture, processing, packing, or holding of medical gases (proposed §§ 213.63, 213.65, 213.67, and 213.68). We received no comments on proposed §§ 213.63, 213.65, and 213.67 and are finalizing them as proposed with a minor technical change made on our own initiative. We received comment only on proposed § 213.68(a), which specified that automatic, mechanical, and electronic equipment used in the manufacture of medical gases shall be routinely calibrated, inspected, and checked according to a written program designed to ensure proper performance, and that written procedures and records of calibration, inspections, and checks shall be maintained.

(Comment 25) One comment suggests that proposed § 213.68(a) be revised to include a minimum frequency for calibration, inspection, and checking of automatic, mechanical, and electronic equipment.

(Response 25) FDA does not believe it is necessary to include specific frequency requirements for such calibration, inspection, and checking of equipment. This is also consistent with § 211.68(a) and affords flexibility to

firms to take steps that will ensure proper performance based on the operations conducted and equipment used.

5. Control of Incoming Designated Medical Gas, Components, and Medical Gas Containers and Closures (Proposed Part 213, Subpart E)

FDA proposed to establish several requirements concerning the control of incoming designated medical gas, components, and medical gas containers and closures (proposed §§ 213.80, 213.82, 213.84, 213.89, and 213.94). We received no comments on proposed §§ 213.80 and 213.89 and are finalizing them as proposed. We respond to the comments on proposed §§ 213.82, 213.84, and 213.94 below.

a. Receipt and Storage of Incoming Designated Medical Gases (Proposed § 213.82)

FDA proposed that, upon receipt of an incoming designated medical gas, the firm shall verify and record that a signed certificate of analysis from the supplier accompanies each different designated medical gas in a shipment, including the supplier's name; name of the incoming designated medical gas; lot number or other unique identification number; actual analytical result obtained for strength, as well as the results of other tests performed; identification of the test method(s) used for analysis; NDA or new animal drug application (NADA) number of the incoming designated medical gas; and the supplier representative's signature and the date of signature (proposed § 213.82(a)(1)). If the incoming designated medical gas is obtained from a supplier other than the original manufacturer, FDA proposed requiring the shipment to include complete information from the original manufacturer's COA, and that the firm establish and maintain a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures (proposed § 213.82(a)(2)). Lastly, FDA proposed requiring that an identity test be performed upon receipt (proposed § 213.82(b)).

(Comment 26) One comment asks that § 213.82(a)(1) be revised to allow receiving firms to conduct full compendial testing on the commingled product as an alternative to verifying that a COA accompanies the shipment. The comment maintains that this is consistent with industry practice.

(Response 26) FDA generally agrees with this comment. The Agency believes that both proposed approaches are appropriate for ensuring that each shipment of each incoming designated medical gas is verified as meeting relevant standards and is appropriate for use. However, FDA does not believe it is appropriate to specify that the full compendial testing be of the commingled product because testing of the gas before it is commingled would also confirm that it meets compendial standards. Further, § 213.82(a)(2) requires that, for incoming designated medical gas from a supplier other than the original manufacturer, each shipment shall also include complete information from the original manufacturer's COA. We are revising § 213.82(a)(1) accordingly to state that, upon receipt of each shipment of each incoming designated medical gas, the firm shall either perform full compendial testing on the gas and record the results, or verify and record that a signed COA from the supplier accompanies each different designated medical gas in a shipment.

(Comment 27) One comment requests that, instead of requiring that ''a signed certificate of analysis from the supplier accompanies each different designated medical gas,'' § 213.82(a)(1) should state that ''a signed *document* from the supplier *is provided for* each different designated medical gas . . . .'' The comment suggests additional edits, including that the document must identify the product as meeting compendial standards, that a COA may be used to satisfy these requirements, and that only if a COA is used would paragraphs (a)(1)(i) through (vii) apply.

(Response 27) FDA does not agree that the term ''certificate of analysis'' should be replaced with the term ''document.'' First, by retaining the term ''certificate of analysis'' after using the more general term ''document,'' the suggested revisions would create ambiguity concerning what requirements would apply to a ''document'' that is not a COA. Second, our intent is that the entity providing this documentation certify the information accompanying the shipment. Therefore, ''document'' is less clear than the term ''certificate of analysis.'' We similarly disagree with including a statement that a COA may be used to satisfy these requirements because FDA is already using that term to refer to the applicable documentation.

FDA disagrees with revising ''accompanies'' to read ''is provided for.'' In general, we believe the terms can be read similarly, and FDA generally intends to interpret ''accompany'' broadly enough to include prompt electronic transmission, as discussed above in response 14.

FDA does not agree that it is necessary to add that the COA identifies the product as meeting applicable compendial standards. This is already covered by § 213.82(a)(1)(ii), (iv), and (vii), which require that the COA identify the name of the designated medical gas, its analytical test results, and a signature from the supplier's representative. For example, a supplier of Oxygen, USP (United States Pharmacopeia) would be certifying that the gas meets compendial standards for Oxygen, USP by identifying the gas by its compendial name and including test results demonstrating that the gas meets applicable standards.

(Comment 28) One comment asks that FDA delete proposed § 213.82(a)(1)(vi) because the inclusion of NDA or NADA information does not provide support for the quality or traceability of the product in addition to the other information provided. The comment maintains that NDA or NADA information may not be accurate in the case of commingled or combined gases, or gases from subsequent manufacturers.

(Response 28) FDA disagrees with the requested deletion. The Agency's intent in § 213.82 is to ensure that adequate information accompanies incoming designated medical gases shipped from original manufacturers to downstream entities, not combined or commingled gases from one subsequent manufacturer to another. However, we recognize that there may be confusion regarding the proposed definition of ''incoming designated medical gas.'' Therefore, we are revising that definition in § 213.3(b)(8) to state that an ''incoming designated medical gas'' is a designated medical gas received from one source that, *after receipt,* is commingled with the same gas from another source, used in a medically appropriate combination of designated medical gases or in the production of another medical gas, or further distributed.

b. Testing and Approval or Rejection of Components, Containers, and Closures (Proposed § 213.84)

FDA proposed requirements for testing and approval or rejection of components, containers, and closures. Proposed § 213.84(a) included requirements either to examine components, containers, and closures prior to manufacturing or filling, or ensure that a statement of verification is provided from the supplier, provided that the firm establishes and maintains a program to ensure the reliability of the supplier's capabilities. Under proposed § 213.84(b), firms shall take appropriate actions to protect against container and closure leaks, including performing leak

tests on containers and closures at the time of fill and after fill but prior to release. Under proposed § 213.84(c), each component shall be sampled, tested, and approved or rejected as appropriate prior to use, either by performing testing for conformance with written specifications or by an identity test on the component accompanied by an acceptable COA from the supplier, provided that the firm establishes and maintains a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures.

(Comment 29) FDA specifically sought comments on the proposed requirement in § 213.84(b) that firms take appropriate actions to protect against container and closure leaks, including performing leak tests on containers and closures at the time of fill and after fill but prior to release. One comment maintains that FDA's proposed requirements would be sufficient. However, one comment asserts that leak testing upon pickup of a container would not be appropriate, both because of staffing and due to the varied timing at which the container is returned.

(Response 29) FDA appreciates this feedback and agrees that, unless an establishment is in receipt of a complaint or complaints of leaking or empty containers, the proposed language and associated testing described in § 213.84(b) is sufficient. Regarding the comment concerning leak testing upon pickup, FDA did not propose to require such testing, but rather noted in the preamble to the proposed rule that such testing may be needed to further protect against container and closure leaks to provide sufficient assurance of the durability of the container closure system throughout its period of use (87 FR 31302 at 31314). FDA does not believe that such testing will always be necessary, and other testing (or no additional testing) could be appropriate depending on the manufacturer's circumstances.

However, we continue to believe that leaking and empty container complaints is a serious concern, in light of the numerous instances of leaking and empty containers described in the proposed rule (87 FR 31302 at 31314) (see also Ref. 2). In several instances, firms did not appropriately evaluate the complaints in that the investigation conducted was inadequate, even when similar complaints were received, lacking steps such as evaluating the durability and suitability of containers and closures to identify a root cause. Therefore, we are adding to the complaint files provision at § 213.198(a) a requirement that all complaints involving leaking containers or closures be reviewed, evaluated, and investigated in accordance with § 213.192.

The level of effort, formality, and documentation of the investigation of complaints should be commensurate with the level of risk. For complaints of leaking and empty containers, an appropriate investigation should include a review of production and testing procedures and records, and will often include additional testing and actions, such as use of more sensitive leak testing methods and use of mechanisms that allow for identification of containers that are the subject of a complaint. Based on the result of the investigation, the firm must take appropriate corrective action under § 213.192 (*e.g.,* additional leak testing, removal of container or closure from circulation, addition of periodic leak testing to support container and closure durability). When there are no complaints of leaking or empty containers, we do not anticipate the need for additional leak testing. But in the event a firm becomes aware of repeated or trending leaks or empty containers, or other information indicating a production issue or container or closure issue that may result in leaking or empty containers, it is important that root causes are identified and corrective actions are taken that result in product and process improvements to ensure that the container closure system operates correctly, and that the gas will be available to the patient when needed.

c. Medical Gas Containers and Closures (Proposed § 213.94)

FDA proposed that medical gas containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the gas beyond the official or established requirements (proposed § 213.94(a)). We also proposed to require that container closure systems provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the gas (proposed § 213.94(b)). Under proposed § 213.94(c), medical gas containers and closures shall be clean to assure that they are suitable for their intended use. Additionally, we proposed that standards or specifications, testing methods, and where indicated, cleaning methods shall be written and followed (proposed § 213.94(d)).

Proposed § 213.94(e) included revisions to the requirements in § 211.94(e), including new proposed requirements. Under proposed § 213.94(e)(1), 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 container's use) except by the manufacturer. FDA proposed to define ''manufacturer'' for purposes of § 213.94(e)(1) to include any individual or firm that fills high-pressure medical gas cylinders or cryogenic medical gas containers. FDA proposed to define ''portable cryogenic medical gas container'' for purposes of § 213.94(e)(1) as one that is capable of being transported and is intended to be attached to a medical gas supply system within a hospital, healthcare entity, nursing home, other facility, or home healthcare setting, or is a base unit used to fill small cryogenic gas containers for use by individual patients. The term would 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 in § 868.5655).

Under proposed § 213.94(e)(2), portable cryogenic medical gas containers as defined in proposed § 213.94(e)(1) as well as small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined in § 868.5655) must have a working gauge sufficient to indicate whether the container has an adequate supply of medical gas for continued use.

Finally, proposed § 213.94(e)(3) required that the labeling specified at § 201.328(a) be affixed to the container in a manner that does not interfere with other labeling, and each 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.

(Comment 30) Regarding the proposed requirements for gas-specific use outlet connections in § 213.94(e)(1), one comment recommends adding ''home healthcare'' before ''base unit'' in the definition of ''portable cryogenic medical gas container.'' The comment intends for this to clarify the term ''base unit'' and to achieve consistency with current safe practices.

(Response 30) FDA does not agree. As discussed above in response 16, although the proposed language for the

definition of ''portable cryogenic medical gas container'' in § 213.94(e)(1) is identical to the current definition in §§ 201.328(a) and 211.94(e)(1), different revisions were proposed for §§ 201.328(a) and 213.94(e)(1). Rather than adding ''home healthcare'' before ''base unit,'' FDA believes that it is most appropriate to remove ''base unit'' to focus on the purpose of the container.

(Comment 31) One comment recommends that the exclusionary language in the last sentence in § 213.94(e)(1) be revised such that ''does not include'' would be revised to ''exclude'' and that ''not'' would be removed before ''designed.'' The comment's requested revisions would read ''[t]he term excludes cryogenic containers that are designed to be connected to a medical gas supply system . . . .'' The comment asserts that these changes would remove the double negative and provide clarity.

(Response 31) FDA agrees that revising ''does not include'' to ''exclude'' is clearer and has made that change in the final rule. However, FDA does not agree with removing ''not'' before ''designed,'' as that revision would change the meaning of the sentence. The first revision is sufficient to remove the double negative. We are also making this change in § 201.328(a). As finalized, the term ''portable cryogenic medical gas container'' excludes cryogenic containers that are not designed to be connected to a medical gas supply system.

(Comment 32) Multiple comments discuss the proposed requirement in § 213.94(e)(2) that portable cryogenic medical gas containers and small cryogenic gas containers for use by individual patients have a working gauge sufficient to indicate whether the container contains an adequate supply of medical gas for continued use. One comment expresses general support but maintains that the gauge should be subject to the testing provisions for components in § 213.84(c). Another comment suggests deleting the phrase ''sufficient to indicate whether the container contains an adequate supply of medical gas for continued use'' because patient use is subjective and determined on an individual basis. Instead, the comment requests that the gauge should indicate container pressure or the amount of liquid in the container.

(Response 32) We appreciate the comment of support and agree that the gauge would be subject to the testing provisions for components, as the gauge is part of the container closure system. Regarding the comment recommending that we revise proposed § 213.94(e)(2), FDA would like to clarify that the intent of this language is to ensure that the gauge allows the user to understand how much of the medical gas remains in the tank. We recognize that it is not possible for a gauge to display patient-specific information. To help clarify this we are revising the codified to read, in pertinent part, that portable cryogenic medical gas containers and small cryogenic gas containers for use by individual patients have a working gauge sufficient to *assist the user in determining* whether the container contains an adequate supply of medical gas for continued use. We agree with the comment that a gauge capable of displaying container pressure or liquid level would satisfy this requirement.

6. Production and Process Controls (Proposed Part 213, Subpart F)

FDA proposed to establish several requirements concerning production and process controls for medical gases (proposed §§ 213.100, 213.101, and 213.110). We received no comments on the proposed provisions and are finalizing them as proposed.

7. Packaging and Labeling Control (Proposed Part 213, Subpart G)

FDA proposed to establish several requirements concerning packaging and labeling controls for medical gases (proposed §§ 213.122, 213.125, and 213.130). We received no comments on proposed §§ 213.122 and 213.130 and are finalizing them as proposed.

In proposed § 213.125(a), we proposed that labeling and packaging operations must be controlled to prevent labeling and product mix-ups, and that procedures shall be written and followed describing in sufficient detail the control procedures employed for the issuance of labeling. In proposed § 213.125(b), we proposed requiring that procedures be used to reconcile the quantities of labeling issued, used, and returned, and that procedures require evaluation of discrepancies when such discrepancies are outside narrow preset limits based on historical operating data (FDA proposed that labeling reconciliation be waived for cut or roll labeling if a 100-percent examination is performed in accordance with § 213.122(f)(2), and for 360° wraparound labels on portable cryogenic medical gas containers). Proposed § 213.125(c) states that all excess lot number stickers or decals bearing lot or control numbers shall be discarded. Lastly, proposed § 213.125(d) exempted bulk or transport containers from § 213.125. We respond to the comments on proposed § 213.125 below.

(Comment 33) Regarding proposed § 213.125(c), one comment requests clarification regarding what constitutes excess lot number stickers or decals. The comment asserts that, if the intent is for a container to only have one label, the wear and tear of medical gas labels may justify multiple labels including the same content.

(Response 33) FDA's intent in proposed § 213.125(c) is to address the risks of excess labeling materials that are unused. FDA does not object to including lot number information in more than one location on the container closure. Rather, our concern is that extra stickers will be inadvertently used for another batch, which would lead to mix-ups. We believe the provision as drafted addresses this concern and do not believe that changes are needed.

8. Holding and Distribution (Proposed Part 213, Subpart H)

FDA proposed to establish warehousing and distribution procedure requirements. Specifically, FDA proposed that written procedures be established and followed describing the distribution of medical gases, including a system by which the distribution of each lot can be readily determined to facilitate its recall (proposed § 213.150(a)). Additionally, FDA proposed that written procedures be established and followed describing the warehousing of medical gases, including quarantine before release by the quality unit (proposed § 213.150(b)).

(Comment 34) Although not directed at a specific provision, one comment discusses the transfilling process and the information that should be tracked. The comment maintains that transfillers should record which lots of medical gas were added as well as the date. The comment further asserts that once transfilling occurs, this information can no longer be tracked.

(Response 34) FDA does not believe that changes are needed to address this issue. Although tracking this information upon adding gas to a transfilling container may enhance traceability to some degree, FDA expects that the benefits would be minimal while the added burden of tracking this information would be significant. Moreover, it would be unclear in the long term what lots are in the cylinder because the gases from multiple batches would commingle and the transfiller would not be able to determine when a lot is no longer present in the container. Therefore, the list of lots could become quite long and unmanageable over time.

9. Laboratory Controls (Proposed Part 213, Subpart I)

FDA proposed to establish several laboratory control requirements (proposed §§ 213.160, 213.165, and 213.166). We received no comments on proposed §§ 213.160 and 213.166 and are finalizing them as proposed.

FDA proposed testing and release requirements in § 213.165. Under proposed § 213.165(a), for each batch of medical gas, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the gas, including the identity and strength, prior to release. Additionally, FDA proposed that any sampling and testing plans shall be described in written procedures that shall be followed, including the method of sampling, the number of units per batch to be tested, and acceptance criteria (proposed § 213.165(b)). Under proposed § 213.165(c), the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented, and such validation and documentation may be accomplished in accordance with § 213.194(a)(2). Also under proposed § 213.165(c), the suitability of all testing methods shall be verified under actual conditions of use. Proposed § 213.165(d) would require rejection of medical gases that fail to meet established standards or specifications and any other relevant quality criteria. This proposal is generally consistent with the requirements described in § 211.165(f), but FDA did not propose to include in § 213.165(d) the provision stating that reprocessing may be performed or the requirements for using reprocessed material because the Agency is not aware of reprocessing that occurs for medical gases. FDA solicited comment on this issue, including any example scenarios in which medical gases are reprocessed. Finally, proposed § 213.165(e) would exempt from this section filling of designated medical gases and medically appropriate combinations of medical gases via liquid to liquid into a container at a delivery site.

(Comment 35) Regarding § 213.165(d)'s proposed requirement to reject medical gases that fail to meet established standards or specifications, one comment notes that they are not aware of any reprocessing of medical gases.

(Response 35) FDA appreciates the additional information. In light of the response received, we do not believe revisions to § 213.165(d) are necessary.

10. Records (Proposed Part 213, Subpart J)

FDA proposed to establish records requirements (proposed §§ 213.180, 213.182, 213.184, 213.186, 213.189, 213.192, 213.194, 213.196, and 213.198). We received no comments on proposed §§ 213.180, 213.184, 213.186, 213.192, 213.194, and 213.198 and are finalizing them as proposed with minor technical and grammatical changes made on our own initiative. We respond to the comments on proposed §§ 213.182, 213.189, and 213.196 below.

a. Equipment Cleaning and Use Log (Proposed § 213.182)

We proposed that a written record of major equipment cleaning, maintenance (except routine maintenance), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed (proposed § 213.182). If equipment is dedicated to manufacture of one product, then individual equipment logs would not be required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, we proposed that the records of cleaning, maintenance, and use shall be part of the batch record. We proposed that the persons performing and double-checking the cleaning and maintenance (or, if using automated equipment under § 213.68, just the person verifying the cleaning and maintenance done by the automated equipment) shall date and sign or initial the log indicating that the work was performed. Lastly, we proposed that entries in the log shall be in chronological order.

(Comment 36) One comment suggests revising § 213.182 to state that cleaning and maintenance is performed on a periodic basis or when there is suspected contamination and is not associated with a batch or lot process. The comment further requests that this provision state that equipment cleaning and non-routine maintenance is documented on separate cleaning or maintenance records. While the comment agrees that keeping a record of maintenance performed on production equipment is necessary, the comment maintains that, because these gases are manufactured and filled in a closed, pressurized system, equipment should not be cleaned between batches and lots. Otherwise, the comment asserts, contaminants could be introduced. Additionally, the comment states that the requirement to keep a use log of production equipment is not needed because this information is included on batch production records and would only increase manufacturers' burden.

(Response 36) FDA disagrees with this comment. The comment's suggested revisions go beyond recordkeeping requirements. The underlying cleaning and maintenance requirements are already addressed in §§ 213.42(c) and 213.67. Additionally, FDA does not believe that this provision as originally proposed suggests or requires cleaning at inappropriate times.

We also do not believe that the proposed requirements in § 213.182 are overly burdensome. Because the requirements in § 213.182 are intended to support good recordkeeping practices, such as the ability to locate records related to the equipment used in medical gas production (without needing to review one or more batch records), we decline to make the suggested revisions.

b. Batch Production and Control Records (Proposed § 213.189)

We proposed to require that batch production and control records be prepared for each batch of medical gas produced (proposed § 213.189(a)). We further proposed in § 213.189(b) that these records shall include documentation that each significant step in the manufacture, processing, packing, or holding of the medical gas produced was accomplished, including dates and times of each significant step, including in-process and laboratory tests as applicable; a description of the container for the medical gas, including the number and size of the containers filled as applicable; specific identification of each component and its source or in-process material used as applicable; measures of components used in the course of processing as applicable; testing results, including any in-process test results and finished product test results; dated signature or initials of the persons performing and directly supervising or checking each significant event in the operation; inspection of the packaging and labeling area before and after use; complete labeling control records, including specimens or copies of all labeling used and label application and reconciliation records as appropriate; and any investigation made according to § 213.192.

