DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

Docket No. FDA-2021-N-1333

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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I. Introduction and Summary

A. Introduction

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.

B. Summary of Costs and Benefits

This final rule establishes, within 21 Code of Federal Regulations (CFR) Part 213, current good manufacturing practice (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 (DMGs). Recommendations for how to request a certification for DMGs are currently included in a draft guidance. This rule makes changes to postmarketing safety reporting regulations for DMGs that address human and animal use and more specifically reflect the development, manufacturing, and distribution of DMGs.

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.

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	
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 not generally 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							

C. Terminology

In Table 2, we describe the key terms we use in this document. We note that these definitions only apply to this document.

Table 2. Key Terms in the Regulatory Impact Analysis

Term	Description
Adverse Event	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.
Applicant	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.
Certification Request	A submission under Section 576 of the Federal Food, Drug, and Cosmetic Act requesting certification of a medical gas as a designated medical gas.
CVM	*Center for Veterinary Medicine*
CDER	*Center for Drug Evaluation and Research*
CFR	*Code of Federal Regulations*
CGMP	*Current good manufacturing practice*
D&B	*Dun & Bradstreet*
DMG	*Designated medical gas*; a drug that is manufactured or stored in a liquefied, nonliquified, or cryogenic state; is administered as a gas; and is defined in Section 575(1) of the Federal Food, Drug, and Cosmetic Act.
ERG	*Eastern Research Group*
FAERS	*FDA Adverse Event Reporting System*
FDASIA	*Food and Drug Administration Safety and Innovation Act of 2012*
FD&C Act	*Federal Food, Drug, and Cosmetic Act*
NAICS	*North American Industry Classification System*
Nonapplicant	Any person other than the applicant whose name appears on the label of a designated medical gas container as a manufacturer, packer, or distributor.
ORA	*Office of Regulatory Affairs*
Quality Unit	Any person or persons designated with the authority and responsibility for overall quality management and other responsibilities as defined in § 213.22.
SBA	*Small Business Administration*
SIC	*Standard Industrial Classification*
SME	*Subject matter experts*
SOC	*Standard Occupation Classification System*
We, our, us	We use these terms to refer to the United States Food and Drug Administration.

D. Comments on the Preliminary Economic Analysis of Impacts and Our Responses

On May 23, 2022, we published the proposed rule "Current Good Manufacturing Practice, Certification, Postmarketing Safety Reporting, and Labeling Requirements for Certain Medical Gases" (87 FR 31302). Accompanying the proposed rule was a preliminary regulatory impact analysis (PRIA) (Ref. 1). We received one comment directed at the PRIA and a few comments on the rule that were 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 1 (Distribution records burden)

One commenter stated 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 1: FDA agrees. We removed "medical air and" from the distribution records section to clarify. This clarification ensures no additional burden for distribution records.

Comment 2 (Transfilling recording burden)

One commenter stated that transfilling should be included in the distribution records and tracked, including which lots of gas material were added and on which date.

Response 2: Including transfilling in the distribution records would be burdensome. However, FDA does not believe that changes are needed to address this issue. The tracking information may be of limited use for traceability due to the use of multiple batches and commingling. Additionally, we expect that the benefits would be minimal while the added burden of tracking this information would be significant.

Comment 3 (Adverse event reporting burden)

One commenter states generally 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 commenter 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 3: Adverse event reporting is already required for applicants and nonapplicants. The 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. FDA 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 requirements is already included in FDA's guidance for industry Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application[1] and draft guidance for industry Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines[2] 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 4 (General comment, burden may be higher)

One commenter stated 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 4: 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 acknowledge additional potential costs and possible sensitivities in the sensitivity analysis of the PRIA.

E. Summary of Changes

We updated the per adverse event report for DMG burden estimates. We removed the 1 hour of practitioners' time because we do not believe that firms will need to hire medical professionals to comply with postmarketing safety reporting requirements. Adverse event reports for DMGs generally do not require an evaluation of expectedness, and, considering the differences in how DMGs come to market compared to other drugs, it is not necessary for applicants or nonapplicants to utilize staff with medical expertise in preparing adverse event reports. We updated the professional time to include the full range from the 2019 Eastern Research Group (ERG) report summarized by the 2023 memorandum to file (Ref. 6) for an estimate of 2 to 4 hours of professional time.

[1] Guidance for industry Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application: https://www.fda.gov/media/77193/download.

[2] Draft guidance for industry Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines: https://www.fda.gov/media/73593/download. When finalized the guidance will represent FDA's current thinking on this issue.

We updated the count of DMG certification requests from 94, the count as of April 24th, 2023, to 98, the count as of December 31st, 2023. We updated the wage rate from General and Operations Managers to Business Operations Specialist to represent the non-medical professional wage rate. Additionally, we updated the data to provide estimates in 2022 dollars.

II. Final Regulatory Impact Analysis

A. Background

The Food and Drug Administration Safety and Innovation Act (FDASIA, Pub. L. 112-144) was signed into law on July 9, 2012, establishing a new marketing pathway and specific requirements for the regulation of DMGs. Section 756 of the Consolidated Appropriations Act, 2017 (Pub. L. 115-31) requires the Food and Drug Administration (FDA) to issue final regulations revising the Federal drug regulations with respect to medical gases by July 15, 2017.

The Agency has engaged with stakeholders and Congress to evaluate the need for regulatory changes within the medical gas industry. This final rule is being published to address the areas for which FDA has determined regulatory changes are needed. We (1) establish regulations regarding the certification of DMGs;[3] (2) amend the requirements for CGMP, postmarketing safety reporting, and labeling that apply to certain medical gases; and (3) clarify the regulatory obligations of entities that manufacture, process, pack, label, or distribute certain medical gases. We recognize the differences in how medical gases are manufactured, packaged, labeled, and distributed compared to other drugs. This final rule reflects that recognition.

B. Market Failure Requiring Federal Regulatory Action

[3] In the Federal Food, Drug, and Cosmetic Act (FD&C Act) § 575(1), the term "designated medical gas" is defined to mean any of the following: "(A) Oxygen that meets the standards set forth in an official compendium. (B) Nitrogen that meets the standards set forth in an official compendium. (C) Nitrous oxide that meets the standards set forth in an official compendium. (D) Carbon dioxide that meets the standards set forth in an official compendium. (E) Helium that meets the standards set forth in an official compendium. (F) Carbon monoxide that meets the standards set forth in an official compendium. (G) Medical air that meets the standards set forth in an official compendium. (H) Any other medical gas deemed appropriate by the Secretary, after taking into account any investigational new drug application or investigational new animal drug application for the same medical gas submitted in accordance with regulations applicable to such applications in title 21 of the Code of Federal Regulations, unless any period of exclusivity for a new drug under Section 355(c)(3)(E)(ii) of this title or Section 355(j)(5)(F)(ii) of this title, or the extension of any such period under Section 355a of this title, or any period of exclusivity for a new animal drug under Section 360b(c)(2)(F) of this title, applicable to such medical gas has not expired."—Link: https://uscode.house.gov/view.xhtml?path=/prelim@title21/chapter9/subchapter5&edition=prelim.

Medical gases need to be regulated because producers and consumers, acting in the unregulated marketplace, are unable to observe the health risks of potentially injurious hazards that are necessary to make well informed choices about the processing, distribution, sale, and final consumption of potentially hazardous medical gases. The absence of observable risk information reduces the incentives for producers to invest in the socially optimal level of drug safety across the supply chain.

The entities manufacturing, processing, and handling medical gases make many decisions about what investments to make to reduce medical gas safety risk for their consumers. When doing so, they consider the probability of their practices causing a medical gas safety risk, the probability that they will be found legally responsible for causing the medical gas safety risk, and the damage the medical gas safety risk would cause to their firm if they are discovered to be responsible. If the probability of the medical gas safety risk, multiplied by the probability of detection, multiplied by the damage to the firm, is equal to or greater than the cost of preventing the medical gas safety risk, then medical gas producers will invest more in prevention of a medical gas safety risk. If the probability of detection is lower than 100 percent, and the private damages are approximately equal to the social damages, then owners will invest less in prevention of a medical gas safety risk than the social optimum.

Many provisions of this final rule, such as recordkeeping requirements, increase the probability of detection of defective medical gases. It is not feasible to increase the probability of detection to 100 percent; therefore, the rule mandates that owners do what they would do in many cases if they knew that the probability of detection was 100 percent.

Government action through regulation may improve social welfare because neither the legal system nor the marketplace may provide adequate economic incentives to produce safe medical gases. Consumers are unable to distinguish between firms and products that have invested in safe medical gas production at socially desirable levels from those that have not because the information is not easily available to consumers. Firms that invest in socially desirable levels of medical gas safety might incur higher production costs causing them to compete at a disadvantage with firms that do not. Consequently, firms may not voluntarily invest sufficiently in medical gas safety.

C. Purpose of the Rule

This final rule will implement Section 756 of the Consolidated Appropriations Act, 2017 (Pub. L. 115-31), which requires FDA to issue final regulations revising the Federal drug regulations with respect to medical gases by July 15, 2017. We recognize that medical gases are manufactured, labeled, distributed, and authorized for marketing differently than most other drugs. The rule is intended to reflect these differences and decrease regulatory burden where appropriate.