(Comment 37) One comment requests that the Agency revise § 213.189(b)(1) by deleting the words ''and times'' from the provision requiring that batch production and control records include ''[d]ates and times of each significant step, including in-process and laboratory tests as applicable.'' The

comment asserts that recording the time of production would not improve medical gas safety in light of the manufacturing processes used for medical gases.

(Response 37) FDA agrees with this comment. The Agency also notes that, considering the long, continuous production processes associated with many of these gases (for example, air separation used to produce oxygen and nitrogen), recording time as part of a firm's batch production and control records may be challenging. Therefore, the Agency is revising § 213.189(b)(1) to delete the reference to the time of significant steps. The finalized language requires that batch production records include the dates of each significant step, including in-process and laboratory tests as applicable.

(Comment 38) One comment asks that we delete § 213.189(b)(8), which would require batch production and control records to include complete labeling control records, including specimens or copies of all labeling used and label application and reconciliation records as appropriate. The comment maintains that the inclusion of labeling information would not provide added safety assurance, as would be the case for other drugs. Additionally, the comment notes that labels are reused, and industry performs a 100 percent inspection of cylinder labels during production.

(Response 38) We decline to delete § 213.189(b)(8). As discussed in the preamble to the proposed rule, because labeling does not always need to be applied due to the reuse of labels, documentation of these labeling control activities is important to help prevent mix-ups and the incorrect application of labeling (87 FR 31302 at 31319). Moreover, the inclusion of labeling control records can help facilitate investigations of complaints and other post-market activities. Due to the industry practice of the reuse of the labels, it is possible that no labels are applied during the manufacturing of a batch. In these instances, a copy of the label or a reproduction of the label is reasonable to include as part of the labeling control activities.

c. Distribution Records (Proposed § 213.196)

We proposed in § 213.196 to require that distribution records contain the name of the product, lot or batch number, name and address of the consignee, and date and quantity shipped, and that, for medical air and medically appropriate combinations of designated medical gases, the distribution record include the percentage of each gas.

(Comment 39) Multiple comments discuss the proposed requirement to include lot or batch number information in distribution records in § 213.196. One comment expresses concern that the exemption in § 211.196 (stating that compressed medical gas products do not need to include lot or control numbers in distribution records) would limit the ability to track a safety event. Another comment requests that ''lot or batch number'' be removed from § 213.196 to be consistent with the current requirements in § 211.196.

(Response 39) FDA declines to revise § 213.196. Regarding the concern about handling safety events, FDA proposed deletion of the exemption in § 211.196 for compressed medical gas products specifically because § 213.196 would fully address this requirement for medical gases. Regarding the proposed revision to § 213.196 to remove ''lot or batch number,'' FDA continues to believe that including the lot or batch number is essential to properly tracking and tracing product in the event a safety issue is discovered (see proposed rule discussion, 87 FR 31302 at 31320).

(Comment 40) One comment requests that FDA revise § 213.196 to explain that distribution records shall contain the required information (the name of the product, lot or batch number, name and address of the consignee, and date and quantity shipped) ''to facilitate a recall if needed.'' The comment asserts this would help achieve FDA's objective of improved traceability.

(Response 40) FDA does not agree. Because distribution records can serve many purposes aside from facilitating a recall, the suggested revision would unduly narrow the provision. As proposed (and finalized), § 213.196 can help a firm facilitate a recall and address other safety concerns that arise.

(Comment 41) One comment maintains that distribution records for medical air should not be required to include the percentage of each gas. The comment contends that, because the compendial standard for medical air specifies the range for the quantity of oxygen in nitrogen, including the specific percentage of oxygen for a shipment would not provide a benefit.

(Response 41) FDA agrees. Because medical air must be shown to meet compendial standards in order to be released, it is not necessary to state the amount of oxygen within the allowable range in the distribution records. Therefore, we have deleted ''medical air and'' from the second sentence of § 213.196 such that the requirement that the distribution record include the percentage of each gas only applies to medically appropriate combinations of designated medical gases.

11. Returned and Salvaged Medical Gases (Proposed Part 213, Subpart K)

FDA proposed to establish requirements for returned and salvaged medical gases (proposed §§ 213.204 and 213.208). We received no comments on proposed § 213.208 and are finalizing it as proposed with a minor grammatical change made on our own initiative.

FDA proposed in § 213.204 to require that returned medical gases be identified as such and held, and that, if the conditions under which the returned gases have been held, stored, or shipped before or during their return, or if the condition of the gas, its container, carton, or labeling, as a result of storage or shipping, cast doubt on its safety, identity, strength, quality, or purity, the returned medical gas shall be destroyed unless examination, testing, or other investigations prove the gas meets appropriate standards of safety, identity, strength, quality, or purity. Moreover, FDA proposed to require that firms maintain certain records of returned medical gases, and if the reason for a medical gas being returned implicates associated batches, an appropriate investigation pursuant to proposed § 213.192 shall be conducted. Procedures for holding, testing, and use of returned medical gases would need to be in writing and followed. FDA proposed that § 213.204 would not apply to the routine refilling of cryogenic medical gas containers in the normal course of business unless the container was returned for a quality issue.

(Comment 42) One comment requests that FDA exempt containers that assure the quality of the residual product prior to refill from the returned medical gases requirements in proposed § 213.204. The comment maintains that certain cylinders have residual pressure valves that prevent backflow.

(Response 42) FDA does not believe this change is necessary to address the comment's concern. As noted in the proposed rule, § 213.204 would apply to situations in which a distributed medical gas is sent back to a firm due to a quality issue (87 FR 31302 at 31321). Proposed § 213.204 included an exception for the routine refilling of cryogenic medical gas containers in the normal course of business because we understand that small amounts of gas are expected to remain in a returned container that will be reused (Id.). In the event a cylinder with a residual pressure valve is returned in the normal course of business for refilling and

redistribution, the requirements in § 213.204 would not apply. We note, however, that such valves could nonetheless fail, and if, for any reason, a cylinder with such a valve were returned and any of the conditions in the second sentence of § 213.204 are present, then the returned gas must be destroyed unless examination, testing, or other investigations prove the gas meets appropriate standards of safety, identity, strength, quality, or purity.

I. Description of Part 230 Comments and FDA Response

1. General Comments

We proposed a new part 230 (21 CFR part 230) to include requirements concerning the certification of designated medical gases and postmarketing safety reporting.

(Comment 43) Some comments make general remarks supporting the proposed certification and safety reporting regulations without focusing on a particular proposed provision.

(Response 43) We appreciate these comments of support.

2. Definitions (Proposed § 230.3)

FDA proposed definitions of several terms used in part 230. We received comments on several of those proposed definitions, as discussed below. We are finalizing as proposed those definitions for which we received no comments with minor technical changes made on our own initiative.

a. Applicant (Proposed § 230.3(b)(2))

We proposed to define ''applicant'' as any person or entity who submits a certification request for a designated medical gas under part 230, including a supplement, and any person or entity who owns a granted certification for a designated medical gas under part 230 (proposed § 230.3(b)(2)).

(Comment 44) One comment asks that we add language to clarify that the applicant is a person or entity who submits a certification request ''as an original manufacturer'' as defined in the medical gas CGMP regulations at § 213.3(b)(13). The comment asserts that this would be consistent with parts 201 and 213 and account for applicants that are both original manufacturers and subsequent manufacturers.

(Response 44) FDA does not agree with these requested revisions. Consistent with section 576(a)(1) of the FD&C Act, § 230.50(a)(1) of the designated medical gas certification regulations makes clear that any person who seeks to *initially* introduce or deliver for introduction a designated medical gas into interstate commerce is the entity that shall file a certification request. We agree that subsequent manufacturers are not required to submit certification requests, but revising the ''applicant'' definition is unnecessary because the applicant is *any* person or entity who submits a certification request. If a subsequent manufacturer erroneously submitted a certification request, FDA may determine that the request was unnecessary and not grant it, but the subsequent manufacturer would still be considered the applicant for purposes of all interactions with the Agency related to the certification request. Moreover, as stated in response 45, FDA does believe it is appropriate to remove ''or entity'' from the definition of ''applicant,'' as the word ''person'' captures all relevant entities.

b. Nonapplicant (Proposed § 230.3(b)(9))

We proposed to define ''nonapplicant'' as any person other than the applicant whose name appears on the label of a designated medical gas container as a manufacturer, packer, or distributor (proposed § 230.3(b)(9)).

(Comment 45) One comment suggests revisions to the proposed ''nonapplicant'' definition in § 230.3(b)(9) for consistency across the regulations applicable to designated medical gases. First, the comment asks that the definition be revised to include any person *or entity,* rather than just any person, meeting the criteria in the definition. This suggested revision is intended to be consistent with the ''applicant'' definition in § 230.3(b)(2). Second, the comment asks that the definition be revised to refer to entities that appear on the label of a designated medical gas container as a subsequent manufacturer or distributor, rather than as a manufacturer, packer, or distributor. The comment asserts that these revisions are intended to account for nonapplicants that are also original manufacturers. The comment maintains that removal of the term ''packer'' would be consistent with industry terminology.

(Response 45) We do not believe that changes are necessary to the ''nonapplicant'' definition. First, FDA routinely uses the word ''person'' to include entities and organizations that are not individuals. The term ''person'' as defined in section 201(e) of the FD&C Act includes an individual, partnership, corporation, and association. Additionally, the definition of ''applicant'' in § 314.3 ''is any person who submits an NDA . . . or ANDA . . . .'' As discussed in response 44 above, FDA also concludes it is not necessary to include ''or entity'' in the definition of ''applicant'' in § 230.3(b)(2). Section 230.50(b)(1) has also been revised to refer to ''person'' and not ''entity.''

Second, we do not agree with the use of the term ''subsequent manufacturer'' or the removal of the term ''packer.'' If an entity is an original manufacturer of a designated medical gas, FDA expects that it would be the applicant as opposed to a nonapplicant. Nonetheless, for a given designated medical gas, whether a firm is the applicant or a nonapplicant will depend on the activities performed for that product. We also note that the terminology used in the proposed definition is consistent with existing § 314.80(c)(1)(iii). While the medical gas industry may not ordinarily use the term ''packing'' to refer to its operations, the activities that subsequent manufacturers perform (such as transfilling, mixing, or filling at a delivery site) are expected to fall within the term ''manufacturer, packer, or distributor.''

3. General Requirements for All Submission Types (Proposed § 230.50)

FDA proposed requirements for all types of certification submissions (proposed § 230.50). We received no comments on the proposed requirements and are finalizing them as proposed with minor technical edits made on our own initiative for clarity.

4. Withdrawal by the Applicant of a Certification Request Before It Is Deemed Granted (Proposed § 230.65)

FDA proposed requirements regarding withdrawal of a certification request prior to it being deemed granted (proposed § 230.65). We received no comments on the proposed requirements and are finalizing them as proposed.

5. Supplements and Other Changes to a Granted Certification (Proposed § 230.70)

FDA proposed requirements regarding supplements and other changes to a granted certification (proposed § 230.70). We received no comments on the proposed requirements and are finalizing them as proposed.

6. Change in Ownership of a Granted Certification (Proposed § 230.72)

FDA proposed requirements regarding the change in ownership of a granted certification (proposed § 230.72). We received no comments on the proposed requirements and are finalizing them as proposed.

7. Annual Report (Proposed § 230.80)

FDA proposed to establish annual report requirements in proposed § 230.80. First, FDA proposed that applicants must submit an annual report each year within 60 calendar days of the anniversary of the date the certification was granted, and that the annual report form must be signed and completed and submitted in an electronic format that FDA can process, review, and archive, or in hard copy by submitting two paper copies to CDER's Central Document Room (proposed § 213.80(a)). Under proposed § 213.80(b), the annual report would contain, for the prior 12 months, a brief summary of significant new information that might affect the safety, effectiveness, or labeling of the designated medical gas, including any actions the applicant has taken or intends to take as a result of this new information; information about the quantity of the designated medical gas distributed by the applicant, including the National Drug Code (NDC) numbers and quantities distributed for domestic use and the quantities distributed for foreign use; any changes to the applicant's name or contact information; and a list of current facilities, as well as a list of facilities that are no longer in use.

(Comment 46) One comment requests that annual reports be submitted after the start of the new calendar year, rather than on the anniversary of the date the certification request was deemed granted. The comment asserts that this would align the annual reporting requirements with reporting requirements stemming from the Coronavirus Aid, Relief, and Economic Security Act (CARES Act) (Pub. L. 116–136). The comment also states that annual reports are provided for activities related to the original manufacturing operations of the applicant, and not for subsequent manufacturing activities.

(Response 46) FDA agrees with this comment. In particular, section 3112(e) of the CARES Act established new section 510(j)(3) of the FD&C Act (21 U.S.C. 360(j)(3)), which requires all drug registrants to report annually on the amount of each listed drug manufactured, prepared, propagated, compounded, or processed for commercial distribution. We recognize that it may create efficiencies for firms to track information across multiple reports if the reports are submitted on the same reporting schedule. Therefore, we have revised § 230.80(a) to require annual reports to be submitted within 60 calendar days of the new calendar year. We also agree that annual reports cover activities related to the original manufacture of the designated medical gas.

(Comment 47) One comment requests deletion of the requirement in proposed § 230.80(b)(2) that annual reports include distribution data because, as required by the CARES Act, section 510(j)(3) of the FD&C Act requires similar distribution data. Specifically, section 510(j)(3)(A) requires that each person who registers with FDA under section 510 of the FD&C Act with regard to a drug must report annually to FDA on the amount of each drug listed that was manufactured, prepared, propagated, compounded, or processed by such person for commercial distribution.

(Response 47) FDA appreciates the need to avoid duplicate submissions of information. However, we conclude it is appropriate to retain the proposed requirement that distribution data be included in designated medical gas annual reports. Certain information, such as the NDC number and quantities of gas distributed for domestic and foreign use, is important to retain.

FDA considers the requirement to submit distribution data in annual reports under § 230.80(b)(2) to have been met if: (1) the registrant of establishments identified in the application submits a timely and complete report under section 510(j)(3) of the FD&C Act; (2) the registrant of establishments identified in the application includes in its section 510(j)(3) report the amount of listed drug product (organized by NDC number) that was distributed for foreign use during the reporting period (in addition to the amount distributed in the United States); (3) the applicant's annual report provides the date(s) of the report(s) submitted under section 510(j)(3) of the FD&C Act that includes the domestic and foreign distribution information; and (4) the applicant's annual report submitted under § 230.80 contains all other information required in § 230.80(b). FDA believes that this would maintain the Agency's access to information that would enhance the Agency's ability to assess, prevent, and mitigate possible drug shortages, and would also address the potential reporting burden for applicants that are subject to both § 230.80 and section 510(j)(3) of the FD&C Act.

(Comment 48) One comment requests that the proposed requirement in § 230.80(b)(4) that the annual report contain a list of ''current facilities'' be revised to require a list of ''the applicant's current original manufacturing facilities'' because only original manufacturing locations are required to be listed.

(Response 48) Our intent in § 230.80(b)(4) is for applicants to submit information regarding their original manufacturing facilities, as opposed to any subsequent manufacturing facilities they operate. In light of the comment received, we have revised § 230.80(b)(4) consistent with the requirement in section 576(a)(1)(C) of the FD&C Act and what we proposed for § 230.50(b)(4), which both address information to be submitted as part of a certification request. Because the purpose of § 230.80(b)(4) is to receive updates of the same information, we have revised the provision to require that the annual report include a list of current facilities *where the designated medical gas is initially produced,* and a list of facilities that are no longer in use.

8. FDA Review of Submissions (Proposed § 230.100)

FDA proposed requirements regarding FDA's review of submissions (proposed § 230.100). We received no comments on the proposed requirements and are finalizing them as proposed with minor technical edits made on our own initiative.

9. When a Submission Is Deemed Granted (Proposed § 230.105)

FDA proposed requirements regarding when a submission is deemed granted (proposed § 230.105). We received no comments on the proposed requirements and are finalizing them as proposed.

10. Withdrawal (Proposed § 230.150)

FDA proposed withdrawal and revocation requirements in proposed § 230.150. We did not receive comments on the proposed revocation requirements in § 230.150(b) and are finalizing those requirements as proposed with minor technical and grammatical changes made on our own initiative.

FDA proposed in § 230.150(a)(1) and (2) several grounds for withdrawing approval of a designated medical gas application, subject to FDA notifying the applicant and affording an opportunity for a hearing. Under proposed § 230.150(a)(3), FDA will withdraw approval of an application if the applicant requests its withdrawal because the designated medical gas subject to the application is no longer being marketed, provided none of the conditions listed in § 230.150(a)(1) and (2) apply. FDA would consider such a written request to be a waiver of an opportunity for hearing, and such withdrawal would be without prejudice

to refiling. FDA proposed in § 230.150(a)(4) that we may notify an applicant that we believe a potential problem associated with a designated medical gas is sufficiently serious that the designated medical gas should be removed from the market and may ask the applicant to waive the opportunity for hearing otherwise provided for under this section, to permit FDA to withdraw approval of the application for the product, and to remove voluntarily the product from the market. Lastly, FDA proposed under § 230.150(a)(5) that, if FDA withdraws an approval, FDA will publish a notice in the **Federal Register** announcing the withdrawal.

(Comment 49) Regarding the proposed withdrawal requirements in § 230.150, one comment states that FDA should include a reason for voluntary withdrawals to clarify whether the designated medical gas was withdrawn for safety reasons. The comment asserts that, without such information, an applicant's reputation may be harmed.

(Response 49) FDA does not believe that posting a withdrawal notification without a rationale would necessarily be interpreted as a statement that the designated medical gas was withdrawn for safety or effectiveness reasons. Because designated medical gases are generally considered appropriate for the uses stated in the statute, many of the considerations relevant to drugs approved under section 505 of the FD&C Act are not applicable. Moreover, the withdrawal of a designated medical gas does not create the same follow-on considerations that the withdrawal of an NDA approved under section 505 of the FD&C Act would create for current and future ANDAs that reference the withdrawn NDA. Therefore, we decline to make the suggested revisions to § 230.150.

However, as discussed in response 61 below, FDA is revising § 230.150(a)(2)(i) to include failure to submit reports under § 314.81(b)(3). Because of this revision, it is unnecessary for § 314.81(d) to continue to apply to designated medical gases.

11. Field Alert Report (Proposed § 230.205)

We proposed field alert reporting requirements for designated medical gases in § 230.205. Specifically, FDA proposed that applicants be required to submit FARs to the FDA district office responsible for the facility involved within 3 working days of receipt by the applicant, and that the information may be provided by telephone or other rapid communication, with prompt written followup. FDA also proposed formatting requirements for the FAR and its mailing cover. In proposed § 230.205(a), FDA proposed that a FAR is required for information concerning any incident that causes the designated medical gas or its labeling to be mistaken for, or applied to, another article. In proposed § 230.205(b), FDA proposed that a FAR is required for information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed designated medical gas, or any failure of one or more distributed batches of the designated medical gas to meet established specifications.

(Comment 50) One comment requests that the field alert reporting requirements apply to nonapplicants as well as applicants. The comment asserts that downstream entities are more directly linked to the end user and would have the most current and detailed information about any issues that might require a FAR.

(Response 50) FDA disagrees. We note that the proposed field alert reporting requirements are drafted for designated medical gases, as opposed to combinations of designated medical gases. This scope is also consistent with the field alert reporting requirements in § 314.81(b)(1), which require that applicants submit reports to the Agency. It is worth noting that the field alert reporting requirements in § 514.80(b)(1) (21 CFR 514.80(b)(1)) require the applicant, or the nonapplicant through the applicant, to report, so in either case the applicant would submit the FAR to FDA.

(Comment 51) One comment expresses support for the proposed 3-working-day reporting period, but asserts that FARs may still be incomplete at that timepoint.

(Response 51) FDA acknowledges the concern that more information may be available after 3 working days, and thus, under the proposed reporting timeframe, FARs may be incomplete in some instances. FDA believes that a 45-day reporting deadline for certain FARs for designated medical gases is appropriate. The 3-working-day reporting period originally proposed would apply if the information suggests that the reportable incident may require a rapid response to address a public health risk. Therefore, as finalized, § 230.205 requires that an applicant submit a FAR as soon as possible but no later than 45 calendar days from the date the applicant, or its agent or contractor, obtained information suggesting that a reportable incident has occurred, and if the information suggests that the reportable incident may require a rapid response to address a public health risk, the applicant must submit the FAR as soon as possible, but no later than 3 working days from obtaining the information. Reporting as soon as possible but no later than 45 calendar days from the date the applicant, or its agent or contractor, obtained information suggesting that a reportable incident has occurred appropriately balances the need to report quickly with helping to ensure that the applicant collects sufficient information to enable an appropriate response.

FDA is not making further revisions to the field alert reporting requirements for designated medical gases to reflect the proposed changes to part 314. The Agency has not received many FARs for designated medical gases. Considering certain characteristics of these drug products (including that they are generally manufactured in a sealed, closed system, which makes contamination and stability less of a concern), we conclude that further revisions are unnecessary. However, as we gain more experience with designated medical gases and with any future revisions to the field alert reporting requirements in part 314, we will consider whether revisions to § 230.205 are needed.

12. General Reporting Requirements for Designated Medical Gas Adverse Events (Proposed § 230.210)

FDA proposed general reporting requirements for designated medical gas adverse events (proposed § 230.210). We received no comments on the proposed requirements and are finalizing them as proposed.

13. Human Postmarketing Safety Reporting (Proposed § 230.220)

FDA proposed human postmarketing safety reporting requirements in § 230.220. Under proposed § 230.220(a)(1), applicants and nonapplicants must submit each ICSR associated with the use of a designated medical gas in humans described in § 230.220(b) as soon as possible but no later than 15 calendar days from the date the applicant or nonapplicant met the reporting criteria and acquired a minimum data set for an ICSR for that adverse event. FDA further proposed that applicants and nonapplicants should not resubmit any ICSRs obtained from FDA's adverse event reporting database or forwarded to the applicant or nonapplicant by FDA (proposed § 230.220(a)(2)). Additionally, FDA proposed that applicants and nonapplicants must submit new information related to a previously submitted ICSR or an ICSR sent to the

applicant by FDA no later than 15 calendar days after the information is received or otherwise obtained (proposed § 230.220(a)(3)).

FDA proposed in § 230.220(b) to specify which adverse events must be reported in an ICSR. FDA proposed that applicants and nonapplicants must submit ICSRs for serious adverse events reported to the applicant or nonapplicant spontaneously (such as a report initiated by a patient, consumer, or healthcare provider) or obtained from published scientific and medical journals (either as case reports or as the result of a formal clinical trial) (proposed § 230.220(b)(1)(i) and (ii)). Proposed § 230.220(b)(1)(iii) explains that ICSRs are not required for reports of the death of a patient who was administered oxygen, unless the applicant or nonapplicant is aware of evidence to suggest that the death was caused by the administration of oxygen. In addition, under proposed § 230.220(b)(2), upon notification by FDA, applicants and nonapplicants must submit, in a timeframe established by FDA, ICSRs for any adverse event that are not required under § 230.220(b)(1).

Under proposed § 230.220(c), FDA proposed to specify how to complete and submit ICSRs required under § 230.220. FDA proposed to require that ICSRs and ICSR attachments be submitted in an electronic format that FDA can process, review, and archive, though applicants and nonapplicants may request, in writing, a temporary waiver of this requirement (proposed § 230.220(c)(1)). FDA further proposed to require that each ICSR be submitted only once, that separate ICSRs be submitted for each patient who experiences a reportable adverse event, that adverse event terms must be coded using standardized medical terminology, that all ICSRs must contain at least the minimum data set for an ICSR, that the applicant or nonapplicant must complete all known, available elements of an ICSR as specified in § 230.220(d), and that an applicant must submit autopsy reports, hospital discharge summaries, or published articles as specified (proposed § 230.220(c)(2)).

Proposed § 230.220(d) sets forth the information that must be included in an ICSR, including patient information, adverse event information, information about the suspect designated medical gas(es), information about the initial reporter, and applicant or nonapplicant information.

Under proposed § 230.220(e), FDA proposed recordkeeping requirements, including that applicants and nonapplicants maintain records of information relating to adverse events for 10 years, whether or not submitted to FDA (proposed § 230.220(e)(1)). FDA further proposed that such records must include raw data, correspondence, and any other information relating to the evaluation and reporting of adverse event information that is received or otherwise obtained by the applicant or nonapplicant (proposed § 230.220(e)(2)). Lastly, FDA proposed that, upon written notice by FDA, the applicant or nonapplicant must submit any or all of these records to FDA within 5 calendar days after receipt of the notice, and the applicant or nonapplicant must permit any authorized FDA employee, at reasonable times, to access, copy, and verify these established and maintained records (proposed § 230.220(e)(3)).

Proposed § 230.220(f) specified that applicants and nonapplicants must develop written procedures needed to fulfill the requirements of § 230.220 for the surveillance, receipt, evaluation, and reporting to FDA of adverse event information.

Proposed § 230.220(g) would establish requirements concerning patient privacy. Specifically, FDA proposed that an applicant or nonapplicant should not include in reports under § 230.220 the names and addresses of individual patients; instead, the applicant or nonapplicant should assign a unique code for identification of the patient. FDA further proposed that the applicant or nonapplicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. Proposed § 230.220(g) further states that as set forth in FDA's public information regulations in 21 CFR part 20, the Agency generally may not disclose the names of patients, individual reporters, healthcare professionals, hospitals, and geographical identifiers submitted to FDA in adverse event reports.

Before discussing the comments received regarding FDA's proposed human postmarketing safety reporting requirements, the Agency notes an additional set of revisions we are making to § 230.220 on our own initiative. We are revising proposed § 230.220(b)(1)(i) to describe more clearly the requirement that applicants and nonapplicants must submit ICSRs for serious adverse events reported to or otherwise received by the applicant or nonapplicant. This revision aligns with the requirement in § 230.210(a) for prompt review of all safety information that the applicant or nonapplicant receives or otherwise obtains from any source and is intended to help ensure that reports of serious adverse events otherwise received (or obtained) by the applicant or nonapplicant are submitted to the Agency. Accordingly, this requirement includes, for example, serious adverse event reports received at the request of the applicant or nonapplicant (such as reports received as part of a patient support program), in addition to unsolicited communications such as reports initiated by a patient, consumer, or healthcare professional.

In the proposed rule, FDA proposed that § 314.80(g) would continue to apply to designated medical gases, and proposed § 230.220(c)(1)(i) and (ii) included cross-references to § 314.80(g). After further consideration, the Agency believes that it would be most helpful and efficient to set forth the electronic format requirements in § 230.220 rather than referencing § 314.80(g). Therefore, we have revised § 230.220(c)(1)(i) to directly include the requirement that ICSRs and ICSR attachments be in an electronic format that FDA can process, review, and archive, rather than cross-reference § 314.80(g)(1). FDA intends to issue guidance on how to provide the electronic submission (*e.g.,* method of transmission, media, file formats, preparation and organization of files). We have also revised § 230.220(c)(1)(ii) to directly state that an applicant or nonapplicant may request, in writing, a temporary waiver of the electronic reporting requirements, and that these waivers will be granted on a limited basis for good cause shown, rather than cross-reference § 314.80(g)(2). FDA intends to issue guidance on requesting a waiver of the requirements in § 230.220(c)(1)(i).

Furthermore, we have revised § 314.1(c) to state that § 314.80, as a whole, does not apply to designated medical gases. These revisions have the same regulatory effect as the language included in the proposed rule on this issue.

(Comment 52) One comment maintains that some nonapplicants may be unable to comply with the proposed ICSR requirements.

(Response 52) FDA believes it is appropriate to apply the proposed ICSR requirements to nonapplicants. We note that nonapplicants are currently required to comply with the postmarketing safety reporting requirements in § 314.80(c)(1)(i) and (ii), although nonapplicants may comply by submitting all reports of serious adverse drug experiences to the applicant. Under § 230.220, the only difference will be that nonapplicants for designated medical gases must report to FDA, rather than the applicant.

Therefore, we do not believe that revisions are necessary.

(Comment 53) Regarding the proposed exception to the ICSR requirements for serious adverse events in proposed § 230.220(b)(1)(iii), one comment recommends expanding the exception to serious injuries of patients administered oxygen, unless the applicant or nonapplicant is aware of evidence to suggest that the serious injury was caused by the administration of oxygen. The comment references the proposed ''no smoking'' and ''no vaping'' warning statements in § 201.161(a)(1)(ii) and maintains that its suggested changes would be consistent with the warning statements.

(Response 53) FDA does not agree that this change is necessary. The purpose of the exception in § 230.220(b)(1)(iii) is to address cases where a patient being administered oxygen dies and there is no reason to believe that the oxygen contributed to the patient's death. This is very common because, as discussed in the proposed rule, oxygen is commonly administered during end-of-life care or to patients with a life-threatening disease or who are otherwise in critical condition (87 FR 31302 at 31329). This provision is not intended to address fire-related injuries.

(Comment 54) One comment expresses support for the proposed minimum data set requirements for human postmarketing safety reporting but asserts that the burden could be significant for firms. The comment maintains that, for purposes of complying with § 230.220(c)(2) or § 230.220 more generally, firms may need to hire or contract with medical professionals to evaluate potential ICSRs.

(Response 54) FDA appreciates the feedback regarding the proposed minimum data set requirements and acknowledges the concern regarding compliance burden. (Section VII below discusses the economic burden of compliance with § 230.220, including § 230.220(c)(2).) Nonetheless, FDA does not believe that firms will need to hire medical professionals. We further note that applicants (and nonapplicants by way of applicants) are currently required to submit adverse event reports to FDA under §§ 314.80 and 514.80 for human adverse drug experiences and animal adverse drug events, respectively. In both cases, this requires determining whether the event is unexpected, something that generally would not be required under § 230.220 or § 230.230. Required reports of serious adverse events must be submitted regardless of expectedness, and a causality assessment is only required in the event there is evidence to suggest that the death of a patient being administered oxygen was caused by such administration of oxygen.

(Comment 55) Regarding the proposed requirement in § 230.220(c)(2)(iii) that event terms in ICSRs be coded using standardized medical terminology, one comment requests that the word ''must'' be revised to ''should.'' The comment also requests that the recommendation that standardized medical terminology be used should only apply if the terminology is provided by the reporter. The comment maintains that medical gas firms do not necessarily have medical expertise available to code ICSR events.

(Response 55) FDA disagrees with these suggested revisions. We do not believe that coding using standardized medical terminology is a significant burden, nor do we believe that medical professionals are needed to code an event correctly. Standardized medical terminology generally includes terms commonly used by laypersons when describing adverse events. Moreover, because the reporter may be the patient or a relative, and thus not necessarily familiar with ICSR reporting or FDA regulation more broadly, it would be unreasonable to rely on the original reporter to properly code an event. Because the use of standardized medical terminology helps FDA track, evaluate, and respond to safety signals, we do not believe the requested revisions are appropriate.

(Comment 56) FDA received one comment concerning proposed § 230.220(c)(2)(vi)(B). The comment states that applicants and nonapplicants should be required to submit a reference to published articles, rather than the articles themselves, due to copyright restrictions. As an alternative, the comment suggests that FDA could require that the article be provided upon request, subject to copyright.

In light of these recommendations, the comment also requests deletion of the provisions requiring translation of the abstract of foreign language articles and describing the requirements for submitting more than one ICSR from the same published article. The comment maintains that the burden of these requirements would be significant, as firms would need to hire medical professionals to evaluate ICSRs.

(Response 56) FDA does not agree with these suggested changes. First, it is unclear why medical professionals would be needed to help an applicant or nonapplicant comply with the requirements in § 230.220(c)(2)(vi)(B). Additionally, we note that § 314.80(d) currently requires that a 15-day Alert report based on information in the scientific literature be accompanied by a copy of the published article.

Regarding the submission of foreign language articles, FDA recognizes that there may be additional burden associated with translating foreign language documents, but we proposed that only the abstract be translated and expect that the burden associated with this activity would be minimal. As such, we believe that requiring translation of only the abstract of a foreign language article is appropriate.

Because we are requiring in this final rule that the applicant or nonapplicant provide a copy of published articles as an attachment, we believe it is important to retain the language concerning the submission of multiple ICSRs from the same article.

(Comment 57) One comment asks that proposed § 230.220(g) be revised to create an exception to the recommendation that the applicant or nonapplicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. Specifically, the comment requests an exception for when the reporter is the patient out of concern for disclosing the patient's personal information.

(Response 57) FDA disagrees. As noted in the sentence that immediately follows the referenced provision in § 230.220(g), FDA acknowledges that, as addressed in the Agency's public information regulations, FDA generally may not disclose the names of patients, individual reporters, healthcare professionals, hospitals, and geographical identifiers submitted to FDA in adverse event reports. Moreover, in situations in which the reporter is the patient, nothing in the submission necessarily makes that fact evident to the reader. Lastly, the language at issue is consistent with the current text of § 314.80(i) indicating that the name of the reporter be included even when the reporter is the patient.

(Comment 58) FDA sought comment on the Agency's decision not to propose periodic safety reporting requirements for designated medical gases and received comments in support and in opposition. Some comments maintain that this decision is consistent with FDA's March 2015 Compliance Program Guidance Manual 7356.002E (Ref. 3), while other comments assert that periodic safety reporting enables cumulative review of safety information.

(Response 58) After considering the comments, FDA does not believe it is necessary to include a periodic safety reporting requirement in this

rulemaking. Medical gases have historically been manufactured, labeled, and distributed in a manner different than most other drugs. Because of these differences, FDA believes that the likelihood of identifying new safety issues for medical gases is low, and that ICSRs are an adequate and efficient means of identifying any new safety issues for these products.

14. Animal Postmarketing Safety Reporting (Proposed § 230.230)

FDA proposed animal postmarketing safety reporting requirements in § 230.230. Under proposed § 230.230(a), applicants and nonapplicants must submit serious adverse events to FDA as soon as possible but no later than within 15 calendar days of first receiving the information. FDA proposed that applicants and nonapplicants must submit reports for each serious adverse event reported to the applicant or nonapplicant spontaneously (such as reports initiated by a patient, consumer, veterinarian, or other healthcare professional), regardless of whether the applicant or nonapplicant believes the events are related to the designated medical gas (proposed § 230.230(a)(1)(i)). FDA also proposed that applicants and nonapplicants must submit reports for each serious adverse event obtained from published scientific and medical literature regardless of whether the applicant or nonapplicant believes the events are related to the designated medical gas (proposed § 230.230(a)(1)(ii)). FDA proposed that adverse event reports not be required for reports of the death of an animal who was administered oxygen, unless the applicant or nonapplicant is aware of evidence to suggest that the death was caused by the administration of oxygen (proposed § 230.230(a)(1)(iii)). Under proposed § 230.230(a)(2), upon notification by FDA, applicants and nonapplicants must submit reports of adverse events associated with the use of a designated medical gas in animals that do not qualify for reporting under § 230.230(a)(1). FDA proposed under § 230.230(a)(3) that applicants and nonapplicants should not resubmit adverse event reports obtained from FDA's adverse event reporting database or forwarded to the applicant or nonapplicant by FDA.

FDA proposed in § 230.230(b) to require that adverse event reports be submitted in an electronic format that FDA can process, review, and archive, and that data provided in electronic submissions must be in conformance with the data elements in Form FDA 1932 and FDA technical documents describing transmission (proposed § 230.230(b)(1)). FDA further proposed that applicants and nonapplicants may request, in writing, a temporary waiver of this requirement (proposed § 230.230(b)(2)).

Under proposed § 230.230(c), FDA proposed recordkeeping requirements, including that applicants and nonapplicants maintain records of information relating to adverse event reports for 5 years, whether or not submitted to FDA (proposed § 230.230(c)(1)). FDA further proposed that such records must include raw data, correspondence, and any other information relating to the evaluation and reporting of adverse event information that is received or otherwise obtained by the applicant or nonapplicant (proposed § 230.230(c)(2)). Lastly, FDA proposed that, upon written notice by FDA, the applicant or nonapplicant must submit any or all of these records to FDA within 5 calendar days after receipt of the notice, and the applicant or nonapplicant must permit any authorized FDA employee, at reasonable times, to access, copy, and verify these established and maintained records (proposed § 230.230(c)(3)).

Before responding to a comment we received regarding the proposed animal postmarketing safety reporting requirements, the Agency notes a revision we have made on our own initiative. We have revised § 230.230(a)(1)(i) to more clearly specify that applicants and nonapplicants must submit reports for serious adverse events reported to or otherwise received by the applicant or nonapplicant. This revision aligns § 230.230(a)(1)(i) with the requirement in § 230.210(a) for prompt review of all safety information that the applicant or nonapplicant receives or otherwise obtains from any source, and helps ensure that reports of serious adverse events otherwise received (or obtained) by the applicant or nonapplicant are submitted to the Agency. Accordingly, § 230.230(a)(1)(i) includes, for example, serious adverse event reports received at the request of the applicant or nonapplicant, in addition to unsolicited communications such as reports initiated by a patient, consumer, veterinarian, or other healthcare professional.

(Comment 59) Regarding the proposed exception to the reporting requirements for serious adverse events in proposed § 230.230(a)(1)(iii), one comment recommends expanding the exception to serious injuries of animals administered oxygen, unless the applicant or nonapplicant is aware of evidence to suggest that the serious injury was caused by the administration of oxygen. The comment references the ''no smoking'' and ''no vaping'' warning statements in proposed § 201.161(a)(1)(ii) and maintains that the suggested changes would be consistent with the warning statements.

(Response 59) As discussed above, FDA does not agree that this change is necessary. The purpose of the exception in § 230.230(a)(1)(iii) is to address cases where an animal being administered oxygen dies and there is no reason to believe that the oxygen contributed to the animal's death. This is very common because, as discussed in the proposed rule, we expect that oxygen will be administered to animals that are in critical condition, and death is expected to be a common outcome (87 FR 31302 at 31331). This provision is not intended to address fire-related injuries.

J. Description of Part 314 Comments and FDA Response

FDA proposed carving out designated medical gases from certain provisions in part 314, either because a corresponding provision specific to designated medical gases was proposed to be added to part 230, or because the provision is not relevant to designated medical gases. Specifically, FDA proposed exempting designated medical gases from §§ 314.50 through 314.72 (concerning certain information required in NDAs); § 314.80, except paragraph (g) (concerning certain postmarketing reporting requirements); § 314.81(a) and (b)(1) and (2) (concerning certain other postmarketing reports); § 314.90 (concerning waivers); subpart C (concerning ANDAs); §§ 314.100 through 314.162 (concerning certain requirements related to FDA action on NDAs and ANDAs; subpart H (concerning accelerated approval); and subpart I (concerning approval of new drugs when human efficacy studies are not ethical or feasible). FDA received comments related to some of these proposed changes, to which we respond below.

(Comment 60) One comment requests that designated medical gases be exempted from § 314.81(b)(3), which includes requirements for submitting advertisements and promotional labeling, special reports requested by the Agency, the process for notifying FDA of a permanent discontinuance of manufacture of a drug product, and withdrawal of an approved drug product from sale. The comment asserts that, in light of the proposed revisions to the labeling requirements in part 201, it is not necessary for these provisions to apply to designated medical gases.

(Response 60) FDA does not agree that designated medical gases should be exempted from § 314.81(b)(3). The

Agency assumes that the comment is primarily focused on § 314.81(b)(3)(i), which concerns the submission of advertisements and promotional labeling, because of the comment's discussion of part 201. The other provisions in § 314.81(b)(3) are unrelated to labeling, and it is not clear how the changes FDA proposed to part 201 would address these requirements. Furthermore, we do not believe that the changes FDA is making to part 201 address the requirements in § 314.81(b)(3)(i), as part 201 does not include requirements for promotional labeling. Because FDA believes it is still important for promotional materials to be submitted to the Agency, we believe it is important to retain this provision.

(Comment 61) One comment requests that designated medical gases be exempted from § 314.81(c) because an original manufacturer will only have one application for each designated medical gas.

(Response 61) We assume the comment concerns only § 314.81(c)(1), regarding the submission of information common to more than one application, as the comment does not discuss the requirements of § 314.81(c)(2). FDA does not expect that designated medical gas applicants will have information common to more than one application. In addition, upon further consideration, FDA concludes it is not necessary to retain the requirements in § 314.81(c)(2) for designated medical gases because patient privacy information is not expected to be included in reports for designated medical gases submitted under § 314.81. For these reasons, we are revising the codified at § 314.1(c) such that § 314.81(c) no longer applies to designated medical gases.

In addition, because § 230.150 now provides for withdrawal of an application for a designated medical gas based on failure to submit reports required under § 314.81(b)(3) (see section V.I.11), it is not necessary for § 314.81(d) (which concerns withdrawal of approval for failure to make required reports) to continue to apply to designated medical gases. Accordingly, FDA has revised § 314.1(c)(3) to read ''Section 314.81, except paragraph (b)(3)''.

K. Part 514

FDA proposed carving out designated medical gases from provisions in part 514 (21 CFR part 514) to align with the provisions specific to designated medical gases that we proposed to add to part 230. We did not receive comments on the proposed revisions and are finalizing the provisions as proposed with minor technical changes made on our own initiative.

VI. Effective Date

This rule is effective December 18, 2025, except for §§ 4.2, 4.3, and 4.4. The effective date for §§ 4.2, 4.3, and 4.4 will be February 2, 2026.

(Comment 62) One comment supports the proposed effective date of 18 months after publication of the final rule. The comment notes that firms will need time to update labeling information to ensure compliance with the new requirements.