A short description of the major changes to 21CFR Parts 201, 213, 230, 314, and 514 follows. See the final rule for a more complete discussion of all provisions and the corresponding sections of the CFR that will be directly affected by the rule (87 FR 31302).

This final rule is being issued for several reasons. First, this rule will amend the requirements for CGMP that apply to medical gases to address the differences between the production, labeling, handling, and distribution of medical gases and other finished drug products. These regulations include many of the same categories of requirements as the general drug product CGMP regulations (Part 211), but are tailored to reflect differences in manufacturing, packaging, labeling, storage, and distribution of medical gases. Examples include certain building and facility requirements, sanitation requirements, and equipment maintenance and cleaning requirements. Further, Part 211 includes limitations on the reuse of labels, intensive laboratory testing requirements, and restrictions on salvaging which are not appropriate to medical gases. This mismatch between suitable government regulations concerning manufacturing, packaging, labeling, storage, and distribution of medical gases and current regulations under Part 211 represents a market inefficiency. Market forces cannot correct this inefficiency without FDA conducting further rulemaking to tailor these CGMP requirements for medical gases.

Second, this final rule will modify the labeling requirements in Part 201. This rule will require medical oxygen containers to have a "no smoking" statement, a "no vaping" statement, and a graphic warning symbol to reduce the risk of fires caused by smoking or vaping near an oxygen tank. This rule will specify the format for the statement of ingredients for DMGs and establish separate requirements for the declaration of net quantity of contents for DMGs.

Third, this final rule will establish the process and requirements for obtaining certification of a DMG. Since the passage of FDASIA, many applicants have sought marketing authorization for a DMG under § 576 of Federal Food, Drug, and Cosmetic Act (FD&C Act), and this rule is intended to codify that process while also providing additional clarity where necessary. Part 230 will contain the requirements for filing a certification request for a DMG for human use, animal use, or both. Because certain provisions within 21 CFR Parts 314 and 514 will no longer be applicable to DMGs or would require revisions to better reflect the certification process, FDA includes conforming edits to Parts 314 and 514 as well.

Fourth, this final rule will modify the requirements for postmarketing safety reporting for DMGs. This rule will clarify what adverse events must be reported. For example, the final rule clarifies that reports of death of a patient or animal who was administered oxygen are not required to be submitted unless the applicant or nonapplicant becomes aware of evidence that the administration of the oxygen was the cause of death, and that fires associated with oxygen use only require an adverse event report if a patient or animal is injured.

D. Baseline Conditions

In our analysis, we use the 2020 DMGs market to characterize the baseline DMGs market. We contracted with Eastern Research Group (ERG) to update the medical gas industry profile that they had developed for us in 2014, and to collect data on practices in the medical gas industry as they relate to the current federal drug regulations. Additionally, ERG researched the possibility that government inspections, based on a direct application of our regulations that

apply to typical drug products, could result in industry expending sizable resources to address inspection results that could have been avoided with regulations that are more finely tuned to the specific attributes of the medical gas industry.

In this analysis, we use average (mean) wage data from the 2022 Bureau of Labor Statistics NAICS code 325400 – Pharmaceutical and Medicine Manufacturing to estimate labor costs to industry. We use 2022 data on FDA fully-loaded Full Time Equivalent (FTE) costs to estimate the fully-loaded FDA-wide wage.[4] The cost of labor is the fully-loaded wage, which includes overhead and benefits. For FDA, overhead is calculated internally. We estimate a fully-loaded FDA FTE of $296,450 for an hourly wage rate estimate of $142.52 (=$296,450 ÷ 2,080 work hours per year). For industry, we assume that the cost of overhead and benefits equals 100 percent of the wage.[5] contains the fully-loaded wages to industry used in this analysis.

ERG completed its final report in January 2020 (Ref. 2). We use information in the updated ERG profile as part of the basis for this analysis. Specifically,

(1) we rely on the ERG counts of firms and facilities that produce DMGs, as well as those downstream persons and entities who distribute DMGs both to healthcare entities and directly to patients (Table 4),[6]
(2) we use ERG's estimates of the number and types of medical gas containers (Table 5),
(3) we use ERG's estimates for DMG manufacturer compliance with current federal regulations, including 21 CFR Parts 211, 314 and 514 (ERG Table 5-1), and, where appropriate,
(4) we use ERG's estimates of per unit cost increases for areas of current noncompliance of our regulations in those cases in which the new regulations will create identical or similar requirements.

We use information concerning DMG industry practices from our internal medical gas subject matter experts (SMEs) to establish the baseline for this analysis. These SMEs have experience with our regulations concerning drug labeling, CGMP requirements, the DMG certification and annual reporting processes, and the postmarketing safety reporting process.

[4] We use the FDA-wide FTE wage rate for this final rule because this rule would affect different centers including Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), and Office of Regulatory Affairs (ORA).
[5] HHS currently assumes that benefits plus indirect costs equal approximately 100 percent of wages. In other words, multiplying wages by a factor of 2 provides an estimate of the fully-loaded wage rate (https://aspe.hhs.gov/system/files/pdf/257746/VOT.pdf).
[6] We did not add facilities to our ERG count for medical gases marketed under applications submitted through Sections 505 and 512 of the FD&C Act. According to the Orange Book, there are only 9 active approved drug applications and many, if not all, of the 6 applicant holders are included in the count for a DMG. Accessed April 21, 2023. Source: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm (search GAS under Dosage Form).

Table 3. The Cost of Labor

Employee Type	Mean Hourly Wage	Fully-Loaded Hourly Wage
Management occupations (11-0000)	$83.84	$167.68
General and operations managers (11-1021)	$89.21	$178.42
Business operations specialists (13-1000)	$45.55	$91.10
Legal occupations (23-0000)	$94.05	$188.10
Veterinarians (29-1131)	$50.02	$100.04
First-line supervisors of production and operating worker (33-1039)	$37.72	$75.44
File clerk (43-4071)	$23.66	$47.32
Plant and system operators (51-8000)	$27.80	$55.60
Helpers—Production workers (51-9198)	$18.51	$37.02

Note: The six-digit code for each Bureau of Labor Statistics Employee Type is the Standard Occupation Classification System (SOC). A list of SOC codes can be found here: https://www.bls.gov/oes/2022/may/naics4_325400.htm

Table 4. Facility Count (ERG Table 2-26)

Entity	Original Manufacturers			Downstream Persons and Entities (Not Engaged in Homecare)			Downstream Persons and Entities (Engaged in Homecare)			Total		
	Small	Large	All	Small	Large	All	Small	Large	All	Small	Large	All
Total Facilities	5	311	316	504	574	1,078	191	111	302	700	996	1,696

Table 5. Quantity of Medical Gas Containers in Thousands (ERG Table 4-4)

	Oxygen	Nitrogen	Nitrous Oxide	Other Anesthesia	Medical Specialty Gases	Total
High-Pressure Cylinders						
Small and Medium Steel	8,312.8	0.0	69.7	0.0	122.5	8,505.0
Large Steel	5,733.8	175.3	409.1	58.4	116.9	6,493.5
Aluminum	17,771.0	0.0	0.0	0.0	17.8	17,788.8
Total High-Pressure Cylinders	31,817.5	175.3	478.8	58.4	257.1	32,787.3
Cryogenic Containers						
Liquid Cylinders	84.9	2.9	0.0	0.0	0.0	87.8
Small Tanks	3.3	0.0	0.0	0.0	0.0	3.3
Healthcare Reservoirs	490.0	0.0	0.0	0.0	0.0	490.0
Small Trucks	1.3	0.0	0.0	0.0	0.0	1.3
Total Cryogenic Containers	579.4	2.9	0.0	0.0	0.0	582.3
Storage and Delivery						
Bulk Tanks	24.6	1.7	0.6	0.0	0.0	26.9
Tanker Trucks	2.6	0.0	0.3	0.0	0.0	2.9
All Container Types	32,424.1	180.0	479.7	58.4	257.1	33,399.4

E. Benefits of the Rule

1. CGMP Requirements Cost Savings

a. Streamlined Inspection Due to Better Tailored Requirements

This final rule will remove or relax certain CGMP requirements that are currently applicable to medical gases under Part 211 and are not specifically tailored to medical gases. This approach is consistent with the draft policy described in the draft guidance for industry entitled *Current Good Manufacturing Practice for Medical Gases* Draft Guidance for Industry;[7] as such, we expect this effect may be small. Further, we believe that the current regulations may lead to firms' confusion with the inspection process. This rule will clarify which regulatory requirements apply to medical gases, which will streamline the inspection process.

This final rule will not include certain provisions on buildings and safety requirements, including lighting, ventilation, air filtration, air heating and cooling, plumbing, sewage and refuse, and washing and toilet facilities, while including a more limited set of sanitation and maintenance requirements.[8] Due to the significant differences between manufacturing most finished pharmaceutical products and manufacturing medical gases, we believe that not including these requirements could allow firms to reduce their time investment in these facility requirements and likely reduce inspection times.