(Response 62) FDA acknowledges this comment, and we believe that 18 months is an appropriate time after publication of the final rule to enable firms to comply with these requirements. However, we note that the recently published final rule ''Medical Devices; Quality System Regulation Amendments'' (the QSRA rule), which will become effective on February 2, 2026,[4] amends provisions of part 4 that are further revised by this rule. To prevent any confusion that may result from multiple amendments to part 4 occurring so close in time, FDA has determined that this rule's amendments to §§ 4.2, 4.3, and 4.4 will be effective on February 2, 2026, the same date the QSRA rule becomes effective.

VII. Economic Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 14094, the Regulatory Flexibility Act (5 U.S.C. 601–612), the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act (5 U.S.C. 801, Pub. L. 104–121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4).

Executive Orders 12866, 13563, and 14094 direct us to assess all benefits, costs, and transfers 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). Rules are ''significant'' under Executive Order 12866 Section 3(f)(1) (as amended by Executive Order 14094) if they ''have an annual effect on the economy of $200 million or more (adjusted every 3 years by the Administrator of [the Office of Information and Regulatory Affairs (OIRA)] for changes in gross domestic product); or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, territorial, or tribal governments or communities.'' OIRA has determined that this final rule is not a significant regulatory action under Executive Order 12866, section 3(f)(1).

Because this rule is not likely to result in an annual effect on the economy of $100 million or more or meets other criteria specified in the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act, OIRA has determined that this rule does not fall within the scope of 5 U.S.C. 804(2).

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this final rule will better tailor the current good manufacturing practice requirements for medical gases and medically appropriate combinations of such gases and creates small net cost savings for small entities, we 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 estimates of anticipated impacts, 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 one year.'' The 2022 threshold after adjustment for inflation is $177 million, using the (2022) Implicit Price Deflator for the Gross Domestic Product. This final rule will not result in an expenditure in any year that meets or exceeds this amount.

This final rule establishes, within part 213, CGMP regulations specific to medical gases. These regulations include many of the same categories of requirements as the general drug product CGMP regulations but are tailored to reflect differences in how medical gases are manufactured, packaged, labeled, stored, and distributed. This rule makes limited changes to the labeling requirements of part 201, including requiring that a ''no smoking'' statement, a ''no vaping'' statement, and graphic warning symbol be added to oxygen containers to reduce the risk of fire. This rule codifies and clarifies the process for obtaining a certification to market designated medical gases. Recommendations for how to request a certification for designated medical gases are currently included in a draft guidance. This rule makes changes to postmarketing safety reporting regulations for designated medical gases that address human and animal use and more specifically reflect

[4] See 89 FR 7496 (February 2, 2024).

the development, manufacturing, and distribution of designated medical gases.

The costs of this final rule are primarily driven by new labeling requirements, clarification leading to firms becoming compliant with existing requirements, and added CGMP requirements, including a requirement for portable cryogenic containers to have a working gauge.

The cost savings of this final rule are primarily driven by removing or relaxing CGMP requirements that do not apply to medical gases, such as removing certain building and facility requirements, which may streamline inspections for industry and FDA.

Table 1 summarizes the estimated benefits and costs of the final rule. The annualized benefits will range from $0.00 million to $7.02 million with a primary estimate of $3.51 million over a 10-year span at a 7 percent discount rate. Annualized at a 3 percent discount rate these benefits will range from $0.00 million to $7.43 million with a primary estimate of $3.72 million. The annualized costs will range from $1.52 million to $5.30 million with a primary estimate of $3.24 million at a 7 percent discount rate. Annualized at a 3 percent discount rate these costs will range from $1.36 million to $5.11 million with a primary estimate of $3.07 million.

The present value of the estimated benefits will range from $0.00 million to $56.33 million with a primary estimate of $28.17 million at a 7 percent discount rate and from $0.00 million to $59.64 million with a primary estimate of $29.82 million at a 3 percent discount rate. The present value of the estimated costs will range from $12.23 million to $42.49 million with a primary estimate of $25.96 million at a 7 percent discount rate and from $12.98 million to $48.72 million with a primary estimate of $29.28 million at a 3 percent discount rate.

TABLE 1—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE FINAL RULE

[Millions of 2022 dollars]

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered (years)	
Benefits:							
Annualized Monetized $millions/year	$3.51	$0.00	$7.02	2022	7	10	Most benefits are cost savings to industry while the remaining are cost savings for FDA due to a more streamlined inspection process.
	3.72	0.00	7.43	2022	3	10	
Annualized Quantified	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
Qualitative	Potential small increase in safety from a reduction in fire risk from graphic warning labels on oxygen containers; flexibility in testing of components, containers, and closures; clarifies calculations of yield requirement does not apply to medical gases; clarifies medical gas salvage is allowed under certain conditions; removes requirement that labels not be susceptible to becoming worn or detached; outlines the certification request process; and clarifies adverse event reports are generally not required for reports of the death of a patient or animal who was administered oxygen and fires associated with the administration of oxygen that do not include an adverse event experienced by the patient or animal.						
Costs:							
Annualized Monetized millions/year	3.24	1.52	5.30	2022	7	10	
	3.07	1.36	5.11	2022	3	10	
Annualized Quantified	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
Qualitative	Maintaining resumes for consultants, and potential cost of relabeling medical air containers.						
Transfers:							
Federal Annualized Monetized millions/year	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
From/To	From:			To:			
Other Annualized Monetized millions/year	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
From/To	From:			To:			

Effects:
State, Local or Tribal Government: None.
Small Business: Not significant.
Wages: None.
Growth: None.

FDA conducted a regulatory flexibility analysis of the impact of the final rule on small entities. Approximately 41 percent of domestic entities that would be affected by the final rule are small according to Small Business Administration size standards. We estimate that the highest single year cost for a firm could be as high as 0.860 percent, while the average costs to receipts ratio is 0.007 percent. Therefore, our analysis of the impact of the final rule on small entities suggests that small firms will not be significantly affected by the final regulation.

We received one comment directed at the preliminary regulatory impact analysis (PRIA) and a few comments on the rule that we considered to be relevant to the economic analysis. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value, importance, or the order in which it was received.

(Comment 63) One comment maintains that entering a specific percentage of oxygen in the distribution records for each medical air cylinder is not necessary, because medical air contains a range of oxygen in nitrogen.

(Response 63) FDA agrees. We removed ''medical air and'' from the distribution records section to clarify. This clarification ensures no additional burden for distribution records.

(Comment 64) One comment suggests that transfilling be included in the distribution records and tracked, including which lots of gas material were added and on which date.

(Response 64) FDA declines to make this change. Including transfilling in the distribution records would be burdensome, and the tracking information might be of limited use for traceability due to the use of multiple batches and commingling.

(Comment 65) One comment states that the potential burden associated with the proposed minimum data set requirements for human postmarketing safety reporting on medical gas firms could be significant based on the number of adverse event reports received and the specific information required for individual case safety reports. The comment asserts that adverse event reporting would require all registered medical gas firms to hire or have available medical professionals or contractors to evaluate potential adverse events.

(Response 65) Adverse event reporting is already required for applicants and nonapplicants. This final rule requires nonapplicants to report adverse events directly to FDA rather than reporting to the applicant who in turn would report the adverse event to FDA. The Agency believes this will be less burdensome in the context of medical gases. Our analysis does anticipate a small increase in adverse event reporting for animals as a result of clarification of the requirements applicable to industry. However, because this is not a new requirement, we believe that the small increase is an accurate estimate of the additional burden for adverse event reports.

We do not anticipate an additional burden per adverse event report as a result of the minimum data set requirements established in the final rule. Collection of the minimum data set is already included in FDA's July 2009 guidance for industry ''Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application,'' and the March 2001 draft guidance for industry ''Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines'' (Refs. 4 and 5), and is industry practice.

FDA does not believe that firms will need to hire medical professionals. Reporters are not required to determine causality but only to report that an adverse event did occur. Additionally, adverse event reporting is not a new requirement.

(Comment 66) One comment maintains that the requirements do not reflect current industry practice and there may be additional economic burden on the industry that is not included in FDA's summary.

(Response 66) We appreciate the comment, but we believe we have sufficiently estimated all direct additional costs for new requirements not determined to be de minimis. We also acknowledged additional potential costs and possible sensitivities in the sensitivity analysis of the PRIA.

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. The full analysis of economic impacts is available in the docket for this final rule (Ref. 6) and at *https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria.*

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h), (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.

IX. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521). The title, description, and respondent description of the information collection provisions are shown in the following paragraphs with an estimate of the annual reporting, recordkeeping, and third-party disclosure burden. Included in the burden 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: Information Collection for Rulemaking of Current Good Manufacturing Practice, Certification, Postmarketing Safety Reporting, and Labeling Requirements for Certain Medical Gases.

Description: This rulemaking is amending existing regulations and establishing new regulatory requirements pertaining to medical gases.

Description of Respondents: Respondents to this information collection are entities who manufacture, process, pack, label, or distribute certain medical gases.

1. Product Jurisdiction and Combination Products; OMB Control No. 0910–0523—Revision

FDA recognizes that some medical gases are marketed as part of a combination product. For example, a medical gas may be marketed with a device constituent part (for example, a portable liquid oxygen unit or a pressure regulator). Combination products are subject to information collection provisions found in parts 3 and 4, which prescribe content and format requirements associated with marketing applications, together with applicable recordkeeping and reporting requirements.

FDA is revising provisions in part 4 to account for combination products that contain a medical gas, as FDA is requiring medical gases to be subject to new part 213, and to clarify (where appropriate) applicable medical gases requirements throughout part 4. We believe that the new regulations impose no new burden associated with information collection currently approved under OMB control number 0910–0523.

2. Labeling Requirements for Prescription Drugs; OMB Control No. 0910–0572—Revision

Regulations in part 201 govern the statement of ingredients and declaration of net quantity of contents with regard to prescription drug product labeling.

The new regulations require that firms identify bulk or transport containers with the name of the product contained therein and that containers be accompanied by documentation that identifies the product as meeting applicable compendial standards. Bulk or transport containers are excluded from the definition of final use containers. Because these large containers are removed from the point of care and we do not expect that patients and healthcare practitioners

will use them directly to administer a designated medical gas, FDA does not believe that firms' bulk or transport containers need to bear the information required under § 201.161(a). However, to prevent mix-ups, it is essential that the identity of the gas inside such containers is evident to individuals who handle and transport the containers. FDA expects that these requirements will help prevent mix-ups and ensure that recipients of medical gases in bulk or transport containers are provided information indicating that such gases meet applicable compendial standards.

We estimate that 1,696 firms will label 4,000 containers and anticipate firms will expend 6 minutes (0.1 hours) to identify the containers with the name of the product and place documentation that identifies the product as meeting applicable compendial standards, totaling 400 hours annually.

Section 201.328(d) provides that the owner of a designated medical gas container or a container of a medically appropriate combination of designated medical gases may be identified on the container. This statement may appear on a separate sticker or decal on the container (that is, it need not be contiguous with other labeling on the container), but if the container owner is not the manufacturer, packer, or distributor of the gas, that information shall be clearly stated. FDA recognizes the complex distribution system for designated medical gases and medically appropriate combinations of designated medical gases and the importance of each entity in the distribution chain being clearly identified so that patients and healthcare professionals can contact the appropriate entity if necessary. We intend for this provision to help ensure that appropriate entities can be contacted about quality issues or adverse events. In addition, the labeling requirement facilitates the return of cylinders to owners who may not also be medical gas manufacturers. FDA believes that including the container owner's information will not cause the container owner to be a ''relabeler'' for purposes of FDA's registration and listing requirements.

We estimate that 1,696 firms will identify on a designated medical gas container or a container of a medically appropriate combination of designated medical gases the name of the container owner who may not also be the manufacturer, packer, or distributor of the gas. We estimate firms would include this label on 4,000 containers and will expend 6 minutes (0.1 hours) to perform this activity, totaling 400 hours annually.

We estimate the burden of the information collection as follows:

TABLE 2—ESTIMATED ANNUAL THIRD-PARTY DISCLOSURE BURDEN [1]

Activity; 21 CFR Section	Number of respondents	Number of disclosures per respondent	Total annual disclosures	Average burden per disclosure (hours)	Total hours
Labeling of bulk or transport containers used to hold designated medical gases; § 201.161(b).	1,696	2.36	4,000	0.1 (6 minutes)	400
Identify the owner of a designated medical gas container or a container of a medically appropriate combination of designated medical gases on the container label. If the container owner is not the manufacturer, packer, or distributor of the gas, identify that information on the label; § 201.328(d).	1,696	2.36	4,000	0.1 (6 minutes)	400
Total	.....	.....	8,000	.....	800

[1] There are no capital costs or operating and maintenance costs associated with the information collection.

3. Current Good Manufacturing Practice for Medical Gases; OMB Control No. 0910–0906

FDA is establishing new part 213 setting forth CGMP requirements applicable to medical gases. Part 213 applies to firms that manufacture a medical gas and establishes requirements applicable to firms that subsequently combine, commingle, refill, or distribute medical gases.

The regulations also include recordkeeping requirements pertaining to personnel qualifications and responsibilities of persons who are engaged in the manufacturing, processing, packing, or holding of a medical gas.

Provisions under § 213.42(c) include recordkeeping to document the development and implementation of written procedures to ensure that firms maintain a clean condition for any building used to manufacture, process, pack, or hold a medical gas so as to ensure the safety, identity, strength, quality, and purity of the gas. Firms also need to develop written procedures that apply to recordkeeping for cleaning and maintaining buildings. Based on available data, we estimate 1,696 firms will each develop and implement written procedures to maintain and clean buildings. We estimate it will take 13 hours to perform this activity, totaling 22,048 hours initially. Firms will also update these written procedures annually. Based on available data, we estimate 1,696 firms would each update written procedures to maintain and clean buildings and that it will take 39 minutes (0.65 hours) to perform this activity, totaling 1,102 hours annually.

Provisions under § 213.100 include development and maintenance of written procedures to ensure that production and process controls are designed to assure that medical gases have the appropriate qualities (identity, strength, quality, and purity) they are purported to possess. Based on available data, we estimate 1,696 firms will each develop and implement written procedures. We estimate it will take 13 hours to perform this activity, totaling 22,048 hours. Firms will also update these written procedures annually. Based on available data, we estimate 1,696 firms would each update written procedures to maintain and clean buildings and that it will take 39 minutes (0.65 hours) to perform this activity, totaling 1,102 hours annually.

In concert with §§ 213.42 and 213.80, under § 213.150, firms are required to establish and follow written procedures regarding warehousing and distribution of medical gases, including procedures for the quarantine of such gases before release by the quality unit. The distribution procedures are also required to include a system by which the distribution of each lot can be readily determined, to facilitate any necessary recalls. Based on available data, we estimate 1,696 firms will each develop and implement written procedures for warehousing and distribution of medical gases. We anticipate it will take approximately 13 hours to perform this activity totaling 22,048 hours initially. Firms will also update these written procedures annually. Based on available data, we estimate 1,696 firms would each update these written procedures annually and

that it will take 39 minutes (0.65 hours) to perform this activity, totaling 1,102 hours annually.

Similarly, under § 213.208, firms are required to develop and implement written procedures for the holding, testing, and use of salvaged medical gases. Based on available data, we estimate 1,696 firms will develop and implement written procedures for the holding, testing, and use of salvaged medical gases. We estimate it will take 13 hours for firms to perform this activity, totaling 22,048 hours. In addition, based on available data, we estimate that 1,696 firms will update their written procedures (1 procedure each) for the holding, testing, and use of salvaged medical gases. We estimate it takes 0.65 hours to perform the updates, totaling 1,102 hours annually.

The regulations under § 213.25 provide that employee training be included in the firm operations. Recordkeeping would be established to demonstrate that qualified individuals conduct training on a continuing basis and with sufficient frequency to allow employees to remain familiar with applicable requirements. Based on available data, we estimate that 1,696 firms will prepare written documentation pertaining to employee training. We estimate that 10 employees per firm will create 16,960 records (10 records per firm) and that it will take 5 minutes (0.083 hours) to prepare each record, for a total of 1,408 hours annually.

Under § 213.34, records demonstrating that consultants have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained will be required. Based on available data, we estimate that 1,696 firms will maintain 571 records of consultants' education, training, and experience, or any combination thereof and expect that it will take 30 minutes (0.5 hours) to perform this activity, totaling 286 hours annually.

In addition, under § 213.67(c), we estimate that 1,696 firms will maintain 74,230 records of equipment maintenance and cleaning and anticipate it will take 15 minutes (0.25 hours) to perform this activity, totaling 18,557 hours annually. We also anticipate that, under § 213.68(d), 1,696 firms will develop and implement 11,420 written procedures for automatic, mechanical, and electronic equipment and that firms will expend 15 minutes (0.25 hours) to perform this activity, totaling 2,855 hours annually.

As provided in the new regulation under § 213.82, once a shipment of an incoming designated medical gas is received, the firm will perform full compendial testing on the gas and record the results or verify and record that a signed certificate of analysis accompanies the shipment. If an incoming designated medical gas is obtained from a supplier other than the original manufacturer, the shipment would also need to include specific information. To ensure the reliability of appropriate assessment and testing, firms will be required to establish and maintain a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures. We estimate that 1,380 firms would verify and document records upon receipt of a designated medical gas. We anticipate that firms will maintain 575,460 records (417 records each (1 delivery per week of oxygen for 1 year (52 deliveries) plus 1 delivery per day of nitrogen for 1 year (365 deliveries)). We further estimate firms will expend 15 minutes (0.25 hours) each (104 hours in total for each firm) to perform this activity, totaling approximately 143,865 hours annually.

Section 213.89 requires that firms identify and control rejected components, containers, and closures under a quarantine system designed to prevent their use in operations for which they are unsuitable. Section 213.89 also applies to incoming designated medical gases. Quarantine systems would not need to include physical quarantining because other methods can adequately ensure that unsuitable products are not used. We estimate that 1,380 downstream firms would need to assess and document 33.4 million medical gas components, containers, and closures annually. We estimate that firms would reject 0 to 0.1 percent of all containers. These firms will maintain a total of 33,400 records of rejected components and we estimate they will expend 5 minutes (0.083 hours) to perform this activity, totaling 2,772 hours annually.

Under § 213.122(c), firms need to maintain records for each shipment received of each different labeling and packaging material indicating receipt, examination, and whether accepted or rejected. Based on available data, we estimate 1,696 firms will prepare 74,230 records to document each shipment received of each different labeling and packaging material indicating receipt, examination, and whether accepted or rejected. We estimate it will take 15 minutes (0.25 hours) to perform this activity, totaling 18,558 hours annually.

Under § 213.130(e), firms are required to document results of inspections concerning packaging and labeling in the batch production records. Based on available data, we estimate 1,696 firms will document results of inspections in the batch production records in approximately 114,200 records. We estimate it will take 15 minutes (0.25 hours) per record to perform this activity, totaling 28,550 hours annually.

Under § 213.180(d), firms are required to maintain written records so that data therein can be used for evaluating, at least annually, the quality standards of each medical gas to determine the need for changes in specifications or manufacturing or control procedures. Based on available data, we estimate 1,696 firms will prepare 457 records. We estimate it will take 15 minutes (0.25 hours) to perform this activity, totaling 114 hours annually.

Under § 213.182, firms are required to maintain a written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use. Based on available data, we estimate 1,696 firms will prepare 2,969 records documenting major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use. We estimate it will take 10 minutes (0.16 hours) to perform this activity, totaling 475 hours annually.

Under § 213.184, firms are required to maintain certain records concerning components, medical gas containers and closures, and labeling. We estimate 1,696 firms will prepare 4,454 records for components, medical gas containers and closures, and labeling. We estimate firms will expend 19.8 minutes (0.33 hours) to perform this activity, totaling 1,470 hours annually.

Under § 213.186, to ensure uniformity from batch to batch, firms are required to prepare, date, and sign master production and control records for each medical gas. We estimate 1,696 firms will prepare and maintain approximately 22,840 master production and control records and estimate that it will require 2 hours for firms to perform this activity, totaling 45,680 hours annually.

Under § 213.189, firms are required to maintain batch production and control records. These records would need to include documentation that the firm has accomplished each significant step in the manufacturing, processing, packing, or holding of the medical gas produced, including in-process and laboratory tests. We estimate 1,696 firms will prepare and maintain 37,115 batch production and control records. We anticipate it will require 78 minutes (1.3 hours) for firms to perform this activity, totaling 48,250 hours annually.

Section 213.192(a) describes production record review. Per paragraph (a), firms are required to maintain a written record of any investigation of errors, unexplained discrepancies in production, or failure of a batch or any component of a batch to meet specifications and include the conclusions and followup. We estimate 1,696 firms will prepare and maintain 4,568 laboratory records and that it will require 1 hour for firms to perform this activity, totaling 4,568 hours annually.

Under § 213.194(b) through (e), firms are required to maintain certain laboratory records. Based on available data, we estimate 1,696 firms will prepare and maintain 57,100 laboratory records and estimate it will require 30 minutes (0.5 hours) for firms to perform this activity, totaling 28,550 hours annually.

Section 213.196 describes certain requirements for distribution records. Based on available data, we estimate 1,696 firms will prepare and maintain 57,100 distribution records and estimate it will require 15 minutes (0.25 hours) for firms to perform this activity, totaling 14,275 hours annually.