This final rule will include more limited equipment maintenance and cleaning requirements. These requirements reflect the difference in appropriate practices for routine cleaning of equipment for medical gases.

Additional requirements codify existing practices or clarify specific requirements that are currently subject to enforcement discretion. We save a discussion of these for the qualitative benefits or additional benefits sections.

We believe removing these facility requirements, reducing equipment and cleaning requirements, and reducing sampling requirements will save an investigator 0 minutes to 15 minutes per week per firm for an annual time savings of 0 hours to 13 hours. ERG experts believe that it takes the host company twice as many person-hours as the investigator to address these requirements because the host company often requires at least double the number of people to provide the information sought (Ref. 3). Consequently, we estimate removing and relaxing these requirements will save first-line supervisors 0 hours to 26 hours annually per firm. During the records review, one or more of the host staff will be required to be present.

We believe that first-line supervisors and investigators will experience cost savings from more streamlined inspections. We use the 2022 wage rate for First-line Supervisors of

[7] Current Good Manufacturing Practice for Medical Gases Draft Guidance for Industry link: https://www.fda.gov/media/70973/download.

[8] FDA believes that lighting is sufficiently addressed in the requirements in § 213.42 to ensure that the design, space, and placement of equipment in a facility help protect against mix-ups.

Production and Operating Worker and double it for a fully-loaded wage rate of $75.44. We use the 2022 FDA-wide FTE value to estimate the fully-loaded wage rate of $142.52.

Table 6 shows the ongoing cost savings to affected entities and FDA. The estimated ongoing cost savings for firms from removing these facility requirements, reducing equipment and cleaning requirements, and reducing sampling requirements will range from $0.00 million to $3.33 million with a primary estimate of $1.62 million. The estimated ongoing cost savings for FDA from removing buildings and facilities requirements will range from $0.00 million to $3.14 million with a primary estimate of $1.57 million.[9]

Table 6. Cost Savings Streamlining the Inspection Process

	Original Manufacturers	**Downstream Persons and Entities Not Engaged in Homecare**	**Downstream Persons and Entities Engaged in Homecare**	**Total**
Affected entities	316	1,078	302	1,696
Wage rate (first-line supervisor)	$75.44	$75.44	$75.44	$75.44
FDA-wide FTE	$142.52	$142.52	$142.52	$142.52
Reduction in inspection time low (hours)	0	0	0	0
Reduction in inspection time high (hours)	26	26	26	26
Firms ongoing cost savings (millions)				
Total ongoing cost savings (low)	$0.00	$0.00	$0.00	$0.00
Total ongoing cost savings (high)	$0.62	$2.11	$0.59	$3.33
FDA ongoing cost savings (millions)				
Total ongoing cost savings (low)	$0.00	$0.00	$0.00	$0.00
Total ongoing cost savings (high)	$0.59	$2.00	$0.56	$3.14

b. Removes First-in, First-out Requirement for Medical Gases

This final rule will not include the first-in, first-out requirement for medical gases. These gases are not expected to expire or degrade over long periods of time under ordinary storage conditions. Consequently, FDA does not believe it is necessary to require using the oldest approved stock first or require retesting products that have been stored for long periods of time or exposed to air.

We believe not including the first-in, first-out requirement may lead to small time savings for Helpers who will have more flexibility in which containers of medical gas they choose to use. We believe not including this requirement may save firms between 0 minutes and 15 minutes per week, which translates to 0 hours to 13 hours per year.

[9] Many estimates throughout this report lent well to approximating upper and lower bound benefits. Consequently, we approximate the primary estimate by taking a mean and assuming a triangular distribution of benefit across the upper and lower bound where not otherwise specified.

We use the 2022 wage rate for Helpers and double it for a fully-loaded wage rate of $37.02. Table 7 shows the ongoing cost savings of removing the first-in, first-out requirement for medical gas containers. The ongoing cost savings from not including first-in, first-out ranges from $0.00 million to $0.82 million with a primary estimate of $0.41 million.

Table 7. Cost Savings Removing First-in, First-Out Requirement

	Original Manufacturers	Downstream Persons and Entities Not Engaged in Homecare	Downstream Persons and Entities Engaged in Homecare	Total
Affected entities	316	1,078	302	1,696
Wage rate (helper)	$37.02	$37.02	$37.02	$37.02
Reduction in time no first in, first out low (hours)	0	0	0	0
Reduction in time no first in, first out high (hours)	13	13	13	13
Total ongoing costs (millions)				
Total ongoing cost savings (low)	$0.00	$0.00	$0.00	$0.00
Total ongoing cost savings (high)	$0.15	$0.52	$0.15	$0.82

c. Allows Reuse of Labels

This final rule will allow the reuse of labels if they are legible and properly affixed to the container. Medical gas containers, unlike most drug containers, are reused many times and made of extremely durable materials. The reuse of labels is not addressed in current regulations. We believe that industry is currently largely reusing labels that are legible and properly affixed.

We believe some firms may be discarding legible and properly affixed labels due to the lack of inclusion of specific requirements for the reuse of labels under the current regulations. However, we believe that discarding labels that are legible and properly affixed is rare and include the possibility that no firms are doing so. We estimate that 0 percent to 1 percent of all legible and properly affixed medical gas labels are discarded each year. We believe that adding this requirement may reduce this to 0 percent.

We use the primary per label estimate of $0.25 from the labeling cost model (Table 12). The labeling cost model is discussed further in II.F.2 Labeling Costs. Table 8 shows the ongoing cost savings from allowing the reuse of labels. The estimated ongoing cost savings for firms from allowing the reuse of labels will range from $0.00 million to $0.08 million with a primary estimate of $0.04 million.

Table 8. Cost Savings from Allowing the Reuse of Labels

	Oxygen	Nitrogen	Nitrous Oxide	Other Anesthesia	Medical Specialty Gases	Total
All container types	32,424.1	180.0	479.7	58.4	257.1	33,399.4
Legible label discard rate (low)	0%	0%	0%	0%	0%	0%
Legible label discard rate (high)	1%	1%	1%	1%	1%	1%
Cost per label	$0.25	$0.25	$0.25	$0.25	$0.25	$0.25
Ongoing cost savings (millions)						
Ongoing cost savings (low)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Ongoing cost savings (high)	$0.08	$0.00	$0.00	$0.00	$0.00	$0.08

d. Flexibility in Curbside Filling Written Permission

This final rule will allow production and control records at a delivery site to have a quality unit review within one business day of transfer of a medical gas from one container to another. Current regulations require the quality unit to review production records for errors or unexplained discrepancies prior to batch release. In practice, this quality unit review requires a sign-off from the manager. This requirement will allow the quality unit review to occur within one day of a transfer from one container to another (this is sometimes referred to as “transfilling” or “curbside filling”) instead of needing prior approval.

We believe that allowing quality unit managers to sign off on all curbside filling within one day of the filling will save time for both the quality unit and the delivery technician relative to sign-off through multiple phone calls throughout the day. We estimate that this requirement may save first-line supervisors and Helpers each 0 minutes to 30 minutes per week for annual time savings of 0 hours to 26 hours. We believe that it is likely that many firms are noncompliant with the current requirement. We estimate only 0 percent to 10 percent of firms are currently receiving prior approval for curbside filling.

We use the 2022 wage rate for First-line Supervisors of Production and Operating Worker and double it for a fully-loaded wage rate of $75.44. We use the 2022 wage rate for Helpers and double it for a fully-loaded wage rate of $37.02. shows the ongoing cost savings of allowing quality unit managers to sign off on curbside filling within one day of the filling. The cost savings of this added flexibility range from $0.00 million to $0.40 million with a primary estimate of $0.20 million.

Table 9. Cost Savings from Flexibility in Curbside Filling Written Permission

	Downstream Persons and Entities Not Engaged in Homecare	Downstream Persons and Entities Engaged in Homecare	Total
Affected entities	1,078	302	1,380
Compliance (low)	0%	0%	0%
Compliance (high)	10%	10%	10%
Time saving removing prior approval low (hours)	0	0	0
Time saving removing prior approval high (hours)	26	26	26
Wage rate (first-line supervisor)	$75.44	$75.44	$75.44
Wage-rate (helper)	$37.02	$37.02	$37.02
Ongoing cost savings (millions)			
Ongoing cost savings (low)	$0.00	$0.00	$0.00
Ongoing cost savings (high)	$0.32	$0.09	$0.40

2. Summary of Quantitative Cost Savings

The cost savings of this final rule will be due to relaxing and removing certain CGMP requirements for medical gases. The primary cost savings are from streamlining the inspection process. Except for the provisions that amend 21 CFR part 4, which will go into effect on February 2, 2026,[10] this rule has an effective date one and a half years after publication; consequently, each cost savings has been discounted by one and a half years at the corresponding discount rate.

In Table 10, we estimate the total annualized quantified cost savings of the final rule over a 10-year timeline. The annualized benefits will range from $0.00 million to $7.02 million with a primary estimate of $3.51 million at a 7 percent discount rate.