Under § 213.198, firms are required to maintain written records of each complaint regarding medical gases. We estimate 1,696 firms will maintain 11,420 records of complaints. We estimate it will require approximately 1 hour for firms to perform this activity, totaling 11,420 hours annually.

We estimate the burden of the information collection as follows:

TABLE 3—ESTIMATED ONE-TIME RECORDKEEPING BURDEN [1]

Activity; 21 CFR section	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping (hours)	Total hours
New Start Up SOP—Cleaning, Maintenance and Operation; § 213.42	1,696	1	1,696	13	22,048
New Start Up SOP—Medical Gases Production and Process Controls; § 213.100	1,696	1	1,696	13	22,048
New Start Up SOP—Warehousing and Distribution; § 213.150	1,696	1	1,696	13	22,048
New Start Up SOP—Salvaging of Medical Gases; § 213.208	1,696	1	1,696	13	22,048
Total			6,784		88,192

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 4—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

Activity; 21 CFR section	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping (hours)	Total hours
SOP Maintenance—cleaning, maintenance, and operation; § 213.42	1,696	1	1,696	0.65 (39 minutes)	1,102
SOP Maintenance—Medical Gases Production and Process Controls; § 213.100.	1,696	1	1,696	0.65 (39 minutes)	1,102
SOP Maintenance—salvaging of medical gases; § 213.208	1,696	1	1,696	0.65 (39 minutes)	1,102
SOP Maintenance—Medical Gases Warehousing and distribution; § 213.150	1,696	1	1,696	0.65 (39 minutes)	1,102
Documentation of completion of training; § 213.25(a)	1,696	10	16,960	0.083 (5 minutes)	1,408
Consultants' records of sufficient education, training, and experience, or any combination thereof; § 213.34.	1,696	0.34	571	0.5 (30 minutes)	286
Firms' records of equipment maintenance and cleaning; § 213.67(c)	1,696	43.77	74,230	0.25 (15 minutes)	18,558
Maintain records for modifications to automatic, mechanical, and electronic equipment; § 213.68(d).	1,696	6.73	11,420	0.25 (15 minutes)	2,855
Receipt and storage of incoming designated medical gases; § 213.82(a)	1,380	417	575,460	0.25 (15 minutes)	143,865
Records of rejected components; § 213.89	1,380	24.2	33,400	0.083 (5 minutes)	2,772
Maintain records for each shipment received of each different labeling and packaging material indicating receipt, examination, and whether accepted or rejected; § 213.122(c).	1,696	43.77	74,230	0.25 (15 minutes)	18,558
Document results of inspections in the batch production records; § 213.130(e)	1,696	67.33	114,200	0.25 (15 minutes)	28,550
Maintain written records so that data therein can be used for evaluating, at least annually, the quality standards of each medical gas to determine the need for changes in specifications or manufacturing or control procedures; § 213.180(d).	1,696	0.27	457	0.25 (15 minutes)	114
Maintain record of equipment cleaning and use log maintenance; § 213.182	1,696	1.76	2,969	0.16 (10 minutes)	475
Maintain records for components, medical gas containers and closures, and labeling; § 213.184.	1,696	2.63	4,454	0.33 (19.8 minutes).	1,470
Maintain master production and control records; § 213.186	1,696	13.47	22,840	2 hours	45,680
Maintain batch production and control records; § 213.189	1,696	21.88	37,115	1.3 hours	48,250
Maintain record of the investigation; § 213.192(a)	1,696	2.69	4,568	1 hour	4,568
Maintain laboratory records; § 213.194(b) through (e)	1,696	33.67	57,100	0.5 (30 minutes)	28,550
Maintain distribution records; § 213.196	1,696	33.67	57,100	0.25 (15 minutes)	14,275
Maintain written records of each complaint; § 213.198	1,696	6.73	11,420	1 hour	11,420
Total			1,105,278		376,061

[1] There are no capital costs or operating and maintenance costs associated with the information collection.

4. Certification and Postmarketing Reporting for Designated Medical Gases; OMB Control No. 0910–0906

Section 230.50 establishes the general requirements for requesting a designated medical gas certification for all submission types and outlines the information that must be included in certification request submissions (Form FDA 3864). The new regulations require applicants to include facility information in certification requests. Such information would include, among others, name and address of the original manufacturing facility or facilities where the gas is or will be manufactured.

Section 230.50 also provides for the submission of additional information if FDA deems it appropriate to determine

whether a medical gas meets the definition of a designated medical gas. This information would generally be in the form of a written request by FDA for the additional information. We estimate that five respondents will submit a total of five certification requests annually, including certification forms for original and resubmissions, and each certification request will require 3 hours to prepare and submit, totaling 15 hours annually.

Under § 230.65, applicants will be allowed to withdraw a certification request that has not been deemed granted. An applicant may notify FDA that it withdraws its certification request at any time before the certification is granted. Upon an applicant's withdrawal of a certification request, FDA will retain the certification request, and if the applicant requests a copy via a Freedom of Information Act request, FDA will provide it pursuant to the fee schedule in FDA's public information regulations. Since the passage of the Food and Drug Administration Safety and Innovation Act, FDA has received several certification requests but has not received any withdrawal requests. FDA has no other data on which to provide a burden estimate. Therefore, the Agency does not expect to receive withdrawal requests except in exceedingly rare situations.

Section 230.70 requires applicants to submit a supplement if any information in the granted certification has changed. The regulation prescribes information to be included in a supplement to the marketing application. We estimate four applicants will submit supplements, and each submission will require 3 hours to prepare, totaling 12 hours annually.

Section 230.72 governs changes in ownership of a granted certification. An example of when a change in ownership could occur is during a merger or acquisition. Upon a change in ownership, the regulations require that both the new and previous owner notify FDA. Based on related submissions received by FDA over the last few years and averaged accordingly, we estimate two respondents will submit four letters or other supporting documents, requiring 2 hours to complete each of the tasks, totaling 8 hours annually.

To assist respondents with the requirements associated with § 230.80 (annual reports), we are developing an annual report form (Form FDA 5025). We estimate that 57 applicants will submit 123 annual reports to FDA. We estimate firms will expend 2 hours per report to perform this activity, totaling 246 hours annually.

Our estimate associated with requirements in § 230.205 for field alert reporting for designated medical gases is based on our prior experience with similar reports that FDA receives. We estimate that FDA will receive a total of 3 field alert reports from the pool of 1,380 applicants and nonapplicants. We anticipate the respondents will each expend approximately 8 hours to perform this activity, totaling 24 hours annually.

Section 230.210 requires that applicants and nonapplicants promptly review all safety information that the applicant or nonapplicant receives or otherwise obtains from any source (including both foreign and domestic sources). Applicants and nonapplicants will generate reports from review of the safety information and will submit the reports under §§ 230.220 and 230.230. As described in § 230.220(a) through (d), firms are required to submit ICSRs associated with the use of a designated medical gas in humans.

Section 230.220 contains requirements for submission of ICSRs associated with the use of a designated medical gas in humans. Under § 230.220(a)(1), applicants and nonapplicants are required to submit each ICSR as soon as possible, but no later than 15 calendar days from the date the applicant or nonapplicant meets the reporting criteria under § 230.220(b) and acquires a minimum data set for an ICSR for that adverse event.

Under § 230.220(a)(3), applicants and nonapplicants will submit new information they receive or otherwise obtain about an ICSR previously submitted to FDA. The regulation prescribes reporting schedules to ensure FDA becomes aware of any new information about the adverse event in a timely manner.

Section 230.220(b) describes the types of ICSRs that applicants and nonapplicants are required to report for human use. Under § 230.220(b)(1), applicants and nonapplicants would be required to submit ICSRs for serious adverse events. Under § 230.220(b)(2), upon notification by FDA, an applicant is required to report to FDA, in a timeframe established by FDA, ICSRs for any adverse events that would not be required under § 230.220(b)(1).

Section 230.220(c) and (d) include additional requirements for the content and format of human designated medical gas ICSRs. Under § 230.220(a) through (d), we estimate that 1,430 applicants and nonapplicants will submit to FDA 172 ICSRs annually. We previously estimated it would take 6 hours for respondents to perform this activity. Upon considering recent estimates for safety reporting that describe a lower time burden (Ref. 6), we estimate it will be less burdensome than we previously expected in the proposed rule for designated medical gas applicants and nonapplicants to comply with ICSR reporting requirements. Moreover, we do not anticipate that safety reporting compliance will be more burdensome for human reports than for animal reports. Therefore, we estimate that it will take 4 hours for respondents to perform this activity, totaling 688 hours annually.

Under § 230.230(a)(1), an applicant or nonapplicant will submit serious adverse events related to the use of a designated medical gas in animals to FDA as soon as possible but no later than 15 calendar days from first receiving the information. The applicant or nonapplicant will submit the report to FDA in electronic format as described under § 230.230(b)(1), unless the applicant or nonapplicant obtains a waiver under § 230.230(b)(2) or FDA requests the report in an alternate format.

Under § 230.230(a)(2), upon notification by FDA, applicants and nonapplicants will submit reports of adverse events associated with the use of a designated medical gas in animals that do not qualify for reporting under § 230.230(a)(1). The notice will specify the adverse events to be reported and the reason for requiring the reports. We anticipate that eight records will be submitted per year. We previously estimated that it will take approximately 5 hours to perform this activity. Upon considering recent estimates for safety reporting that describe a lower time burden (Ref. 6; see also 84 FR 24798, May 29, 2019), we estimate it will be less burdensome than we previously expected in the proposed rule for designated medical gas applicants and nonapplicants to comply with adverse event reporting requirements. Therefore, we estimate that it will take 4 hours for respondents to perform this activity, totaling 32 hours annually.

Under § 230.230(b)(2), an applicant or nonapplicant may request, in writing, a temporary waiver of the electronic submission requirements under § 230.230(b)(1). An applicant or nonapplicant will provide the initial request by telephone or email to Center for Veterinary Medicine's (CVM's) Division of Pharmacovigilance and Surveillance, with prompt written followup submitted as a letter to the granted certification or certifications. FDA will grant waivers on a limited basis for good cause shown. If FDA

grants a waiver, the applicant or nonapplicant is required to comply with the conditions for reporting specified by FDA upon granting the waiver. We estimate eight waiver requests will be submitted annually and anticipate it will take 5 hours to prepare and submit the request totaling 40 hours annually.

TABLE 5—ESTIMATED ANNUAL REPORTING BURDEN [1]

Activity; 21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response (hours)	Total hours
Submission of certification requests and certification form (Form FDA 3864) that includes any resubmissions and amendments to pending requests; § 230.50	5	1	5	3	15
Submission of supplements to certification requests and other changes; § 230.70	4	1	4	3	12
Submission of requests to transfer ownership of certification, including new address and the owner's submission of any change in the conditions in the granted certification; § 230.72	2	2	4	2	8
Submission of annual reports (Form FDA 5025); § 230.80	57	2.15	123	2	246
Submission of field alert reports; § 230.205	1,380	0.002	3	8	24
CDER: Submission of ICSRs (§ 230.220(a) through (d))	1,430	0.12	172	4	688
CVM: Submission of adverse event reports; § 230.230(a)	1,696	0.0044	8	4	32
CVM: Waiver request from electronic submission requirement; § 230.230(b)	1,696	0.0044	8	5	40
Total			327		1,065

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Section 230.220(e) prescribes requirements for keeping records pertaining to human designated medical gas adverse events. For a period of 10 years from the initial receipt of information, each applicant or nonapplicant is required to maintain records of information relating to adverse events, whether or not submitted to FDA. These records must include raw data, correspondence, and any other information relating to evaluating and reporting adverse event information that is received or otherwise obtained by the applicant or nonapplicant. Upon written notice by FDA, the applicant or nonapplicant will submit any and all of these records to FDA within 5 calendar days after receipt of the notice. The applicant or nonapplicant will permit any authorized FDA employee, at reasonable times, to access, copy, and verify the established and maintained records described in this section. We anticipate that 1,430 manufacturers will create 686 records pertaining to human designated medical gas requirements and it will take approximately 16 hours to perform this activity, totaling 10,976 hours annually.

Section 230.230(c) prescribes requirements for records to be maintained for animal designated medical gas adverse events. For a period of 5 years from the initial receipt of information, each applicant or nonapplicant is required to maintain records of information relating to adverse events, whether or not submitted to FDA. These records must include raw data, correspondence, and any other information relating to evaluating and reporting adverse event information that is received or otherwise obtained by the applicant or nonapplicant. Upon written notice by FDA, the applicant or nonapplicant will submit any and all of these records to FDA within 5 calendar days after receipt of the notice. The applicant or nonapplicant will permit any authorized FDA employee, at reasonable times, to access, copy, and verify the established and maintained records described in this section. We anticipate that 1,696 manufacturers will create eight records pertaining to animal designated medical gas requirements and it will take approximately 5 hours to perform this activity, totaling 40 hours annually.

TABLE 6—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

Activity; 21 CFR section	Number of record-keepers	Number of records per recordkeeper	Total annual records	Average burden per response (hours)	Total hours
CDER's maintenance of records for human designated medical gas ICSR requirements; § 230.220(e)	1,430	0.48	686	16	10,976
CVM's recordkeeping requirements related to adverse event reports; § 230.230(c)	1,696	0.0044	8	5	40
Total			694		11,016

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

The information collection provisions in this final rule have been submitted to OMB for review as required by section 3507(d) of the Paperwork Reduction Act of 1995. 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.

X. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have 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.

XI. Consultation and Coordination With Indian Tribal Governments

We have analyzed this rule in accordance with the principles set forth in Executive Order 13175. We have determined that the rule does not contain policies that have substantial direct effects on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. Accordingly, we conclude that the rule does not contain policies that have tribal implications as defined in the Executive order and, consequently, a tribal summary impact statement is not required.

XII. References

The following references are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m. Monday through Friday; they are also available electronically at *https://www.regulations.gov.* Although FDA has verified the website addresses in this document, please note that websites are subject to change over time.

1. FDA draft guidance for industry ''Certification Process for Designated Medical Gases,'' November 2015, available at *https://www.fda.gov/media/85013/download.*
2. Kreiter, P., T.G. Bizjak, and R.L. Friedman, ''Preventing Patients From Receiving Leaking or Empty Containers of Medical Gas: A Review of Inspectional Findings From 2003 to 2021,'' CDER Office of Manufacturing Quality, December 2021, U.S. Food and Drug Administration.
3. FDA, Compliance Program Guidance Manual 7356.002E, ''Compressed Medical Gases,'' March 15, 2015, available at *https://www.fda.gov/media/75194/download.*
4. FDA guidance for industry ''Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application,'' July 2009; available at *https://www.fda.gov/media/77193/download.*
5. FDA draft guidance for industry ''Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines,'' March 2001, available at *https://www.fda.gov/media/73593/download.*
6. FDA, Final Regulatory Impact Analysis: Current Good Manufacturing Practice, Certification, Postmarketing Safety Reporting, and Labeling Requirements for Certain Medical Gases, available at *https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-riahttps://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-riahttps://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria.*

The following standards appear in the amendatory text of this document and were approved for § 4.4 in the final rule published at 89 FR 7496 (which will be effective February 2, 2026): ISO 13485 and ISO 9000. No changes are proposed to the incorporation by reference (IBR) material.

List of Subjects

21 CFR Part 4

Biologics, Drugs, Human cells and tissue-based products, Incorporation by reference, Medical devices.

21 CFR Part 16

Administrative practice and procedure.

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 210

Drugs, Packaging and containers.

21 CFR Part 211

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

21 CFR Part 213

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

21 CFR Part 230

Administrative practice and procedure, Animal drugs, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 514

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, chapter I of title 21 of the Code of Federal Regulations is amended as follows:

PART 4—REGULATION OF COMBINATION PRODUCTS

■ 1. The authority citation for part 4 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360b–360f, 360h–360j, 360l, 360hh–360ss, 360aaa–360bbb, 360ddd, 360ddd–1, 371(a), 372–374, 379e, 381, 383, 394; 42 U.S.C. 216, 262, 263a, 264, 271.

■ 2. Effective February 2, 2026, revise § 4.2 to read as follows:

§ 4.2 How does FDA define key terms and phrases in this subpart?

The terms listed in this section have the following meanings for purposes of this subpart:

Biological product has the meaning set forth in § 3.2(d) of this chapter. A biological product also meets the definitions of either a drug or device as these terms are defined under this section.

Combination product has the meaning set forth in § 3.2(e) of this chapter.

Constituent part is a drug, device, or biological product that is part of a combination product.

Co-packaged combination product has the meaning set forth in § 3.2(e)(2) of this chapter.

Current good manufacturing practice operating system means the operating system within an establishment that is designed and implemented to address and meet the current good manufacturing practice requirements for a combination product.

Current good manufacturing practice requirements means the requirements set forth under § 4.3(a) through (e).

Device has the meaning set forth in § 3.2(f) of this chapter. A device that is a constituent part of a combination product is considered a finished device within the meaning of the Quality Management System Regulation (QMSR).

Drug has the meaning set forth in § 3.2(g) of this chapter and includes medical gas as defined in section 575(2) of the Federal Food, Drug, and Cosmetic Act. Medical gas includes designated medical gases as defined in section 575(1) of the Federal Food, Drug, and Cosmetic Act and medical gases approved under section 505 of the Federal Food, Drug, and Cosmetic Act. A drug other than a medical gas that is a constituent part of a combination product is considered a drug product within the meaning of the drug current good manufacturing practice (CGMP) requirements. A drug that is a medical gas that is a constituent part of a combination product is considered a medical gas within the meaning of the medical gas CGMP requirements.

Drug CGMP requirements refers to the current good manufacturing practice regulations set forth in parts 210 and 211 of this chapter.

HCT/Ps refers to human cell, tissue, and cellular and tissue-based products,

as defined in § 1271.3(d) of this chapter. An HCT/P that is not regulated solely under section 361 of the Public Health Service Act may be a constituent part of a combination product. Such an HCT/P is subject to part 1271 of this chapter and is also regulated as a drug, device, and/or biological product.

Manufacture includes, but is not limited to, designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage.

Medical gas CGMP requirements refers to the current good manufacturing practice regulations set forth in part 213 of this chapter.

QMSR refers to the requirements under part 820 of this chapter.

Single-entity combination product has the meaning set forth in § 3.2(e)(1) of this chapter.

Type of constituent part refers to the category of the constituent part, which can be either a biological product, a device, or a drug, as these terms are defined under this section.

■ 3. Effective February 2, 2026, amend § 4.3 by revising paragraphs (a), (c), and (d) and adding paragraph (e) to read as follows:

§ 4.3 What current good manufacturing practice requirements apply to my combination product?

* * * * *

(a) The current good manufacturing practice requirements in parts 210 and 211 of this chapter apply to a combination product that includes a drug constituent part other than a medical gas;

* * * * *

(c) The current good manufacturing practice requirements among the requirements (including standards) for biological products in parts 600 through 680 of this chapter apply to a combination product that includes a biological product constituent part to which those requirements would apply if that constituent part were not part of a combination product;

(d) The current good tissue practice requirements including donor eligibility requirements for HCT/Ps in part 1271 of this chapter apply to a combination product that includes an HCT/P; and

(e) The current good manufacturing practice requirements in part 213 of this chapter apply to a combination product that includes a drug constituent part that is a medical gas.

■ 4. Effective February 2, 2026, amend § 4.4 by:

■ a. Revising paragraphs (b)(1) introductory text and (b)(2) introductory text;

■ b. Redesignating paragraphs (b)(3) and (4) as paragraphs (b)(4) and (5), respectively;

■ c. Adding new paragraph (b)(3); and

■ d. Revising paragraph (e).

The revisions and addition read as follows:

§ 4.4 How can I comply with these current good manufacturing practice requirements for a co-packaged or single-entity combination product?

* * * * *

(b) * * *

(1) If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the drug CGMP requirements or the medical gas CGMP requirements, as applicable, the following clauses of ISO 13485 (together with the definitions in Clause 3 of ISO 9000), which is incorporated by reference into the QMSR under § 820.7 of this chapter, and certain other provisions within the QMSR must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the QMSR need be made:

* * * * *

(2) If the combination product includes a device constituent part and a drug constituent part other than a medical gas, and the current good manufacturing practice operating system has been shown to comply with the QMSR requirements for devices, the following provisions of the drug CGMP requirements must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the drug CGMP requirements need be made:

* * * * *

(3) If the combination product includes a device constituent part and a drug constituent part that is a medical gas, and the current good manufacturing practice operating system has been shown to comply with the QMSR regulation, the following provisions of the medical gas CGMP requirements must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the medical gas CGMP requirements need be made:

(i) Section 213.84 of this chapter. Testing and approval or rejection of components, containers, and closures.

(ii) Section 213.94 of this chapter. Medical gas containers and closures.

(iii) Section 213.122 of this chapter. Materials examination and usage criteria.

(iv) Section 213.165 of this chapter. Testing and release for distribution.

(v) Section 213.166 of this chapter. Stability testing and expiration dating for medical gases marketed under applications submitted under section 505 or section 512 of the Federal Food, Drug, and Cosmetic Act.

(vi) Section 213.204 of this chapter. Returned medical gases.

(vii) Section 213.208 of this chapter. Salvaging of medical gases.

* * * * *

(e) The requirements set forth in this subpart and in parts 210, 211, 213, 820, 600 through 680, and 1271 of this chapter listed in § 4.3, supplement, and do not supersede, each other unless the regulations explicitly provide otherwise. In the event of a conflict between regulations applicable under this subpart to combination products, including their constituent parts, the regulations most specifically applicable to the constituent part in question shall supersede the more general.

* * * * *

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

■ 5. The authority citation for part 16 continues to read as follows:

Authority: 15 U.S.C. 1451–1461; 21 U.S.C. 141–149, 321–394, 467f, 679, 821, 1034; 28 U.S.C. 2112; 42 U.S.C. 201–262, 263b, 364.

■ 6. Amend § 16.1 by revising paragraph (b)(2) to read as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

(2) The regulatory provisions are as follows:

TABLE 1 TO PARAGRAPH (b)(2)

Sections 1.634 and 1.664, relating to revocation of recognition of an accreditation body and withdrawal of accreditation of third-party certification bodies that conduct food safety audits of eligible entities in the food import supply chain and issue food and facility certifications.	
Section 1.1173, relating to the revocation of recognition of an accreditation body, and the disqualification of a laboratory, with respect to food testing conducted under part 1, subpart R of this chapter.	

TABLE 1 TO PARAGRAPH (b)(2)—Continued

Section 1.1174, relating to the issuance of a directed food laboratory order by FDA pursuant to § 1.1108.
Section 56.121(a), relating to disqualifying an institutional review board or an institution.
Section 58.204(b), relating to disqualifying a testing facility.
Section 71.37(a), relating to use of food containing a color additive.
Section 80.31(b), relating to refusal to certify a batch of a color additive.
Section 80.34(b), relating to suspension of certification service for a color additive.
Section 99.401(c), relating to a due diligence determination concerning the conduct of studies necessary for a supplemental application for a new use of a drug or device.
Sections 112.201 through 112.213, (see part 112, subpart R of this chapter), relating to withdrawal of a qualified exemption.
Sections 117.251 through 117.287 (part 117, subpart E of this chapter), relating to withdrawal of a qualified facility exemption.
Section 130.17(1), relating to a temporary permit to vary from a food standard.
Section 170.17(b), relating to use of food containing an investigational food additive.
Section 202.1(j)(5), relating to approval of prescription drug advertisements.
Section 230.150(b), relating to revocation of the grant of a certification for a designated medical gas.
Section 312.70, relating to whether an investigator is eligible to receive test articles under part 312 of this chapter and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.
Sections 312.70(d) and 312.44, relating to termination of an IND for a sponsor.
Section 312.160(b), relating to termination of an IND for tests in vitro and in laboratory research animals for a sponsor.
Section 507.60 through 507.85 (part 507, subpart D of this chapter) relating to withdrawal of a qualified facility exemption.
Section 511.1(b)(5), relating to use of food containing an investigational new animal drug.
Section 511.1(c)(1), relating to whether an investigator is eligible to receive test articles under part 511 of this chapter and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products; and any nonclinical laboratory study intended to support an application for a research or marketing permit for a new animal drug.
Section 511.1(c)(4) and (d), relating to termination of an INAD for a sponsor.
Section 812.119, relating to whether an investigator is eligible to receive test articles under part 812 of this chapter and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.
Section 814.46(c) relating to withdrawal of approval of a device premarket approval application.
Section 822.7(a)(3), relating to an order to conduct postmarket surveillance of a medical device under section 522 of the act.
Section 830.130, relating to suspension or revocation of the accreditation of an issuing agency.
Section 895.30(c), regarding a proposed regulation to ban a medical device with a special effective date.
Section 900.7, relating to approval, reapproval, or withdrawal of approval of mammography accreditation bodies or rejection of a proposed fee for accreditation.
Section 900.14, relating to suspension or revocation of a mammography certificate.
Section 900.25, relating to approval or withdrawal of approval of certification agencies.
Section 1003.11(a)(3), relating to the failure of an electronic product to comply with an applicable standard or to a defect in an electronic product.
Section 1003.31(d), relating to denial of an exemption from notification requirements for an electronic product which fails to comply with an applicable standard or has a defect.
Section 1004.6, relating to plan for repurchase, repair, or replacement of an electronic product.
Section 1107.1(d), relating to rescission of an exemption from the requirement of demonstrating substantial equivalence for a tobacco product.
Section 1107.50, relating to rescission of an order finding a tobacco product substantially equivalent.
Section 1210.30, relating to denial, suspension, or revocation of a permit under the Federal Import Milk Act.
Section 1270.43(e), relating to the retention, recall, and destruction of human tissue.
Section 1271.440(e) relating to the retention, recall, and destruction of human cells, tissues, and cellular and tissue-based products (HCT/Ps), and/or the cessation of manufacturing HCT/Ps.

PART 201—LABELING

■ 7. The authority citation for part 201 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 343, 351, 352, 353, 355, 358, 360, 360b, 360ccc, 360ccc–1, 360ddd, 360ddd–1, 360ee, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

■ 8. Amend § 201.1 by revising paragraph (b) to read as follows:

§ 201.1 Drugs; name and place of business of manufacturer, packer, or distributor.

* * * * *

(b) As used in this section, and for purposes of section 502(a) and (b)(1) of the Federal Food, Drug, and Cosmetic Act, the manufacturer of a drug product is the person who performs all of the following operations that are required to produce the product:

(1) Mixing;
(2) Granulating;
(3) Milling;
(4) Molding;
(5) Lyophilizing;
(6) Tableting;
(7) Encapsulating;
(8) Coating;
(9) Sterilizing;
(10) Filling sterile or aerosol drugs into dispensing containers; and
(11) With respect to a medical gas, fabricating the gas by chemical reaction, physical separation, compression of atmospheric air, purification (*e.g.,* reprocessing an industrial gas into a medical gas), combining two or more distinct medical gases, or other process.

* * * * *

■ 9. Amend § 201.10 by revising paragraph (d)(2) to read as follows:

§ 201.10 Drugs; statement of ingredients.

* * * * *

(d) * * *

(2) A statement of the percentage of an ingredient in a drug shall, if the term *percent* is used without qualification, mean percent weight-in-weight, if the ingredient and the drug are both solids, or if the ingredient is a liquid and the drug is a solid; percent weight in

volume at 68 °F (20 °C), if the ingredient is a solid and the drug is a liquid; percent volume in volume at 68 °F (20 °C), if both the ingredient and the drug are liquids, except that alcohol shall be stated in terms of percent volume of absolute alcohol at 60 °F (15.56 °C); and percent volume in volume if the ingredient is a designated medical gas (as defined in § 201.161(c)(1)).

* * * * *

■ 10. Amend § 201.51 by revising paragraphs (a) and (b) to read as follows:

§ 201.51 Declaration of net quantity of contents.

(a) The label of a prescription or insulin-containing drug in package form shall bear a declaration of the net quantity of contents. This shall be expressed in the terms of weight, measure, numerical count, or a combination of numerical count and weight or measure. The statement of quantity of drugs in tablet, capsule, ampule, or other unit dosage form shall be expressed in terms of numerical count; the statement of quantity for drugs in other dosage forms shall be in terms of weight if the drug is solid, semi-solid, or viscous, in terms of fluid measure if the drug is liquid, or in terms of volume measure if the drug is a designated medical gas (as defined in § 201.161(c)(1)) or a medically appropriate combination of designated medical gases in a gaseous state. When the drug quantity statement is in terms of the numerical count of the drug units, it shall be augmented to give the weight or measure of the drug units or the quantity of each active ingredient in each drug unit or, when quantity does not accurately reflect drug potency, a statement of the drug potency.

(b) Statements of weight of the contents shall in the case of prescription drugs be expressed in terms of avoirdupois pound, ounce, and grain or of kilogram, gram, and subdivisions thereof. A statement of liquid measure of the contents shall in the case of prescription drugs other than designated medical gases and medically appropriate combinations thereof be expressed in terms of the U.S. gallon of 231 cubic inches and quart, pint, fluid-ounce, and fluid-dram subdivisions thereof, or of the liter and milliliter, or cubic centimeter, and shall express the volume at 68 °F (20 °C). A statement of the liquid measure of the contents in the case of insulin-containing drugs shall be expressed in terms of the liter and milliliter, or cubic centimeter, and shall express the volume at 68 °F (20 °C). A statement of the measure of the contents shall in the case of designated medical gases (as defined in § 201.161(c)(1)) and medically appropriate combinations thereof be expressed as follows:

(1) If in a gaseous state in a high-pressure container, it shall be expressed in liters or cubic feet based on the filled pressure at 70 °F (21 °C);

(2) If in a liquefied compressed gas state in a high-pressure container, it shall be expressed in gaseous liters or by an appropriate net weight statement;

(3) If in a liquefied state in a portable cryogenic container, it shall be expressed in gaseous liters, liquid liters (if identified as a liquid measure), gallons, or by an appropriate net weight statement at the time of fill; and

(4) If in a bulk or transport container (as defined in § 201.161(c)(3)), labeling for net quantity of contents is not required.

* * * * *

■ 11. Amend § 201.105 by revising the introductory text to read as follows:

§ 201.105 Veterinary drugs.

A drug subject to the requirements of section 503(f)(1) of the act shall be exempt from section 502(f)(1) of the act if it is a designated medical gas (as defined in § 201.161(c)(1)) or a medically appropriate combination of designated medical gases and is in compliance with § 201.161, or if all the following conditions are met:

* * * * *

■ 12. Revise § 201.161 to read as follows:

§ 201.161 Medical gases.

(a) The requirements of sections 503(b)(4) and 502(f) of the Federal Food, Drug, and Cosmetic Act are deemed to have been met for a designated medical gas or a medically appropriate combination of designated medical gases if the labeling on its final use container bears the following:

(1) In the case of oxygen:

(i) 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) A clear and prominent warning containing the statements ''No Smoking'' and ''No Vaping'' and a graphic symbol conveying that smoking, vaping, and open flames near oxygen are dangerous.

(2) In the case of a designated medical gas other than oxygen, and in the case of medically appropriate combinations of any designated medical gases:

(i) 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.

(ii) The symbol ''Rx only.''

(3) Appropriate directions and warnings concerning storage and handling.

(b) A designated medical gas or medically appropriate combination of designated medical gases in a bulk or transport container must be identified with the name of the product contained therein and accompanied by documentation identifying the product as meeting applicable compendial standards.

(c) For purposes of this section:

(1) A *designated medical gas* means a drug that:

(i) Is manufactured or stored in a liquefied, nonliquefied, or cryogenic state;

(ii) Is administered as a gas; and

(iii) Meets the definition in section 575(1) of the Federal Food, Drug, and Cosmetic Act.

(2) A *final use container* means a container that is for direct use or access by a patient or healthcare provider to administer a designated medical gas or medically appropriate combination of designated medical gases. The term *final use container* does not include bulk or transport containers and does not include containers that are described in § 868.5655 of this chapter.

(3) A *bulk or transport container* means a container used to transport or store designated medical gases or medically appropriate combinations of designated medical gases and that is not used directly to administer such gases to a patient.

■ 13. Amend § 201.328 by revising paragraphs (a) introductory text and (a)(1) introductory text and adding paragraph (d) 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 used to fill small cryogenic gas containers for use by individual patients. The term excludes 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 § 213.94(e)(3) of this chapter and the following additional requirements.

* * * * *

(d) *Statement identifying owner or return address of medical gas containers.* Notwithstanding § 201.1, a container filled with a designated medical gas (as defined in § 201.161(c)(1)) or medically appropriate combination of designated medical gases may bear a statement identifying the name of the owner of the container or the address to which the container should be returned after use. Such statement may appear on a separate sticker or decal. If the owner of the medical gas container is not the manufacturer, packer, or distributor of the designated medical gas or medically appropriate combination of designated medical gases, that shall be clearly stated on the container. The addition of such statement shall not cause the owner of the cylinder to be a ''relabeler'' for purposes of registration and listing under part 207 of this chapter.

PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

■ 14. The authority citation for part 210 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 360ddd, 360ddd–1, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

■ 15. Amend § 210.1 by revising paragraphs (a) and (b) to read as follows:

§ 210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in parts 211, 213, 225, and 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211, 213, 225, and 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

* * * * *

■ 16. Amend § 210.2 by revising paragraphs (a) and (b) to read as follows:

§ 210.2 Applicability of current good manufacturing practice regulations.

(a) The regulations in this part and in parts 211, 213, 225, and 226 of this chapter as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use; and in part 1271 of this chapter as they are applicable to a human cell, tissue, or cellular or tissue-based product (HCT/P) that is regulated as a drug (subject to premarket review under an application submitted under section 505 of the act or under a biologics license application under section 351 of the Public Health Service Act); shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part and in parts 211, 213, 225, 226, 600 through 680, and 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which the person is engaged.

* * * * *

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

■ 17. The authority citation for part 211 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 360ddd, 360ddd–1, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

■ 18. Amend § 211.1 by revising paragraph (a) to read as follows:

§ 211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products (excluding positron emission tomography drugs and medical gases as defined in § 213.3(b)(12) of this chapter) for administration to humans or animals.

* * * * *

§ 211.94 [Amended]

■ 19. Amend § 211.94 by removing paragraph (e).

■ 20. Amend § 211.125 by revising paragraph (c) to read as follows:

§ 211.125 Labeling issuance.

* * * * *

(c) Procedures shall be used to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with § 211.192. Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination for correct labeling is performed in accordance with § 211.122(g)(2).

* * * * *

■ 21. Amend § 211.132 by revising paragraph (c)(1) introductory text to read as follows:

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

* * * * *

(c) * * *

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

* * * * *

■ 22. Amend § 211.170 by revising paragraph (b) introductory text to read as follows:

§ 211.170 Reserve samples.

* * * * *

(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with § 211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. The retention time is as follows:

* * * * *

■ 23. Revise § 211.196 to read as follows:

§ 211.196 Distribution records.

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product.

■ 24. Add part 213 to subchapter C to read as follows:

PART 213—CURRENT GOOD MANUFACTURING PRACTICE FOR MEDICAL GASES

Subpart A—General Provisions

Subpart B—Organization and Personnel

Subpart C—Buildings and Facilities

Subpart D—Equipment

Subpart E—Control of Incoming Designated Medical Gas, Components, and Medical Gas Containers and Closures

Subpart F—Production and Process Controls

Subpart G—Packaging and Labeling Control

Subpart H—Holding and Distribution

Subpart I—Laboratory Controls

Subpart J—Records

Subpart K—Returned and Salvaged Medical Gases

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360b, 360ddd, 360ddd–1, 371, 374.

Subpart A—General Provisions

§ 213.1 Scope.

The regulations in this part contain the minimum current good manufacturing practice for preparation of medical gases for administration to humans or animals.

§ 213.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act shall be applicable to such terms when used in this part.

(b) The following definitions of terms apply to this part:

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

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

(3) *Commingling or commingled* refers to the act of combining one lot of designated medical gas or component with another lot or lots of the same designated medical gas or component.

(4) *Component* means any ingredient intended for use in the manufacture of a medical gas, including those that may not appear in such gas. It does not include an incoming designated medical gas.

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

(6) *FDA* means the Food and Drug Administration.

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

(8) *Incoming designated medical gas* means a designated medical gas received from one source that, after receipt, is commingled with the same gas from another source, used in a medically appropriate combination of designated medical gases or in the production of another medical gas, or further distributed.

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

(10) *Lot number, control number, or batch number* means any distinctive

combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of medical gas or other material can be determined.

(11) *Manufacture, processing, packing, or holding of medical gases* includes packaging and labeling operations, testing, and quality control.

(12) *Medical gas* has the meaning given the term in section 575(2) of the Federal Food, Drug, and Cosmetic Act.

(13) *Original manufacturer* means the person that initially produces a designated medical gas by chemical reaction, physical separation, compression of atmospheric air, purification (*e.g.,* re-processing an industrial gas into a medical gas), or other means.

(14) *Quality unit* means any person or persons designated with the authority and responsibility for overall quality management and other responsibilities as defined in § 213.22.

(15) *Strength* means:

(i) The concentration of the medical gas (for example, weight/weight, weight/volume, or unit dose/volume basis); and/or

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

Subpart B—Organization and Personnel

§ 213.22 Responsibilities of quality unit.

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

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

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

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

(e) Quality unit personnel may perform other functions provided appropriate written controls are in place to ensure any other functions are performed separately from quality unit responsibilities and such other functions do not interfere with the quality unit's responsibilities or subordinate the quality unit's responsibilities to any other unit.

§ 213.25 Personnel qualifications and responsibilities.

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

(b) There shall be an adequate number of qualified personnel to perform the manufacture, processing, packing, or holding of each medical gas.

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

§ 213.34 Consultants.

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

Subpart C—Buildings and Facilities

§ 213.42 Design and construction features.

(a)(1) Any buildings and facilities used in the manufacture, processing, packing, or holding of a medical gas shall be of adequate design, including having adequate space, for the orderly placement of equipment and materials to prevent mix-ups between:

(i) Components;

(ii) Incoming designated medical gases;

(iii) Medical gas containers and closures;

(iv) Labeling;

(v) In-process materials; or

(vi) Medical gases.

(2) Such buildings and facilities shall also allow for adequate cleaning, maintenance, and proper operations.

(b)(1) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures:

(i) Receipt, identification, storage, and withholding from use of components, incoming designated medical gases, medical gas containers and closures, and labeling, pending the appropriate sampling, testing, or examination by the quality unit before release for manufacturing or packaging;

(ii) Holding rejected components, incoming designated medical gases, medical gas containers and closures, and labeling before disposition;

(iii) Storage of released components, incoming designated medical gases, medical gas containers and closures, and labeling;

(iv) Storage of in-process materials;

(v) Manufacturing and processing operations;

(vi) Packaging and labeling operations;

(vii) Quarantine storage before release of medical gases;

(viii) Storage of medical gases after release; and

(ix) Control and laboratory operations.

(2) The flow of components, incoming designated medical gases, medical gas containers and closures, labeling, in-process materials, and medical gases through the buildings and facilities shall be designed to prevent contamination and mix-ups.

(c) Any building or facility used in the manufacture, processing, packing, or holding of a medical gas shall be maintained in a clean condition so as to assure the safety, identity, strength, quality, and purity of the medical gas. Written procedures applicable to the

maintenance and cleaning of buildings and facilities shall be established and followed.

Subpart D—Equipment

§ 213.63 Equipment design, size, and location.

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

§ 213.65 Equipment construction.

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

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

§ 213.67 Equipment maintenance and cleaning.

(a) Written procedures shall be established, maintained, and followed for adequate cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of medical gases. These procedures shall include, but are not necessarily limited to, the following:

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

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

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

(4) Removal or obliteration of previous batch identification;

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

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

(b) The procedures described in paragraph (a) of this section shall not alter the safety, identity, strength, quality, or purity of the medical gas beyond the established requirements.

(c) Records shall be kept of cleaning, maintenance, and inspection as specified in §§ 213.180 and 213.182.

§ 213.68 Automatic, mechanical, and electronic equipment.

(a) Automatic, mechanical, and electronic equipment used in the manufacture, processing, packing, and holding of medical gases shall be routinely calibrated, inspected, and checked according to a written program designed to ensure proper performance. Written procedures and records of calibration, inspections, and checks shall be maintained.

(b) Computerized systems that record, store, or use data shall be appropriately validated.

(c) A backup file of data entered into the computer system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes.

(d) Appropriate change control shall be used whenever modifications are made to computer systems to assure that any changes do not adversely affect data integrity or product quality. Records of such modifications shall be maintained.

Subpart E—Control of Incoming Designated Medical Gas, Components, and Medical Gas Containers and Closures

§ 213.80 General requirements.

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

(b) Components, incoming designated medical gases, and medical gas containers and closures shall at all times be handled and stored in a manner to prevent contamination and mix-ups.

(c) Lots of incoming designated medical gases or components, whether used directly as supply or commingled with an existing supply, shall be assigned a unique identification number.

§ 213.82 Receipt and storage of incoming designated medical gases.

(a)(1) Upon receipt of each shipment of each incoming designated medical gas, the firm shall either perform full compendial testing on the gas and record the results or verify and record that a signed certificate of analysis from the supplier accompanies each different designated medical gas in a shipment. The certificate of analysis shall include the following:

(i) Supplier's name;

(ii) Name of the incoming designated medical gas;

(iii) Lot number or other unique identification number;

(iv) Actual analytical result obtained for strength, as well as the results of other tests performed;

(v) Identification of the test method(s) used for analysis;

(vi) New drug application and/or new animal drug application number of the incoming designated medical gas; and

(vii) Supplier representative's signature and the date of signature.

(2) If the incoming designated medical gas is obtained from a supplier other than the original manufacturer, the shipment shall also include complete information from the original manufacturer's certificate of analysis. The firm shall establish and maintain a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures.

(b) An identity test shall be performed upon receipt of the incoming designated medical gas.