Table 10. Summary of Quantitative Cost Savings (in $ Millions)

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)
Streamlining Inspection Process	$1.50	$0.00	$3.01
Removing First In, First Out Requirements	$0.37	$0.00	$0.74
Allowing Reuse of Labels	$0.04	$0.00	$0.07
Flexibility in Curbside Filling Written Permission	$0.18	$0.00	$0.36
Gov: Streamlining Inspection Process	$1.42	$0.00	$2.84
Total Cost Savings			

[10] Because the final rule's changes to 21 CFR part 4 are minimal in scope and substance, and because the February 2, 2026, effective date is close in time to the anticipated effective date for the remainder of the final rule, we estimate that the different effective date for the provisions that amend 21 CFR part 4 will not affect the costs or benefits of the final rule.

Total Cost Savings	$3.51	$0.00	$7.02

3. Qualitative Benefits: Labeling

This final rule will require that labeling on oxygen final use containers include both of the statements “no smoking” and “no vaping” and a graphic symbol conveying that smoking, vaping, and open flames near oxygen are dangerous. Fires caused by smoking in the vicinity of an oxygen tank in operation are common. According to a BPR Medical study, there were an estimated 164 deaths and 190 injuries (71 serious and 119 minor) from 311 separate fires involving home medical oxygen therapy over a 20-month period ending in August 2019.[11] This translates to approximately 187 fires involving home medical oxygen therapy, leading to 98 deaths annually and 114 injuries (43 serious and 71 minor) annually. Additional costs of these fires include the medical treatment costs of both the fatal and non-fatal injuries, the cost of the fire damage to residences, and the value of the lives lost due to the fires.

We cannot confidently predict the size of the behavioral change due to the labeling requirements, but we expect that it will result in a small reduction in fires in the vicinity of oxygen containers in operation. Consequently, a reduction in fires may result in benefits from a reduction in medical treatment costs, fire damage costs to residences, and potentially, lives lost.

4. Qualitative Cost Savings: CGMP Requirements

a. Increased Flexibility in Testing of Components, Containers, and Closures

The final rule’s testing requirements provide the option that recipients of medical gases can obtain a statement of verification that the supplier’s component, container, or closure meets specifications that the firm establishes, and that the recipient maintains a program to ensure the reliability of the supplier’s capabilities. This option is likely less burdensome than the current requirement, a report of analysis and appropriate verification of the suppliers’ test results. This program is more consistent with current industry practice and will likely lead to some time savings and a reduced testing burden.

b. Removes Calculation of Yield Requirement

This final rule will not require the calculation of yield and percentages of theoretical yield at appropriate phases of manufacturing, processing, packaging, or holding of the drug product.

[11] BPR study source: http://www.firebreaks.info/wp-content/uploads/2019/09/BPR-Study-Report-2019-v5.1.pdf.

Gas loss is expected during manufacturing and can be variable even under normal operating conditions. The requirements in part 213 are sufficient to determine that the medical gas in the container is the amount and type indicated by the label and required by the final product specifications. Consequently, adding a similar calculation of yield requirement to the requirement in Part 211 would potentially be burdensome and would not provide valuable information to manufacturers or us.

c. Allows Salvaging of Medical Gases

This final rule will allow medical gases in containers that have been subjected to improper storage conditions to be salvaged unless their containers have been subjected to adverse conditions that impact the identity, strength, quality, or purity of the product or integrity of the container closure. Under current regulations, these gases subject to improper storage conditions may not be salvaged. In some instances, such as weather-related cases, the robust packaging of these gases in metal cylinders could provide a sufficient safety margin for salvaging. We believe that manufacturers, processors, packagers, and holders of medical gases are largely noncompliant with the current regulation. However, the more flexible requirement will likely lead to small cost savings for those that were compliant.

5. Potential Additional Cost Savings

a. Removes Requirement that Labels Not Be Susceptible to Becoming Worn or Detached

This final rule will not include the requirement that the labeling not be susceptible to becoming worn or inadvertently detached during normal use. Since medical gas containers are reused and distributed among multiple entities, FDA believes that labeling inspection requirements in this rulemaking will be sufficient to assure that labeling that enters into distribution is complete, accurate, durable, and readable, and that unsuitable labeling is replaced.

The current industry practice for medical gases is that labels are reused. Consequently, labels over their lifetime will become detached or worn, at which point they will need to be replaced under current regulation. This final rule will allow the reuse of labels as long as they are legible and properly affixed to the container. Allowing the reuse of labels may reduce the frequency at which labels are replaced. However, we believe that medical gas manufacturers, processors, packagers, and holders are largely reusing labels and that the cost savings will likely be small if any.

b. Clarifications for the Certification Request Process

This final rule will clarify the certification request process through several new provisions. We believe that most firms are aware of the certification process, but we believe that in some cases when firms are not, this clarification may save firms resources in navigating the

process and may also save FDA resources by reducing the number of requests for clarification from industry. We believe the time saving for including this requirement will be small if any.

c. Clarification of Events that Do Not Require Adverse Event Reports

This final rule will include an exception that adverse event reports are not required for (a) reports of the death of a patient or animal who was administered oxygen, unless the applicant or nonapplicant becomes aware of evidence that the death was caused by the administration of oxygen, or (b) fires associated with the administration of oxygen that do not include an adverse event experienced by the patient or animal. We believe that such reports are not necessary because they are unlikely to reflect an underlying safety signal or provide new information to the Agency. This exception may save firms resources from not submitting the reports and may save FDA resources from not reviewing the reports. We believe the resource savings from this clarification will be small if any.

F. Costs of the Rule

1. Administrative Costs

All entities affected by this final rule will incur a one-time cost for reading and understanding this rule. We use the time required to complete this activity as an estimate of the burden of this activity. To understand this rule, affected entities will read the preamble and codified which together contain around 40,000 words. Following Health and Human Services guidelines, we calculate the cost of reading and understanding this rule assuming industry reviewers read at the average adult reading speed of approximately 200 words to 250 words per minute.[12] We estimate the time to read the regulation is 2.7 hours to 3.3 hours per person. We assume that 1 to 3 people read the rule at each affected entity.

To value the time for complying with reading and understanding the rule, we use composite wages calculated from the Bureau of Labor Statistics' national industry-specific occupational employment and wage estimates for the pharmaceutical and medical manufacturing industry (Ref. 4).[13] To value the time associated with reading and understanding the rule, we use a mix of 50 percent management occupations (occupation code 11-0000) and 50 percent legal occupations (occupation code 23-0000). This mix yields a composite wage of $88.95.[14] We double this to account for benefits and overhead, yielding a fully-loaded wage rate of $177.89.

[12] Guidelines available at: https://aspe.hhs.gov/system/files/pdf/242926/HHS_RIAGuidance.pdf.
[13] May 2020 National Industry-Specific Occupational Employment and Wage Estimates for NAICS 325400 – Pharmaceutical and Medicine Manufacturing. We use estimates from NAICS 325400 because detailed estimates for NAICS 325412 are not available. Data available at https://www.bls.gov/oes/2020/may/naics4_325400.htm.
[14] The calculation is 0.5 x ($94.05) + 0.5 x ($83.84) = $88.95.

We estimate the cost for one person to read the rule ranges from $474 to $593. For each affected entity, these costs range from $474 to $1,779. We estimate that the final rule will affect 1,696 entities. Table 11 summarizes the one-time cost of reading and understanding this rule. The estimated one-time cost for reading and understanding the rule range from $0.80 million to $3.02 million.

Table 11. One-Time Costs for Reading and Understanding the Rule

	Low	Primary	High
Reading time (hours)	2.7	3.0	3.3
Wage (composite)	$177.89	$177.89	$177.89
Affected entities	1,696	1,696	1,696
Number of people reading per entity	1	2	3
One-time cost (millions)			
One-time cost	$0.80	$1.79	$3.02

2. Labeling Costs

The final rule will require that the statements “no smoking” and “no vaping” and a graphic symbol conveying that smoking, vaping, and open flames near oxygen are dangerous will be prominently displayed. This will require a one-time cost to design, create, and attach the new label to medical oxygen containers.

The 2020 ERG report (Ref. 2) estimates that about 22.57 million high-pressure cylinders are used in medical markets. Further, it estimates that oxygen accounts for 89 percent to 100 percent of container contents. We use the midpoint of this range, 95 percent, to produce an estimate of about 21.44 million high-pressure oxygen cylinders used in medical markets. We add to this the ERG estimates of about 88,000 cryogenic containers of oxygen (both liquid containers and small tanks) multiplied by the same 95 percent to produce an estimated 84,000 liquid oxygen containers used in medical markets.[15] The sum of the high-pressure oxygen containers and cryogenic oxygen containers is about 21.53 million oxygen containers for medical use. We exclude from our count the non-medical market of both high-pressure and cryogenic oxygen containers.