§ 213.84 Testing and approval or rejection of components, containers, and closures.

(a) Components, containers, and closures (including valves) shall be examined for conformance with appropriate written procedures and specifications, and approved or rejected, prior to the manufacturing or filling process. In lieu of such examination by the firm, a statement of verification that the component, container, or closure meets specifications may be accepted from the supplier, provided that the firm establishes and maintains a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing provisions. Any rejected items shall be handled in accordance with § 213.89.

(b) Firms shall take appropriate actions to protect against container and closure leaks, which shall include performing leak tests on containers and closures at the time of fill and after fill but prior to release.

(c) Each component shall be sampled, tested, and approved or rejected as appropriate prior to use. This requirement can be met by performing testing for conformance with written specifications or by an identity test on the component accompanied by an acceptable certificate of analysis from the supplier, provided that the firm establishes and maintains a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures.

§ 213.89 Rejected components, incoming designated medical gases, and medical gas containers and closures.

Rejected components, incoming designated medical gases, and medical gas containers and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable and shall be documented and assessed.

§ 213.94 Medical gas containers and closures.

(a) Medical gas containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the gas beyond the official or established requirements.

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

(c) Medical gas containers and closures shall be clean to assure that they are suitable for their intended use.

(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning shall be written and followed for medical gas 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 (e)(1), 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, healthcare entity, nursing home, other facility, or home healthcare setting, or is used to fill small cryogenic gas containers for use by individual patients. The term excludes 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) *Gauges for certain medical gas containers.* Portable cryogenic medical gas containers as described in paragraph (e)(1) of this section and small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined at § 868.5655 of this chapter) must have a working gauge sufficient to assist the user in determining whether the container contains an adequate supply of medical gas for continued use.

(3) *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. 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.

Subpart F—Production and Process Controls

§ 213.100 Written procedures; deviations.

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

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

§ 213.101 Charge-in of components and incoming designated medical gases.

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

(a) Except when a monograph or formulary specifies a range, the batch shall be formulated with the intent to provide 100 percent of the labeled or established amount of each medical gas. When a monograph or formulary specifies a range for the contents of a medical gas, the batch shall be formulated with the intent to provide an amount of the medical gas within such specified range.

(b) Components and incoming designated medical gases added to in-process supply or final product containers shall be weighed or measured as appropriate. In-process and final product containers shall identify the name of the component or designated medical gas or the name and percentage of each component or designated medical gas if they contain multiple components or designated medical gases, and the unique lot number assigned.

§ 213.110 Sampling and testing of in-process materials.

(a) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality unit during the production process.

(b) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes.

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

Subpart G—Packaging and Labeling Control

§ 213.122 Materials examination and usage criteria.

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

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

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

(d) Labels and other labeling materials for each different medical gas, strength,

or quantity of contents shall be stored with suitable identification to avoid mix-ups. Access to the label storage area shall be limited to authorized personnel.

(e) Labels, labeling, and other packaging materials that are obsolete, outdated, or that do not meet applicable requirements shall be destroyed.

(f) Packaging and labeling operations shall include one of the following special control procedures:

(1) Dedication of labeling and packaging lines to each different strength of each different medical gas;

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

(3) Use of visual inspection to conduct a 100-percent examination for correct labeling during or after completion of labeling operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person.

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

(h) Labels may be reused if they are legible, properly affixed to the container, and otherwise meet all applicable requirements.

§ 213.125 Labeling issuance.

(a) Labeling and packaging operations must be controlled to prevent labeling and product mix-ups. Procedures shall be written and followed describing in sufficient detail the control procedures employed for the issuance of labeling.

(b) Procedures shall be used to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of medical gas and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with § 213.192. Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination for correct labeling is performed in accordance with § 213.122(f)(2). Labeling reconciliation is also waived for 360° wraparound labels on portable cryogenic medical gas containers.

(c) All excess lot number stickers or decals bearing lot or control numbers shall be discarded.

(d) Bulk or transport containers (as defined in § 201.161(c)(3) of this chapter) are exempt from this section.

§ 213.130 Packaging and labeling operations.

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

(a) Prevention of mix-ups by physical or spatial separation from operations on other products.

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

(c) Identification of the medical gas with a lot or control number that permits determination of the history of the manufacture and control of the batch. The lot or control number of the medical gas may be identified by use of a separate identification sticker or decal.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record. Product labels, including 360° wraparound labels, can be reused provided they meet all applicable labeling requirements, all information on the label is legible, and the label is in good condition.

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

(f) Bulk or transport containers (as defined in § 201.161(c)(3) of this chapter) are exempt from this section provided they are identified with the name of the product contained therein and accompanied by documentation identifying the product as meeting applicable compendial standards.

Subpart H—Holding and Distribution

§ 213.150 Warehousing and distribution procedures.

(a) Written procedures shall be established, and followed, describing the distribution of medical gases and including a system by which the distribution of each lot can be readily determined to facilitate its recall if necessary.

(b) Written procedures shall be established, and followed, describing the warehousing of medical gases, including quarantine of such gases before release by the quality unit.

Subpart I—Laboratory Controls

§ 213.160 General requirements.

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

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

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

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

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for medical gases. Such

samples shall be representative and properly identified.

(4) The calibration or verification of calibration for instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

§ 213.165 Testing and release for distribution.

(a) For each batch of medical gas, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the medical gas, including the identity and strength, prior to release.

(b) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling, the number of units per batch to be tested, and acceptance criteria. Such written procedures shall be followed.

(c) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with § 213.194(a)(2). The suitability of all testing methods shall be verified under actual conditions of use.

(d) Medical gases failing to meet established standards or specifications and any other relevant quality criteria shall be rejected.

(e) This section does not apply to the filling of a designated medical gas or medically appropriate combination of designated medical gases via liquid to liquid into a container at a delivery site.

§ 213.166 Stability testing and expiration dating for medical gases marketed under applications submitted under section 505 or section 512 of the Federal Food, Drug, and Cosmetic Act.

(a) For medical gases marketed under applications submitted under section 505 or section 512 of the Federal Food, Drug, and Cosmetic Act, any stability testing performed and any expiration date established shall be in accordance with paragraph (b) of this section, subject to the conditions established in their approved applications, if any.

(b) To assure that the medical gas described in paragraph (a) of this section meets applicable standards of identity, strength, quality, and purity at the time of use:

(1) The stability testing program shall be designed to assess the stability characteristics of the medical gas and its container closure system. The results of stability testing shall be used in determining appropriate storage conditions and any expiration date included on the label. The stability program shall include the appropriate sample size, test intervals, container closure systems, and storage conditions for samples retained for testing.

(2) Any expiration dates included on the label shall appear in accordance with the requirements of § 201.17 of this chapter.

(3) Stability shall be evaluated periodically to ensure that the medical gas continues to meet the standards for identity, strength, quality, and purity stated on the labeling to support the expiration date.

Subpart J—Records

§ 213.180 General requirements.

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

(b) *Record requirements.* All records must be legible, stored to prevent deterioration or loss, and original or accurate reproductions of the original records.

(c) *Record retention period.* Except where otherwise provided, all records required to be maintained in compliance with this part must be maintained for a period of at least 3 years after the distribution of the batch of medical gas.

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

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

(2) A review of complaints, recalls, returned or salvaged medical gases, and investigations conducted under § 213.192 for each gas.

(e) *Written procedure requirements.* A firm shall establish and follow written procedures to assure that responsible officials of the firm are notified in writing of any recalls, reports of inspectional observations by FDA, regulatory actions related to good manufacturing practices brought by FDA, or investigations resulting from adverse event complaints.

§ 213.182 Equipment cleaning and use log.

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance (or, if the cleaning and maintenance is performed using automated equipment under § 213.68, just the person verifying the cleaning and maintenance done by the automated equipment) shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

§ 213.184 Records for components, medical gas containers and closures, and labeling.

Records for components, medical gas containers and closures, and labeling shall include the following:

(a) The results of any test or examination performed (including those performed as required by § 213.84 or § 213.122) and the conclusions derived therefrom.

(b) Documentation of the examination and review of labels and labeling for conformity with established specifications in accordance with §§ 213.122 and 213.130.

(c) The disposition of rejected components, medical gas containers and closures, and labeling.

§ 213.186 Master production and control records.

(a) To assure uniformity from batch to batch, master production and control records for each medical gas shall be prepared, dated, and signed. The preparation of master production and control records shall be described in a

written procedure and such written procedure shall be followed.

(b) Master production and control records shall include:

(1) The name and strength of the medical gas;

(2) A complete list of components and any incoming designated medical gases used in manufacturing designated by names or codes sufficiently specific to indicate any special quality characteristic;

(3) A description of the medical gas containers and closures, packaging materials, and labels; and

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

§ 213.189 Batch production and control records.

(a) Batch production and control records shall be prepared for each batch of medical gas produced.

(b) These records shall include documentation that each significant step in the manufacture, processing, packing, or holding of the medical gas produced was accomplished, including:

(1) Dates of each significant step, including in-process and laboratory tests as applicable;

(2) A description of the container for the medical gas, including the number and size of the containers filled as applicable;

(3) Specific identification of each component and its source or in-process material used as applicable;

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

(5) Testing results, including any in-process test results and finished product test results;

(6) Dated signature or initials of the persons performing and directly supervising or checking each significant step in the operation;

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

(8) Complete labeling control records, including specimens or copies of all labeling used and label application and reconciliation records as appropriate; and

(9) Any investigation made according to § 213.192.

§ 213.192 Production record review.

(a) Manufacturing production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality unit to determine compliance with all established, approved written procedures before a batch is released or distributed. The quality unit must review production records to determine whether errors or unexplained discrepancies have occurred prior to batch release. If errors or unexplained discrepancies have occurred, or a batch or any component of the batch fails to meet any of its specifications, the firm must thoroughly investigate and take appropriate corrective actions. A written record of the investigation shall be made and shall include the conclusions and followup.

(b) For production and control records of filling at a delivery site, quality unit review as described in paragraph (a) of this section shall be within one business day after fill.

§ 213.194 Laboratory records.

(a) Laboratory records related to the manufacture of a medical gas must include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A description of the sample, the batch or lot number to be tested, the date the sample was taken, and the date the sample was tested.

(2) The method used in the testing of the sample, the result of the test, how the results compare with established standards of identity, strength, quality, and purity for the component, container, closure, in-process materials (as applicable), and medical gas tested, a record of any calculations performed in connection with each test and any calculated results, and the unit of measurement of the result for each test. It is not necessary to provide the actual calculation where the result is evident through use of simple addition and subtraction.

(3) Where applicable, any graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, in-process material, or medical gas for each lot tested.

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

(b) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

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

(d) Complete records shall be maintained of the periodic calibration or verification of calibration of laboratory instruments, apparatus, gauges, and recording devices required by § 213.160(b)(4).

(e) Complete records shall be maintained of all stability testing performed in accordance with § 213.166.

§ 213.196 Distribution records.

Distribution records shall contain the name of the medical gas, lot or batch number, name and address of the consignee, and date and quantity shipped. For medically appropriate combinations of designated medical gases, the distribution record shall include the percentage of each gas.

§ 213.198 Complaint files.

(a) Written procedures shall be established and followed for the receipt and handling of all written or oral complaints concerning a medical gas. These procedures must include quality unit review of any complaint involving the possible failure of a medical gas to meet any of its specifications and provisions for determining the need for an investigation in accordance with § 213.192 as well as determining whether the complaint represents an event that is required to be reported to FDA under part 230 of this chapter. Any complaint involving a possible leak of a container or closure must be reviewed, evaluated, and investigated in accordance with § 213.192.

(b) A written record of each complaint regarding a medical gas must be maintained. The record must include the name of the gas, the lot or batch number, the name of the complainant, the date the complaint was received, the nature of the complaint, and the response to the complaint. It must also include the findings of any investigation and followup. Where an investigation is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

(c) Complaint files shall be maintained in a manner such that they are readily available for inspection by the firm or by FDA during an inspection. Complaint files shall be maintained for at least 1 year after the date the complaint was received or for at least 3 years after distribution of the medical gas, whichever is longer.

Subpart K—Returned and Salvaged Medical Gases

§ 213.204 Returned medical gases.

Returned medical gases shall be identified as such and held. If the conditions under which such returned gases have been held, stored, or shipped before or during their return, or if the condition of the gas, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality, or purity of the gas, the returned gas shall be destroyed unless examination, testing, or other investigations prove the gas meets appropriate standards of safety, identity, strength, quality, or purity. Records of returned medical gases shall be maintained and shall include the name, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned gas. If the reason for a medical gas being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of § 213.192. Procedures for the holding, testing, and use of returned medical gases shall be in writing and shall be followed. This section is not applicable to the routine refilling of cryogenic medical gas containers in the normal course of business unless the cryogenic medical gas container was returned due to a quality issue.

§ 213.208 Salvaging of medical gases.

Medical gases in containers that have been subjected to improper storage conditions may be salvaged unless their containers have been subjected to adverse conditions that impact the identity, strength, quality, and purity of the gas or integrity of the container closure. Whenever there is a question whether medical gases have been subjected to such conditions, salvaging operations may be conducted only if there is evidence from laboratory tests that such gases meet all applicable standards of identity, strength, quality, and purity, and the integrity of the container closure system is not compromised. Procedures for the holding, testing, and use of salvaged medical gases shall be in writing and shall be followed.

■ 25. Add part 230 to subchapter C to read as follows:

PART 230—CERTIFICATION AND POSTMARKETING REPORTING FOR DESIGNATED MEDICAL GASES

Subpart A—General Provisions

Sec.

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 355f, 356, 356a, 356b, 356c, 356e, 360b, 360cc, 360ddd, 360ddd–1, 371, 374, 379e, 379k–1, 381.

Subpart A—General Provisions

§ 230.1 Scope of this part.

This part sets forth procedures and requirements for the submission to, and the review by, the Food and Drug Administration of certifications to market designated medical gases under sections 575 and 576 of the Federal Food, Drug, and Cosmetic Act, as well as amendments and supplements to those certifications. This part also sets forth the postmarketing safety reporting requirements for designated medical gases.

§ 230.2 Purpose.

The purpose of this part is to establish an efficient process for the certification of designated medical gases and to establish an effective system for surveillance of such gases.

§ 230.3 Definitions.

(a) The definitions and interpretations contained in sections 201 and 575 of the Federal Food, Drug, and Cosmetic Act apply to those terms when used in this part.

(b) The following definitions of terms apply to this part:

(1) *Adverse event* means any untoward medical occurrence associated with the use of a designated medical gas in humans or animals, whether or not it is considered related to the designated medical gas. An adverse event can occur in the course of the use of a designated medical gas; from overdose of a designated medical gas, whether accidental or intentional; from abuse of a designated medical gas; from discontinuation of the designated medical gas (*e.g.,* physiological withdrawal); and it includes any failure of expected pharmacological action.

(2) *Applicant* means any person who submits a certification request for a designated medical gas under this part, including a supplement, and any person who owns a granted certification for a designated medical gas under this part.

(3) *Certification request* means a submission under section 576 of the Federal Food, Drug, and Cosmetic Act requesting certification of a medical gas as a designated medical gas.

(4) *FDA* or *Agency* means the Food and Drug Administration.

(5) *Individual case safety report* (ICSR) means a description of an adverse event related to an individual patient or subject.

(6) *ICSR attachments* means documents related to the adverse event described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

(7) *Life-threatening adverse event* means any adverse event that places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse event as it occurred, *i.e.,* it does not include an adverse event that, had it occurred in a more severe form, might have caused death.

(8) *Minimum data set for an ICSR for an adverse event* means the minimum four elements required for reporting an ICSR of an adverse event: An identifiable patient, an identifiable reporter, a suspect designated medical gas, and an adverse event.

(9) *Nonapplicant* means any person other than the applicant whose name appears on the label of a designated medical gas container as a manufacturer, packer, or distributor.

(10) *Serious adverse event* means:

(i) An adverse event is considered ''serious'' if it results in any of the following outcomes:

(A) Death;

(B) A life-threatening adverse event;

(C) Inpatient hospitalization or prolongation of existing hospitalization;

(D) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; and/or

(E) A congenital anomaly/birth defect.

(ii) Other events that may be considered serious adverse events: Important medical events that may not result in one of the listed outcomes in this definition may be considered

serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient or study subject and may require medical or surgical intervention to prevent one of the outcomes listed in this paragraph (b)(10). Examples include: Allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of product dependency or product abuse. Additional examples in animals include: Severe hypersensitivity reactions or respiratory distress.

Subpart B—Certification of Designated Medical Gases

§ 230.50 General requirements for all submission types.

(a) *Who must submit a request for certification.* (1) The certification process described in this subpart applies to designated medical gases for the indications described in section 576(a)(3)(A)(i) of the Federal Food, Drug, and Cosmetic Act. Any person who seeks to initially introduce or deliver for introduction a designated medical gas into interstate commerce shall file a request for certification. The certification process is the same for all designated medical gases, regardless of whether it is intended for human use, animal use, or both. The applicant must identify its intention to market its designated medical gas for human use, animal use, or both.

(2) Any person that proposes to market a medical gas that is a new drug for human use must obtain approval under part 314 of this chapter, and any person that proposes to market a medical gas that is a new animal drug for animal use must obtain approval under part 514 of this chapter, unless—

(i) The medical gas meets the definition of a designated medical gas; and

(ii) The medical gas is proposed to be marketed alone or in combination (as medically appropriate) with another designated medical gas or other designated medical gases, for which a certification or certifications have been granted, for a use described under section 576(a)(3)(A)(i) of the Federal Food, Drug, and Cosmetic Act.

(b) *The applicant must include the following information in its certification request*—(1) *Applicant information.* The applicant must identify the name, address, telephone number, and email address of the person requesting certification. If the address of the person requesting certification is not in the United States, the certification request is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2) *Type of submission.* The applicant must indicate the type of submission as one of the following:

(i) *Original certification request.* An initial request submitted by an applicant for certification of a medical gas as a designated medical gas.

(ii) *Amendment to a pending certification request.* Any submission related to a pending submission that revises existing information or provides additional information, including responses to Information Request Letters.

(iii) *Resubmission.* Any submission that has been revised and submitted again following a previous denial. If an applicant chooses to resubmit its submission, it must provide a written response to the deficiencies identified in FDA's denial letter, along with other information required for certification requests.

(iv) *Supplement to a granted certification.* Any submission that contains a change to a granted certification.

(v) *Other.* Any submission that does not fit in one of the other categories.

(3) *Description of medical gas.* A separate certification request is required to be submitted for each designated medical gas for which certification is sought. Each designated medical gas certification request must include the name of the medical gas and a certification statement from the applicant that the designated medical gas meets the appropriate compendial standard.

(4) *Facility information.* Each certification request must include the name and address of the facility or facilities where the designated medical gas will be initially produced. For each facility, include a brief description of the manufacturing or processing activities performed, the FDA Establishment Identifier, if one exists, and the Unique Facility Identifier in accordance with the requirements of part 207 of this chapter and section 510 of the Federal Food, Drug, and Cosmetic Act. For amendments and supplements, only changes to the list of facilities are required to be included.

(5) *Certification of adequate manufacture, processing, packaging, and holding of designated medical gas.* The applicant must certify that the applicant's methods, facilities, and controls used for the manufacture, processing, packing, and holding of the designated medical gas, as applicable, are adequate to ensure its safety, identity, strength, quality, and purity.

(6) *Additional information.* The applicant must provide any other information which FDA deems appropriate to determine whether the medical gas is a designated medical gas. The applicant may also provide other information that the applicant believes will assist FDA in evaluating the request.

(c) *Where and how to submit a request for certification.* The applicant must submit a signed, completed request for certification form either in an electronic format that FDA can process, review, and archive, or in hard copy by submitting two paper copies to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901–B Ammendale Rd., Beltsville, MD 20705.

§ 230.65 Withdrawal by the applicant of a certification request before it is deemed granted.

An applicant may at any time withdraw a certification request that is not yet deemed granted by notifying FDA in writing. A decision to withdraw the certification request is without prejudice to refiling. The Agency will retain the certification request and will provide a copy to the applicant on request under the fee schedule in § 20.45 of this chapter (FDA's public information regulations).

§ 230.70 Supplements and other changes to a granted certification.

(a) The applicant must submit a supplement if any information in the certification request changes after the request has been deemed granted, including, but not limited to, the addition of a new facility manufacturing the designated medical gas, a change in contact information, or a change in the corporate name.

(b) Each supplement must include a signed, completed request for certification form with the updated information in accordance with § 230.50. The updated information must be submitted no later than 30 calendar days after the date the change occurred.

§ 230.72 Change in ownership of a granted certification.

An applicant may transfer ownership of its certification. At the time of transfer the new and former owners are required to submit information to FDA as follows:

(a) The former owner must submit a letter or other document that states that all rights to the certification have been transferred to the new owner.

(b) The new owner must submit a supplement under § 230.70 signed by the new owner describing any changes in the conditions in the granted certification and a letter or other document containing the date that the change in ownership is effective.

§ 230.80 Annual report.