We use the 2014 Labeling Cost Model (LCM) Report from RTI, Inc. (the RTI Report) (Ref. 5) to estimate the one-time cost of this new labeling requirement. Table 4-11 in the RTI Report estimates sticker costs on a per sales unit basis for labeling costs that will be incurred over a time period for which normal labeling changes could not easily be made. These costs are estimated at $0.015 to $0.15. Further, the LCM estimates the application time to range from 0.2

[15] We did not include ERG’s estimate of cryogenic containers of oxygen for medical use in healthcare reservoirs and small trucks because we do not expect these containers to be located in the vicinity of the patient using the medical oxygen and therefore would not be required to display the no smoking, no vaping, and graphic warning symbol statement.

minutes to 0.6 minutes for each labeling sticker, which equates to 100 to 300 labels applied per hour by industry personnel. We note that the size difference between a typical food, medical product, or personal healthcare product (on which the LCM is based) and the much larger oxygen containers implies that the time that will be required to add the statements “no smoking” and “no vaping” and a graphic symbol conveying that smoking, vaping, and open flames near oxygen are dangerous will be closer to the upper range estimate of 0.6 minutes each.

We updated the LCM report to include the 2022 Helper wage rate using the Helpers and double it for a fully-loaded wage rate of $37.02. Table 12 shows the resulting high cost per label is $0.52.

Table 12. Per Label Cost

	Low	**Primary**	**High**
Application time (minutes)	0.2	0.3	0.6
Wage rate (helper)	$37.02	$37.02	$37.02
Cost per application	$0.12	$0.19	$0.37
Sticker cost	$0.02	$0.06	$0.15
Total Cost			
Total cost	$0.14	$0.25	$0.52

We use the 2014 LCM report to estimate the cost to attach the statements “no smoking” and “no vaping” and a graphic symbol conveying that smoking, vaping, and open flames near oxygen are dangerous. We use the high estimate of the total per label cost to account for the added time it will take to attach the “no smoking” statement, “no vaping” statement, and graphic warning symbol and the added cost of printing a larger label. We use the 2022 wage rate for Helpers and double it for a fully-loaded wage rate of $37.02. Table 13 shows the one-time cost of adding a “no smoking” statement, a “no vaping” statement, and a graphic warning symbol to medical market containers. The estimated one-time costs for labeling due to these requirements range from $10.49 to $11.79 million with a primary estimate of $11.20 million.

The total cost estimate above assumes that a relatively simple label containing the graphic warning and statement will be designed, possibly by an industry association, and offered for use to all industry members. We do not include the one-time costs for this effort, but acknowledge that these costs, even if small, will be positive. Further, we expect that the “no smoking” statement, the “no vaping” statement, and graphic warning symbol will not need to be replaced for many years. We have not included an additional cost for the discounted annualized cost of replacement labels but acknowledge that it will be positive.

Table 13. Costs from Adding No Smoking and No Vaping Label

	Low	Primary	High
Cost per sticker	$0.46	$0.46	$0.46
Wage rate (helper)	$37.02	$37.02	$37.02
Medical markets (total containers)	22,660,000	22,660,000	22,660,000
Medical oxygen (% of total containers)	89%	95%	100%
Medical markets (total oxygen containers)	20,167,578	21,527,190	22,660,200
Labor hours	201,676	215,272	226,602
One-time cost (millions)			
Applying stickers	$7.47	$7.97	$8.39
Cost of stickers	$3.03	$3.23	$3.40
Total cost	$10.49	$11.20	$11.79

3. Full Compliance CGMP Requirements Costs

There are several Part 211 sections that currently apply to medical gases that have parallel or have similar language in Part 213. We believe that this final rule will clarify that these regulations apply to medical gases and may result in 100 percent compliance from industry. We use 2020 ERG report (Ref. 2) estimates where there is noncompliance with Part 211 and ERG's noncompliance estimates (ERG Table 5-1) to estimate the added burden on industry of moving to full compliance with these specific sections.

a. Full Compliance Quality Units

Under current regulations, the responsibilities of the quality unit require facilities to: (1) establish a quality control unit, (2) establish and follow written procedures for the quality unit, and (3) provide adequate laboratory facilities. The new requirements are similar in scope with one notable change. FDA will use the term "quality unit" instead of the previous term "quality control unit." ERG interviews with the industry indicate that most medical gas facilities have quality units and written procedures that detail those units' responsibilities. However, ERG estimates the range of baseline compliance is between 85 to 100 percent for small firms and 100 percent for large firms. This translates to 0 to 6 percent noncompliance for all firms for quality units.

ERG's industry expert suggested that firms that are not fully compliant with current quality unit requirements will likely hire a consultant for an estimated one-time cost of $4,000 to help set up a quality unit, provide a procedure manual, assist with other duties such as registration and listing, and provide training. This would be the least costly option. For a small firm, the research into requirements and the procedure development itself would take a significant number of labor hours and therefore cost more.

In addition, based on input from ERG's industry expert, ongoing quality unit activities resulting from the new quality unit might take an additional hour per week, or 52 hours per year, for a small firm. We use the 2022 wage rate for General and Operations Managers. The 2022 wage rate is $89.21, and we double it to account for benefits and other overhead costs for a fully-loaded wage rate of $178.42. We multiply the annual time estimate by the fully-loaded wage rate for an ongoing cost of approximately $9,000 to implement and document the activity. These estimates can be found in Table 14.

Table 14. Quality Unit Costs (ERG Table 6-2)

Costs	Fee/Labor Hours		Wages	Unit Costs	
	Small	Large		Small	Large
One-Time Costs (per firm) – Develop New Procedures					
Consultant fee to set up QU and develop procedures	$4,000	NA	NA	$4,000	$0
Total unit cost				$4,000	$0
Ongoing costs (per firm) – Implement and Document Activity					
One hour per week for general manager	52	NA	$178	$9,278	$0
Total unit cost				$9,278	$0

Table 15 shows the one-time costs of hiring a consultant and the ongoing costs of implementing and documenting the quality unit for noncompliant small firms. The total one-time cost for the quality unit ranges from $0.00 million to $0.42 million with a primary estimate of $0.21 million. The total ongoing costs range from $0.00 million to $0.97 million with a primary estimate of $0.49 million.

Table 15. Costs of Full Compliance with the Quality Unit Requirement

	Original Manufacturers	Downstream Persons and Entities Not Engaged in Homecare	Downstream Persons and Entities Engaged in Homecare	Total
Affected entities	316	1,078	302	1,696
Noncompliance quality unit (low)	0%	0%	0%	0%
Noncompliance quality unit (high)	~0%	7%	9%	6%
One-time cost (millions)				
Consulting fee	$4,000.00	$4,000.00	$4,000.00	$4,000.00
Total one-time cost (low)	$0.00	$0.00	$0.00	$0.00
Total one-time cost (high)	$0.00	$0.30	$0.11	$0.42
Ongoing costs (millions)				
Time per facility (hours)	52	52	52	52
Wage rate (manager)	$178.42	$178.42	$178.42	$178.42
Total ongoing cost (low)	$0.00	$0.00	$0.00	$0.00
Total ongoing cost (high)	$0.01	$0.70	$0.27	$0.97

b. Full Compliance Personnel Qualifications and Responsibilities

Under the current regulations all personnel are required to have the education, training, and experience necessary to perform their duties. This final rule will add a requirement that manufacturers maintain written documentation demonstrating employees' accomplishment of training, including the date, type of training, and training results such as test results. We will address that cost in section II.F.4.a. Here we will only address the costs of firms moving to full compliance.

Based on consultant input, ERG estimates 100 percent compliance with annual training requirements for large firms and 50 to 100 percent compliance for small firms. This translates to 0 to 21 percent noncompliance for all firms.

For firms that are currently noncompliant we assume an ongoing cost for annual training. Using ERG estimates we assume that all employees of establishments currently subject to Part 211 will need to take the training, including all quality control, production, and delivery personnel. Small firms can take advantage of available online training tutorials that include an examination, although the ERG consultant reports that in-person training is also common. Given that the least costly option is to utilize online training, ERG estimates training costs based on fees for a one-day online course from a private firm, which provides finished pharmaceuticals FDA-CGMP training for $339.96 for 10 employees. ERG estimates the typical small facility will train 5 employees and one supervisor. ERG assumes that the training requires eight hours and estimates training for small firms might average around $3,000 per firm (see Table 16), including maintaining the records of this training.

Table 16. Per Firm Cost of Training for Personnel Qualifications and Responsibilities

Ongoing Costs (per Firm)	Labor Hours		Wages/Cost per Unit	Unit Costs	
	Small	Large		Small	Large
Annual Training					
Fee for online course for average firm	NA	NA	$340	$340	$0
Eight hours of training for one plant supervisor	8	NA	$75	$604	$0
Eight hours of training for 5 plant and system operators	40	NA	$56	$2,224	$0
Total cost					
Total unit cost				$3,167	$0

Table 17 shows the costs of small firms becoming compliant with the personnel qualifications and responsibilities. We use ERG's estimate of an annual cost to small firms of $3,167.48 to estimate the total ongoing cost for small firms that are currently noncompliant with current personnel qualifications and responsibilities requirements. The total ongoing costs range from $0.00 million to $1.11 million with a primary estimate of $0.55 million.