(a) The applicant must submit each year within 60 calendar days of the new calendar year an annual report containing the information described in paragraph (b) of this section. The applicant must submit a signed, completed annual report form either in an electronic format that FDA can process, review, and archive, or in hard copy by submitting two paper copies to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901–B Ammendale Rd., Beltsville, MD 20705.

(b) The report must contain, for the prior calendar year, the following information in the order listed:

(1) *Summary.* A brief summary of significant new information that might affect the safety, effectiveness, or labeling of the designated medical gas, including any actions the applicant has taken or intends to take as a result of this new information.

(2) *Distribution data.* Information about the quantity of the designated medical gas distributed by the applicant. The information must include the National Drug Code (NDC) numbers, the quantities distributed for domestic use, and the quantities distributed for foreign use. Disclosure of financial or pricing data is not required.

(3) *Administrative changes.* Any changes to the applicant's name or contact information.

(4) *Current facilities.* A list of current facilities where the designated medical gas is initially produced, and a list of facilities that are no longer in use.

§ 230.100 FDA review of submissions.

(a) In reviewing a submission pursuant to § 230.50, FDA will consider information provided with the submission along with any other available, relevant information of which FDA becomes aware, including information obtained from State or Federal officials, FDA inspection reports, or any other source.

(b) FDA will deny a submission if FDA finds that:

(1) The medical gas that is the subject of the submission is not a designated medical gas;

(2) The submission does not contain the required information or otherwise appears to lack sufficient information to determine that the medical gas is a designated medical gas;

(3) The applicant's methods, facilities, and controls used for the manufacture, processing, and handling of the designated medical gas, as applicable, are not adequate to ensure its safety, identity, strength, quality, and purity; or

(4) Denying the request is otherwise necessary to protect the public health.

(c) Within 60 calendar days of filing of a submission, FDA may contact the applicant to request additional information regarding the submission if it determines that required information is not included in the submission, that FDA needs such information to determine whether the medical gas is a designated medical gas, or that FDA determines such information is necessary to protect the public health. Upon receipt of an amendment to a pending certification request, this 60-day review period will restart. If FDA is not able to contact the applicant to obtain and evaluate the information within the 60-day review period, FDA may find that the submission lacks sufficient information to permit a determination that the medical gas is a designated medical gas and deny the submission. If FDA is able to contact the applicant but is not provided with the additional information requested within the 60-day review period, FDA may find that the request lacks sufficient information to permit a determination that the medical gas is a designated medical gas and deny the submission.

(d) Within 60 calendar days of filing of a submission, if FDA makes one of the findings described in paragraph (b) of this section, FDA will notify the applicant in writing that the submission is denied and provide the basis for FDA's determination.

§ 230.105 When a submission is deemed granted.

Unless FDA makes one of the findings described in § 230.100(b) and notifies the applicant within 60 calendar days of filing that the submission is denied, the certification is deemed to be granted and the designated medical gas will be deemed to have in effect an approved application under section 505 or section 512 of the Federal Food, Drug, and Cosmetic Act, or both, as applicable, for the indications described in section 576(a)(3)(A)(i) of the Federal Food, Drug, and Cosmetic Act. FDA will notify the applicant in writing.

§ 230.150 Withdrawal or revocation of approval of an application.

(a) *Withdrawal.* (1) FDA will notify the applicant, and afford an opportunity for a hearing on a proposal to withdraw approval of the application under the procedure in § 314.200 of this chapter, § 514.200 of this chapter, or both, as applicable, if any of the following apply:

(i) The Secretary of Health and Human Services has suspended the approval of the application for a designated medical gas on a finding that there is an imminent hazard to the public health. FDA will promptly afford the applicant an expedited hearing following summary suspension on a finding of imminent hazard to health.

(ii) FDA finds:

(A) That clinical or other experience, tests, or other scientific data show that the designated medical gas is unsafe for use under the conditions of use upon the basis of which the application was approved; or

(B) That new evidence of clinical experience not available to FDA until after the application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application was approved, evaluated together with the evidence available when the application was approved, reveal that the designated medical gas is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or

(C) Upon the basis of new information before FDA with respect to the designated medical gas, evaluated together with the evidence available when the application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in § 314.126 of this chapter, that the designated medical gas will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or

(D) That the application contains any untrue statement of a material fact.

(2) FDA may notify the applicant, and afford an opportunity for a hearing on a proposal to withdraw approval of the application under the procedure in § 314.200 of this chapter, § 514.200 of this chapter, or both, as applicable, if the Agency finds:

(i) That the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain required records or to make required reports applicable to designated medical gases, including under sections 505(k) and 512(l) of the Federal Food, Drug, and Cosmetic Act and this part, part 213 of this chapter, and § 314.81(b)(3) of this chapter, or that the applicant has refused to permit access to, or copying or verification of, its records.

(ii) That on the basis of new information before FDA, evaluated together with the evidence available when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the designated medical gas are inadequate to ensure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Agency.

(iii) That on the basis of new information before FDA, evaluated together with the evidence available when the application was approved, the labeling of the designated medical gas, based on a fair evaluation of all material facts, is false or misleading in any particular, and the labeling was not corrected by the applicant within a reasonable time after receipt of written notice from the Agency.

(iv) That the applicant has failed to comply with the notice requirements of section 510(j)(2) of the Federal Food, Drug, and Cosmetic Act.

(3) FDA will withdraw approval of an application if the applicant requests its withdrawal because the designated medical gas subject to the application is no longer being marketed, provided none of the conditions listed in paragraphs (a)(1) and (2) of this section applies to the designated medical gas. FDA will consider a written request for a withdrawal under this paragraph (a)(3) to be a waiver of an opportunity for hearing otherwise provided for in this section. Withdrawal of approval of an application under this paragraph (a)(3) is without prejudice to refiling.

(4) FDA may notify an applicant that it believes a potential problem associated with a designated medical gas is sufficiently serious that the designated medical gas should be removed from the market and may ask the applicant to waive the opportunity for hearing otherwise provided for under this section, to permit FDA to withdraw approval of the application for the product, and to remove voluntarily the product from the market. If the applicant agrees, the Agency will not make a finding under paragraph (a)(1) or (2) of this section, but will withdraw approval of the application in a notice published in the **Federal Register** that contains a brief summary of the Agency's and the applicant's views of the reasons for withdrawal.

(5) If FDA withdraws an approval, FDA will publish a notice in the **Federal Register** announcing the withdrawal of approval.

(b) *Revocation.* FDA may revoke the grant of a certification if FDA determines, after providing the applicant with notice and opportunity for an informal hearing in accordance with part 16 of this chapter, that the request for certification contains any material omission or falsification.

Subpart C—Postmarketing Quality and Safety Reporting

§ 230.205 Field alert reports.

The applicant shall submit a field alert report containing all information described in paragraphs (a) and (b) of this section about distributed designated medical gases and articles to the FDA district office that is responsible for the facility involved as soon as possible but no later than 45 calendar days from the date the applicant, or its agent or contractor, obtained information suggesting that a reportable incident has occurred. If the information suggests that the reportable incident may require a rapid response to address a public health risk, the applicant must as soon as possible, but no later than 3 working days from obtaining the information, submit a field alert report. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: ''Designated Medical Gas—Field Alert Report.''

(a) Information concerning any incident that causes the designated medical gas or its labeling to be mistaken for, or applied to, another article.

(b) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed designated medical gas, or any failure of one or more distributed batches of the designated medical gas to meet established specifications.

§ 230.210 General reporting requirements for designated medical gas adverse events.

(a) *Review of safety information.* Each applicant and nonapplicant must promptly review all safety information that the applicant or nonapplicant receives or otherwise obtains from any source, foreign or domestic, such as information derived from commercial marketing experience, reports in the published scientific and medical literature, unpublished scientific papers, and reports from regulatory authorities.

(b) *Safety reporting disclaimer.* (1) A report or information submitted by an applicant or nonapplicant (and any release by FDA of that report or information) under § 230.220 or § 230.230 does not necessarily reflect a conclusion by the applicant or nonapplicant or by FDA that the report or information constitutes an admission that the designated medical gas caused or contributed to an adverse effect.

(2) An applicant or nonapplicant need not admit, and may deny, that the report or information submitted under § 230.220 or § 230.230 constitutes an admission that the designated medical gas caused or contributed to an adverse effect.

§ 230.220 Human designated medical gas ICSR requirements.

(a) *ICSR reporting*—(1) *General.* Except as provided in paragraph (c) of this section, applicants and nonapplicants must submit each ICSR associated with the use of a designated medical gas in humans described in paragraph (b) of this section to FDA as soon as possible but no later than 15 calendar days from the date when the applicant or nonapplicant has met the reporting criteria described in paragraph (b) of this section and acquired a minimum data set for an ICSR for an adverse event.

(2) *Copies of ICSRs obtained from FDA.* An applicant or nonapplicant should not resubmit under this section any ICSRs obtained from FDA's adverse event reporting database or forwarded to the applicant or nonapplicant by FDA.

(3) *Followup information.* Applicants and nonapplicants must submit any new information that is related to a previously submitted ICSR or an ICSR that was sent to the applicant or nonapplicant by FDA no later than 15 calendar days after the information is received or otherwise obtained.

(b) *Reporting requirements*—(1) *Serious adverse events*—(i) *Reported to or otherwise received by the applicant or nonapplicant.* Applicants and nonapplicants must submit ICSRs for serious adverse events reported to or otherwise received by the applicant or nonapplicant (such as a report initiated by a patient, consumer, or healthcare professional, or received at the request of the applicant or nonapplicant).

(ii) *Reported from the scientific literature.* Applicants and nonapplicants must submit ICSRs for serious adverse events obtained from published scientific and medical journals either as case reports or as the result of a formal clinical trial.

(iii) *Exception to reporting requirements for serious adverse events.* Notwithstanding paragraphs (b)(1)(i) and (ii) of this section, ICSRs are not required for reports of the death of a patient who was administered oxygen, unless the applicant or nonapplicant is aware of evidence to suggest that the

death was caused by the administration of oxygen.

(2) *Other adverse event reports to be submitted upon notification by FDA.* Upon notification by FDA, applicants and nonapplicants must submit, in a timeframe established by FDA, ICSRs for any adverse events that are not required under paragraph (b)(1) of this section. The notification will specify the adverse events to be reported and the reason for requiring the reports.

(c) *Completing and submitting ICSRs.* This paragraph (c) describes how to complete and submit ICSRs required under this section.

(1) *Electronic format for submissions.* (i) ICSRs and ICSR attachments must be in an electronic format that FDA can process, review, and archive.

(ii) An applicant or nonapplicant may request, in writing, a temporary waiver of the requirements in paragraph (c)(1)(i) of this section. These waivers will be granted on a limited basis for good cause shown.

(2) *Submitting ICSRs*—(i) *Single submission of each ICSR.* Submit each ICSR only once.

(ii) *Separate ICSR for each patient.* The applicant or nonapplicant must submit a separate ICSR for each patient who experiences an adverse event reportable under paragraph (b) of this section.

(iii) *Coding terms.* The adverse event terms described in the ICSR must be coded using standardized medical terminology.

(iv) *Minimum data set.* All ICSRs submitted under this section must contain at least the minimum data set for an ICSR for an adverse event. The applicant or nonapplicant must actively seek the minimum data set in a manner consistent with the written procedures under paragraph (f) of this section. Applicants and nonapplicants must document and maintain records of their efforts to obtain the minimum data set.

(v) *ICSR elements.* The applicant or nonapplicant must complete all known, available elements of an ICSR as specified in paragraph (d) of this section.

(A) For adverse events, applicants and nonapplicants must actively seek any information needed to complete all applicable elements, consistent with their written procedures under paragraph (f) of this section.

(B) Applicants and nonapplicants must document and maintain records of their efforts to obtain the missing information.

(vi) *Supporting documentation.* An applicant or nonapplicant must submit the following types of supporting documentation in an ICSR, if available:

(A) A copy of the autopsy report if the patient died, or a copy of the hospital discharge summary if the patient was hospitalized. The applicant or nonapplicant must submit each document as an ICSR attachment. The ICSR attachment must be submitted either with the initial ICSR or no later than 15 calendar days after obtaining the document. English translations of foreign language documents must be provided.

(B) A copy of the published article as an ICSR attachment for each ICSR of an adverse event obtained from the published scientific and medical literature. Foreign language articles must be accompanied by an English translation of the abstract. When submitting more than one ICSR from the same published article, the applicant or nonapplicant must submit only one copy of the article with one of the ICSRs. For the remaining ICSRs not accompanied by a copy of the published article, the applicant or nonapplicant must include the cross-reference to the specific ICSR to which the article is attached.

(d) *Information reported on ICSRs.* ICSRs must include the following information, subject to paragraph (c)(2)(v) of this section:

(1) Patient information, which includes:

(i) Patient identification code;

(ii) Patient age at the time of adverse event, or date of birth;

(iii) Patient sex; and

(iv) Patient weight.

(2) Adverse event, which includes:

(i) Outcome attributed to adverse event;

(ii) Date of adverse event;

(iii) Date of ICSR submission;

(iv) Description of adverse event;

(v) Adverse event term(s);

(vi) Description of relevant tests conducted, including dates and laboratory data; and

(vii) Other relevant patient history, including preexisting medical conditions.

(3) Suspect designated medical gas(es), which includes:

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the adverse event abated after the use of the designated medical gas(es) stopped or the dose was reduced;

(vi) Whether the adverse event reappeared after reintroduction of the designated medical gas(es);

(vii) Lot number;

(viii) National Drug Code (NDC) number; and

(ix) Concomitant medical products and therapy dates.

(4) Initial reporter information, which includes:

(i) Name, address, email address, and telephone number;

(ii) Whether the initial reporter is a healthcare professional; and

(iii) Occupation, if a healthcare professional.

(5) Applicant or nonapplicant information, which includes:

(i) Applicant or nonapplicant name, address, email address, and telephone number;

(ii) Report source, such as spontaneous, literature, or study;

(iii) Date the report was received by applicant or nonapplicant;

(iv) New drug application and/or new animal drug application number;

(v) Whether the ICSR is an expedited report;

(vi) Whether the ICSR is an initial report or followup report; and

(vii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(e) *Recordkeeping.* (1) For a period of 10 years from the initial receipt of information, each applicant or nonapplicant must maintain records of information relating to adverse events under this section, whether or not submitted to FDA.

(2) These records must include raw data, correspondence, and any other information relating to the evaluation and reporting of adverse event information that is received or otherwise obtained by the applicant or nonapplicant.

(3) Upon written notice by FDA, the applicant or nonapplicant must submit any or all of these records to FDA within 5 calendar days after receipt of the notice. The applicant or nonapplicant must permit any authorized FDA employee, at reasonable times, to access, copy, and verify these established and maintained records described in this section.

(f) *Written procedures.* The applicant or nonapplicant must develop written procedures needed to fulfill the requirements in this section for the surveillance, receipt, evaluation, and reporting to FDA of adverse event information, including procedures for employee training and for obtaining and processing adverse event information from other applicants and nonapplicants.

(g) *Patient privacy.* An applicant or nonapplicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant or nonapplicant

should assign a unique code for identification of the patient. The applicant or nonapplicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. As set forth in FDA's public information regulations in part 20 of this chapter, FDA generally may not disclose the names of patients, individual reporters, healthcare professionals, hospitals, and geographical identifiers submitted to FDA in adverse event reports.

§ 230.230 Animal designated medical gas adverse event reporting requirements.

(a) *Report for adverse events.* This report provides information on each adverse event associated with the use of a designated medical gas in animals, regardless of the source of the information.

(1) *Serious adverse events.* The applicant or nonapplicant must submit serious adverse events to FDA as soon as possible but no later than within 15 calendar days of first receiving the information. The report must be submitted to the Agency in electronic format as described in paragraph (b)(1) of this section, unless the applicant or nonapplicant obtains a waiver under paragraph (b)(2) of this section or FDA requests the report in an alternate format.

(i) *Reported to or otherwise received by the applicant or nonapplicant.* Applicants and nonapplicants must submit reports for *each serious adverse event* reported to or otherwise received by the applicant or nonapplicant (such as reports initiated by a patient, consumer, veterinarian, or other healthcare professional, or received at the request of the applicant or nonapplicant), regardless of whether the applicant or nonapplicant believes the events are related to the designated medical gas.

(ii) *Reported from the scientific and medical literature.* Applicants and nonapplicants must submit reports for each serious adverse event obtained from the published scientific and medical literature regardless of whether the applicant or nonapplicant believes the events are related to the designated medical gas.

(iii) *Exception to reporting requirements for serious adverse events.* Notwithstanding paragraphs (a)(1)(i) and (ii) of this section, reports are not required to be submitted for the death of an animal that was administered oxygen, unless the applicant or nonapplicant becomes aware of evidence to suggest that the death was caused by the administration of oxygen.

(2) *Other adverse event reports to be submitted upon notification by FDA.* Upon notification by FDA, applicants and nonapplicants must submit reports of adverse events associated with the use of a designated medical gas in animals that do not qualify for reporting under paragraph (a)(1) of this section. The notice will specify the adverse events to be reported and the reason for requiring the reports.

(3) *Copies of adverse event reports obtained from FDA.* An applicant or nonapplicant should not resubmit under this section any adverse event reports obtained from FDA's adverse event reporting database or forwarded to the applicant or nonapplicant by FDA.

(b) *Format for submissions*—(1) *Electronic submissions.* Reports submitted to FDA under this section must be submitted in an electronic format that FDA can process, review, and archive. Data provided in electronic submissions must be in conformance with the data elements in Form FDA 1932 and FDA technical documents describing transmission. As necessary, FDA will issue updated technical documents on how to provide the electronic submission (*e.g.,* method of transmission and processing, media, file formats, preparation and organization of files). Unless requested by FDA, paper copies of reports submitted electronically should not be submitted to FDA.

(2) *Waivers.* An applicant or nonapplicant may request, in writing, a temporary waiver of the electronic submission requirements in paragraph (b)(1) of this section. The initial request may be provided by telephone or email to the Center for Veterinary Medicine's Division of Pharmacovigilance and Surveillance, with prompt written followup submitted as a letter to the granted certification(s). FDA will grant waivers on a limited basis for good cause shown. If FDA grants a waiver, the applicant or nonapplicant must comply with the conditions for reporting specified by FDA upon granting the waiver.

(c) *Records to be maintained.* (1) For a period of 5 years from the initial receipt of information, each applicant or nonapplicant must maintain records of information relating to adverse event reports under this section, whether or not submitted to FDA.

(2) These records must include raw data, correspondence, and any other information relating to the evaluation and reporting of adverse event information that is received or otherwise obtained by the applicant or nonapplicant.

(3) Upon written notice by FDA, the applicant or nonapplicant must submit any or all of these records to FDA within 5 calendar days after receipt of the notice. The applicant or nonapplicant must permit any authorized FDA employee, at reasonable times, to access, copy, and verify these established and maintained records described in this section.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

■ 26. The authority citation for part 314 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 355f, 356, 356a, 356b, 356c, 356e, 360cc, 360ddd, 360ddd–1, 371, 374, 379e, 379k–1.

■ 27. Amend § 314.1 by redesignating paragraph (c) as paragraph (d) and adding new paragraph (c) to read as follows:

§ 314.1 Scope of this part.

* * * * *

(c) The following provisions do not apply to designated medical gases, which are subject to the certification and postmarketing reporting requirements under part 230 of this chapter:

(1) Sections 314.50 through 314.72;

(2) Section 314.80;

(3) Section 314.81, except paragraph (b)(3);

(4) Section 314.90;

(5) Subpart C of this part;

(6) Sections 314.100 through 314.162;

(7) Subpart H of this part; and

(8) Subpart I of this part.

* * * * *

PART 514—NEW ANIMAL DRUG APPLICATIONS

■ 28. The authority citation for part 514 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 354, 356a, 360b, 360ccc, 360ddd, 360ddd–1, 371, 379e, 381.

■ 29. Amend § 514.1 by adding a sentence to the end of paragraph (a) to read as follows:

§ 514.1 Applications.

(a) * * * The following provisions do not apply to designated medical gases, which are subject to the certification requirements under part 230 of this chapter: §§ 514.1(b) and (c), 514.3 through 514.8, 514.12, and 514.15, and subpart B of this part.

* * * * *

■ 30. Amend § 514.80 by:

■ a. In the introductory text table, adding an entry after the sixth entry; and

■ b. Adding paragraph (a)(6).

The additions read as follows:

§ 514.80 Records and reports concerning experience with approved new animal drugs.

The following table outlines the purpose for each paragraph of this section:

Purpose	21 CFR paragraph and title
* * * * * * *	
Does this section apply to designated medical gases subject to the certification requirements under part 230?	514.80(a)(6)
* * * * * * *	

(a) * * *

(6) This section does not apply to designated medical gases, which are subject to the certification requirements under part 230 of this chapter. Part 230 of this chapter contains requirements related to records and reports concerning experience with the use of a designated medical gas in animals.

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Dated: June 10, 2024.

Robert M. Califf,

Commissioner of Food and Drugs.

[FR Doc. 2024–13190 Filed 6–17–24; 8:45 am]

BILLING CODE 4164–01–P