Table 17. Cost of Full Compliance with Personnel Qualifications and Responsibilities

	Original Manufacturers	Downstream Persons and Entities Not Engaged in Homecare	Downstream Persons and Entities Engaged in Homecare	Total
Affected Entities	316	1,078	302	1,696
Percent noncompliant establishments (low)	0%	0%	0%	0%
Percent noncompliant establishments (high)	1%	23%	32%	21%
Noncompliant establishments count (low)	0	0	0	0
Noncompliant establishments count (high)	2	252	96	350
Cost (per firm)	$3,167.48	$3,167.48	$3,167.48	$3,167.48
Ongoing costs (millions)				
Total ongoing cost (low)	$0.00	$0.00	$0.00	$0.00
Total ongoing cost (high)	$0.01	$0.80	$0.30	$1.11

4. CGMP Requirements Costs

a. Written Procedures for Personnel Qualifications and Responsibilities

This final rule will require manufacturers maintain written documentation demonstrating employees' accomplishment of training, including the date, type of training, and results (e.g., test results).

SMEs estimate that maintaining documentation demonstrating employees' accomplishments of training will take 2.5 minutes to 5 minutes per employee per year. The 2020 ERG report (Ref. 2) estimates that small firms will have 6 employees taking training and will need training documentation (ERG Table 6-4). We double ERG's estimate for number of employees taking trainings for large firms for a total of 12 employees. The estimates in Table 18 are the average number of employees by entity type weighted by the ratio of small firms to large firms. A detailed table on number of affected entities can be found in Table 5.

We use the 2022 wage rate for File Clerk and double it for a fully-loaded wage rate of $47.32. Table 18 shows the ongoing cost of requiring documentation of written procedures for personnel qualifications and responsibilities. The total ongoing costs range from $0.03 million to $0.06 million with a primary estimate of $0.05 million. Because we recognize that most firms already adequately train their employees, and their personnel records will demonstrate this training, we believe our estimate reflects an upper bound cost estimate.

Table 18. Costs of Written Procedures for Personnel Qualifications and Responsibilities

	Original Manufacturers	**Downstream Persons and Entities Not Engaged in Homecare**	**Downstream Persons and Entities Engaged in Homecare**	**Total**
Affected entities	316	1,078	302	1,696
Number of employees (per firm)	12	9	10	10
Time per document low (minutes)	2.5	2.5	2.5	2.5
Time per document high (minutes)	5	5	5	5
Wage rate (file clerk)	$47.32	$47.32	$47.32	$47.32
Ongoing costs (millions)				
Total ongoing cost (low)	$0.01	$0.02	$0.00	$0.03
Total ongoing cost (high)	$0.01	$0.03	$0.01	$0.06

b. Rejected Containers Must be Documented and Assessed

This final rule will add the requirement that rejected components, incoming DMGs, and medical gas containers and closures must be documented and assessed. We use the ERG estimates of 33.4 million DMG containers. We estimate a 0 to 0.1 percent rejection rate. We estimate it will take 5 minutes to document and assess components, containers, and closures.

We use the 2022 wage rate for General and Operations Managers and double it for a fully-loaded wage rate of $178.42. Table 19 shows the ongoing cost of the added requirement

that rejected DMG containers must be documented and tracked. The total ongoing costs range from $0.00 million to $0.50 million with a primary estimate of $0.25 million.

Table 19. Costs from Documenting and Assessing Rejected Containers

	Oxygen	Nitrogen	Nitrous Oxide	Other Anesthesia	Medical Specialty Gases	Total
All Container Types (thousands)	32,424.12	179.97	479.72	58.44	257.14	33,399.40
Percentage of containers rejected (low)	0%	0%	0%	0%	0%	0%
Percentage of containers rejected (high)	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Time to document and track (minutes)	5	5	5	5	5	5
Wage rate	$178.42	$178.42	$178.42	$178.42	$178.42	$178.42
Ongoing costs (millions)						
Ongoing cost (low)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Ongoing cost (high	$0.48	$0.00	$0.01	$0.00	$0.00	$0.50

c. Portable Cryogenic Containers Working Gauge Requirement

This final rule will add the requirement that all portable cryogenic containers for use by individual patients (including portable liquid oxygen units) must have a working gauge sufficient to assist the user in determining whether the container has an adequate supply of medical gas for continued use.[16] We use the 2020 ERG report estimate of 490,000 portable cryogenic containers used for home reservoirs. We believe that there is already some compliance with this requirement. SMEs estimate that 50 percent of portable cryogenic containers already have working gauges and that 12 percent of portable cryogenic containers are rotated out each year. They further assume that the oldest portable cryogenic containers are being rotated out and that new containers are now being manufactured with working gauges. Except for the provisions that amend 21 CFR part 4, this rule will have a 1.5-year effective date so this requirement will only affect the current containers that do not have a working gauge after 1.5 years.

SMEs estimate the price of a working gauge is approximately $20. We use the estimate of the working gauge as a lower bound estimate. We assume that there may be some additional assembly costs for new containers that have working gauges up to an additional $20. We therefore use a price range of $20 to $40.

[16] 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 cares, or small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined at 21 CFR 868.5655).

Table 20 shows the one-time cost of adding working gauges to portable cryogenic containers. We estimate the total one-time cost to range from $1.72 million to $9.70 million with a primary estimate of $4.70 million.

Table 20. Costs of Adding Working Gauges

	Low	Primary	High
Number of cryogenic containers	490,000	490,000	490,000
Current compliance	60%	50%	40%
Percent newly compliant annually	15%	12%	7%
Number of years to effectiveness date	1.5	1.5	1.5
Percent that will voluntarily comply by effective date	83%	68%	51%
Percent noncompliant by effective date	18%	32%	49%
Estimated number of containers requiring gauges	85,750	156,800	242,550
Cost of gauge (per unit)	$20	$30	$40
One-time cost (millions)			
One-time cost of adding gauges	$1.72	$4.70	$9.70

5. Postmarketing Safety Reporting Costs

Under current requirements, adverse event reports (AERs) must be reported for all adverse drug events for animals. However, the requirement makes no specific mention of AERs for medical gases. The FDA is currently receiving no AERs for animals from applicants and nonapplicants of medical gases. This final rule clarifies that AERs for animals are required from applicants and nonapplicants of medical gases.

SMEs from the Center for Veterinary Medicine (CVM) estimate that we will receive 5 to 10 AERs annually for animals from applicants and nonapplicants of medical gases as a result of this clarification. We use these as our lower and upper bound estimates and we take the average, 7.5, as our primary estimate. A 2023 memorandum to file (Ref. 6) summarizes relevant information from a 2019 ERG report on postmarketing safety reporting. The report estimates that it will take between 2 and 4 hours of professional time and 1 hour of a practitioner's time per report. As we have noted in the preamble to the final rule, we do not believe that applicants or nonapplicants will need to utilize staff with medical expertise in preparing AERs for DMGs. Therefore, the 1 hour of practitioner's time is not applicable to DMG safety reporting.

To estimate the burden for professional time we use the 2022 wage rate for Business Operations Specialists and double it for a fully-loaded wage rate of $91.10. Under these assumptions the cost to prepare an AER for animals from applicants and nonapplicants of medical gases will range from $182.20 to $364.40 with a primary estimate of $273.30. The total ongoing costs range from $911 to $3,644 with a primary estimate of $2,050. These estimates are reported in .

Table 21. Adverse Event Reports for Animals

	Low	Primary	High
Number of added adverse event reports	5	7.5	10
Time per adverse event report	4	4	4
Wage rate (professional)	$91.10	$91.10	$91.10
Ongoing costs			
Cost AERs for animals	$911.00	$2,049.75	$3,644.00

6. Certification Costs

a. Submission for a Certification Request

This final rule outlines the requirements for submission of a certification request. Recommendations for how to request a certification are currently included in the draft guidance for industry *Certification Process for Designated Medical Gases.*[17] We have received 98 certification requests through the end of 2023 from 57 distinct entities.[18] Based on the average receipts from 2018-2020, SMEs estimate that 5 additional firms will submit certification requests as a result of this rulemaking.

A certification request is a submission requesting to introduce or deliver for introduction into interstate commerce a DMG. Once a certification request is granted, a DMG is deemed to have in effect an approved application. Manufacturers of DMGs will be required to submit a certification request for each DMG that they produce. The number of requests for certification each firm must submit will range from 1 to 7, which represents the current range of DMGs that could be introduced into interstate commerce via certification request. SMEs estimate that a firm required to submit a certification request will submit 5 certification requests on average.

We believe that submitting a certification request will take a manager approximately 3 hours to perform. We use the 2022 wage rate for General and Operations Managers and double it for a fully-loaded wage rate of $178.42.

Table 22 shows the one-time cost of submitting a certification request for firms who have not already submitted that request to us. The estimated one-time costs of submitting a certification request range from $2,676 to $18,734 with a primary estimate of $13,382.

Table 22. Costs of Submitting Certification Requests

	Low	Primary	High
Affected entities	5	5	5
Certification requests (per firm)	1	5	7
Certification requests submitted	5	25	35

[17] Certification Process for Designated Medical Gases; Revised Draft Guidance available at: https://www.fda.gov/media/85013/download.

[18] Certifications granted as of 12-31-2023

Wage rate (manager)	$178.42	$178.42	$178.42
Time per certification (hours)	3	3	3
One-time costs			
Cost certification request	$2,676.30	$13,381.50	$18,734.10

b. FDA Must Create Certification Request Form

This final rule will require us to create the form for certification requests. SMEs estimate between 4 and 14 FDA employees will work on preparing the certification request form. They estimate 4 to 12 hours per person to create and approve the form.

We use 2022 FDA-wide FTE value to estimate the fully-loaded wage rate of $142.52. Table Table 23 shows the one-time costs of FDA designing a certification request form. The total one-time cost of the FDA forms committee creating this form will range from $2,280 to $23,944 with a primary estimate of $10,262.

Table 23. Cost of Creating Certification Request Form

	Low	Primary	High
Number of non-managers on forms committee	4	9	14
FDA-wide FTE	$142.52	$142.52	$142.52
Hours per individual	4	8	12
One-time cost			
One-time cost of approving form	$2,280.38	$10,261.73	$23,944.04

c. Annual Report for Granted Certifications

This final rule will require manufacturers to submit an annual report each year within 60 calendar days of the new calendar year. We have received 98 certification requests through the end of 2023 and anticipate 25 additional certification requests as a result of this rulemaking. This regulation for the annual report requires less information than under the current regulation. However, because FDA has exercised enforcement discretion with respect to the submission of annual reports under § 314.81(b)(2), as explained in FDA's Compliance Program Guidance Manual 7356.002E, compliance with this requirement represents an added cost to firms submitting annual reports for granted certifications.[19]

We believe that submitting an annual report on granted certifications will take a manager approximately 1 to 3 hours to perform. We use the 2022 wage rate for General and Operations Managers and double it for a fully-loaded wage rate of $178.42. Table 24 shows the ongoing cost

[19] FDA, Compliance Program Guidance Manual 7356.002E, "Compressed Medical Gases," March 15, 2015, available at https://www.fda.gov/media/75194/download.

of submitting annual reports. The estimated ongoing costs of submitting annual reports range from $0.02 million to $0.07 million with a primary estimate of $0.04 million.

Table 24. Cost of Submitting Annual Reports

	Low	Primary	High
Annual Reports	123	123	123
Wage rate (manager)	$178.42	$178.42	$178.42
Time per certification (hours)	1	2	3
Ongoing costs (millions)			
Cost certification request	$0.02	$0.04	$0.07

d. FDA Must Create Annual Report Form for Granted Certifications

This final rule will require us to create the form for annual reports. SMEs estimate between 4 and 14 FDA employees will work on preparing the annual report form. They estimate 4 to 12 hours per person to create and approve the form.

We use 2022 FDA-wide FTE value to estimate the fully-loaded wage rate of $142.52. Table 25 shows the one-time costs of FDA designing an annual report form. The total one-time cost of the FDA forms committee creating this form will range from $2,280 to $23,944 with a primary estimate of $10,262.

Table 25. Cost of Creating Annual Report for Granting Certification Form

	Low	Primary	High
Number of non-managers on forms committee	4	9	14
FDA-wide FTE	$142.52	$142.52	$142.52
Hours per individual	4	8	12
One-time cost			
One-time cost of approving form	$2,280.38	$10,261.73	$23,944.04

7. Potential Costs

a. Full Compliance Consultants

Under the current regulations, consultants must have significant education, training, and experience. However, ERG estimates only 50 percent baseline compliance with this requirement at small firms. Firms typically meet it by keeping resumes on file for any consultants used. Given

that use of consultants will vary and the labor hours associated with this requirement on behalf of the firm will be negligible, ERG did not estimate a unit cost for this requirement.

b. Qualitative Cost of Relabeling Medical Air Containers

The Compressed Gas Association (CGA) recommends that their members include a statement on their medical air labeling saying "providing medical air may be used for breathing support without a prescription when used by properly trained personnel, and for all other medical applications a prescription is required" (Ref. 7). The Agency remains unaware of any uses for medical air that would be appropriate for nonprescription use, and no new information supporting such uses has been provided since the Agency last addressed this issue in a petition response to CGA (Ref. 8). This final rule will require that medical air be prescribed and only administered by, or under the supervision of, a licensed practitioner. As a result, industry will need to replace labels containing the above statement recommended by CGA.

The CGA 2018 Report does note "information contained in this document was obtained from sources believed to be reliable and is based on technical information and experience currently available from members of the Compressed Gas Association, Inc. and others." As a result, we do not know what percentage of entities are following the CGA 2018 Report standards nor did the ERG 2020 Report (Ref. 2) provide a count of medical gas containers. Without this information we cannot accurately estimate this potential burden on industry.

8. Summary of Quantitative Costs

The quantifiable costs of this final rule include the new "no smoking" statement, the "no vaping" statement, and graphic warning symbol requirement, clarification leading to firms becoming compliant with existing requirements, an increase in the number of adverse event reports, and added CGMP requirements including a requirement for portable cryogenic containers to have a working gauge. Except for the provisions that amend 21 CFR part 4, this rule will have an effective date one and a half years after publication; consequently, each cost has been discounted by one and a half years at the corresponding discount rate.

In Table 26, we present the total annualized quantified costs of the final rule, if finalized, over a 10-year timeline. The annualized costs will range from $1.52 million to $5.29 million with a primary estimate of $3.23 million at a 7 percent discount rate.

Table 26. Summary of Quantitative Costs (in $ Millions)

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)
Reading and Understanding the Rule	$0.22	$0.10	$0.38
New Label for Oxygen Containers	$1.26	$1.18	$1.33
Full Compliance Quality Units	$0.41	$0.00	$0.93

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)
Full Compliance Personnel Qualifications and Responsibilities	$0.50	$0.00	$1.00
Written Procedures for Personnel Qualifications and Responsibilities	$0.04	$0.03	$0.06
Rejected Containers Must Be Documented and Assessed	$0.22	$0.00	$0.45
Portable Cryogenic Containers Working Gauge Requirement	$0.53	$0.19	$1.09
CVM Adverse Events	$0.00	$0.00	$0.00
Submission of Certification Request	$0.00	$0.00	$0.00
Annual Report for Granted Certifications	$0.04	$0.02	$0.07
Gov: FDA Created Forms	$0.00	$0.00	$0.01
Total Cost			
Total Cost	$3.24	$1.52	$5.30

G. Summary of Costs and Benefits

The benefits of the final rule are primarily driven by removing or relaxing CGMP requirements that do not apply to medical gases, such as removing certain buildings and facilities requirements, leading to a reduction in inspection time and net cost savings from more flexible sampling requirements. The costs are primarily driven by the new labeling requirement, 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.

Table 27 summarizes the estimated benefits and costs of the final rule. The annualized benefits of the rule will range from $0.00 million to $7.02 million with a primary estimate of $3.51 million at a 7 percent discount rate over 10 years. 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.

Table 27. Summary of Costs and Benefits (in $ Millions)

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)
Total Cost Savings	$3.51	$0.00	$7.02
Total Costs	$3.24	$1.52	$5.30
Total Net Costs[α]	($0.27)	$1.52	($1.72)

[α] Numbers in () represent net cost savings.

H. Uncertainty Analysis

Due to uncertainty with many of our inputs, we provide plausible lower and upper bounds around a simulated mean. We obtained 5 percent estimates, means, and 95 percent estimates of the costs and cost savings using the Monte Carlo simulation[20] method with @Risk.[21] The Monte Carlo simulation provides 5 percent estimates and 95 percent estimates that allow us to quantify the degree of uncertainty in the outputs (e.g., costs and cost savings).[22]

Table 28 shows the annualized costs over a 10-year time horizon at a 7 percent discount rate using the mean, 5th percentile, and 95th percentile outputs from the Monte Carlo simulation. The upper and lower bound for total costs of this 90 percent confidence interval fall between $2.09 million and $4.67 million.

Table 28. Monte Carlo Simulation Costs (in $ Millions)

	5th Percentile	Mean	95th Percentile
Reading and Understanding the Rule	$0.14	$0.23	$0.33
New Label for Oxygen Containers	$1.21	$1.26	$1.31
Full Compliance Quality Units	$0.14	$0.44	$0.77
Full Compliance Personnel Qualifications and Responsibilities	$0.16	$0.50	$0.84
Written Procedures for Personnel Qualifications and Responsibilities	$0.03	$0.04	$0.05
Rejected Containers Must Be Documented and Assessed	$0.07	$0.22	$0.38
Portable Cryogenic Containers Working Gauge Requirement	$0.32	$0.59	$0.93
CVM Adverse Events	$0.00	$0.00	$0.00
Submission of Certification Request	$0.00	$0.00	$0.00
Annual Report for Granted Certifications	$0.03	$0.04	$0.05
Gov: FDA Created Forms	$0.00	$0.00	$0.00
Total Cost			
Total Cost	$2.09	$3.32	$4.67

Table 29 shows the annualized cost savings over a 10-year time horizon at a 7 percent discount rate using the mean, 5th percentile, and 95th percentile inputs from the Monte Carlo simulation. The upper and lower bound for cost savings of this 90 percent confidence interval fall between $1.11 million and $5.91 million.

[20] Palisade offers a succinct description of Monte Carlo simulations at https://www.palisade.com/risk/monte_carlo_simulation.asp. We run 10,000 iterations of our model, using an initial seed of 1.

[21] A Microsoft Excel add-in from Palisade Corporation used to simulate values from a probability distribution (@Risk™ version 7.6, Palisade Corporation http://www.palisade.com).

[22] We assume a triangular distribution using the low, primary, and upper level of inputs, that vary.

Table 29. Monte Carlo Simulation Cost Saving (in $ Millions)

	5th Percentile	Mean	95th Percentile
Streamlining Inspection Process	$0.48	$1.50	$2.53
Removing First in, first out Requirements	$0.12	$0.37	$0.62
Allowing Reuse of Labels	$0.01	$0.04	$0.06
Flexibility in Curbside Filling Written Permission	$0.06	$0.18	$0.30
Gov: Streamlining Inspection Process	$0.45	$1.42	$2.39
Total Cost Savings			
Total Cost Savings	$1.11	$3.51	$5.91

I. Distributional Effects

We do not expect significant distributional effects across income groups, ethnic groups, geographical regions, gender, or age groups. We do not anticipate any major transfer payments as a result of this final rule. This rule will affect facilities within each entity type (manufacturer, downstream person or entity (not engaged in homecare), and downstream person or entity (engaged in homecare)) proportionally.

J. International Effects

The requirements of the final rule are the same for domestic and foreign facilities. Further, we believe that very few downstream entities or manufacturers are foreign facilities. ERG (Ref. 2) identified two foreign owned firms and eleven U.S. facilities owned by foreign parent firms (ERG Table 2-9). We do not believe this rule will impose significant costs on foreign facilities.

K. Sensitivity Analysis

Our analysis assumes that it is industry practice for downstream entities to verify and record upon receipt of a DMG that the shipment contains a signed certificate of analysis (COA) from the supplier.[23] Here we quantitatively explore the cost if 10 percent, 50 percent, or 100

[23] Firms could elect to perform full compendial testing on the gas rather than verify and record the COA. We believe this will be less common as it would be more burdensome for industry.

percent of downstream entities are not currently verifying and recording that the shipment contains a signed COA.

SMEs estimate it will take approximately 15 minutes per shipment to verify and record the shipment contains a COA. Further SMEs estimated a representative scenario where an average downstream entity receives 417 shipments (daily nitrogen shipments and weekly oxygen shipments) per year. The ERG report estimates there are 1,380 downstream entities that we believe will need to verify and record shipments of DMGs contain a signed COA. We use the 2022 wage rate for Helpers and double it for a fully-loaded wage rate of $37.02.

The annual cost of verifying and recording shipments contain a signed COA per downstream entity is $3,859.34 (417 shipments x .25 hours per shipment x $37.02 Helper wage rate). Assuming 10 percent, 50 percent, and 100 percent of downstream entities are not currently verifying that a shipment contains a signed COA, the additional annual cost of this requirement will be $0.53 million, $2.66 million, or $5.33 million, respectively.

L. Analysis of Regulatory Alternatives to the Rule

1. Delayed Effective Date for Working Gauge

Except for the provisions that amend 21 CFR part 4, this final rule will have a one-and-a-half-year effective date. We believe that with the one-and-a-half-year effective date, between 18 percent and 50 percent of working gauges will have to be replaced. If we extended the effective date for working gauges to a three-year effective date, we estimate a range of 0 percent to 39 percent of working gauges will need to be replaced.[24]

Under this alternative, the primary one-time cost of replacing portable cryogenic containers without working gauges would fall from $4.70 million to $2.06 million, the low cost would fall from $1.72 million to $0 because all working gauges would already have been replaced, while the high one-time cost of replacing portable cryogenic containers without working gauges would fall from $9.70 million to $7.64 million. Further, the one-time high cost would occur one and a half years later.

Under this alternative, the costs would range from $1.33 million to $5.07 million with a primary estimate of $2.94 million over a ten-year horizon annualized at a 7 percent discount rate. The costs with the current one-and-a-half-year effective date for working gauges range from $1.52 million to $5.30 million with a primary estimate of $3.24 million at a 7 percent discount rate. The reduction in costs would be $0.19 million for the lower bound estimate, $0.30 million for the primary estimate, and $0.23 million for the upper bound estimate.

[24] We use the same rates of replace from before (15 percent replacement per year for low, 12 percent replacement per year for primary, and 7 percent replacement for high) to estimate the percentage of portable cryogenic containers that would need to be replaced as a result of this delay in compliance.

2. One Year Earlier and One Year Later Effective Dates

We examine the effect on costs and costs savings of a one year shorter and a one year longer effective dates (half-year and two-and-a-half-year). An earlier effective date would affect costs and costs savings in two ways. First, it would shift most costs and cost savings earlier, causing them to be discounted by fewer years. Second, it would give firms less time to adjust, which may increase the costs of compliance for some components of this regulation. A later effective date would have the opposite effects. Under our assumptions, the shorter effective date only directly affects the cost of firms adding working gauges to portable cryogenic containers and the discount factor; however, it is possible that shorter effective dates would increase other costs or lead to noncompliance.

The primary estimate for annualized cost savings over a ten-year time horizon fall as the effective date is increased. The primary annualized cost savings estimate falls from $3.76 million for a half-year effective date to $3.51 million for a year-and-a-half effective date, and then falls further to $3.28 million for a two-and-a-half-year compliance. These values can be found in Table 30.

Table 30. Cost Savings Under Alternative Effective Dates (in $ Millions)

	Primary Estimate (7%)	Low Estimate (7%)	High Estimate (7%)
Half-year Effective Date	$3.76	$0.00	$7.51
Year-and-a-half Effective Date (baseline)	$3.51	$0.00	$7.02
Two-and-a-half-year Effective Date	$3.28	$0.00	$6.56

The primary estimate for annualized costs over a ten-year time horizon fall as the effective date is extended. The primary annualized costs estimate falls from $3.45 million for a half-year effective date to $3.24 million for a year-and-a half effective date, and then falls further to $3.04 million for a two-and-a-half-year effective date. These values can be found in Table 31.

The impact of an earlier effective date is an increase to both costs and cost savings and the net effect is small. Based on our assumptions an earlier effective date does not result in the primary estimate of costs exceeding cost savings; however, it may be the case that too short an effective date adversely affects firms' ability to be compliant with the new requirements and may lead to additional costs, which we have not accounted for, or lead to noncompliance if firms require a learning and implementation period.

Table 31. Costs Under Alternative Effective Dates (in $ Millions)

	Primary Estimate	Low Estimate	High Estimate

	(7%)	(7%)	(7%)
Half-year Effective Date	$3.45	$1.62	$5.64
Year-and-a-half Effective Date (baseline)	$3.24	$1.52	$5.30
Two-and-a-half-year Effective Date	$3.04	$1.43	$4.97

III. Initial Small Entity Analysis

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this final rule better tailors CGMP requirements for medical gases and only creates small single-year costs, we certify that the final rule will not have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

To assess the final rule's economic impact on small entities, we compare each establishment's revenues with its rule-related costs [= (establishment's expected rule-induced costs) / (establishment's annual revenues)]. Analyzing the effects of the rule on small businesses requires revenue and cost data, and a measure to assess whether the establishment is "small." We explain the data we use and our conclusion in this section.

FDA has examined the economic implications of the final rule as required by the Regulatory Flexibility Act. FDA does not believe that the rule will directly impact a significant percentage of small business entities. The analysis that follows shows that the estimated cost per small entity for most small firms represents a small percentage of the average annual sales for each firm. 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.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities if a rule will have a significant economic impact on a substantial number of small entities. Our analysis does not suggest that the final rule will have a significant impact on a substantial number of small entities. Therefore, we do not provide additional options to the regulation.

A. Description and Number of Affected Small Entities

We use data from the 2020 ERG report (Ref. 2) to identify the number of small firms. ERG used the Dun & Bradstreet (D&B) database to identify the total count of small firms. ERG identified 700 total small entities (41.3 percent of all entities). Of those small entities: 5 were original manufacturers (1.6 percent of all original manufacturers), 504 were downstream persons and entities not engaged in homecare (46.8 percent of all downstream entities not engaged in homecare), and 191 were downstream persons and entities engaged in homecare (63.2 percent of

all downstream entities engaged in homecare). We determine that both downstream persons and entity categories have a substantial number of small entities.

We use the four subcategories that comprise the industry group, Pharmaceutical and Medicine Manufacturing, NAICS code 325400, to identify the Small Business Administration's (SBA) threshold. Table 32 displays the SBA 2023 size standards for the industries affected by the final rule.[25]

Table 32. Small Business Administration Size Standards for Industries Affected by the Final Rule

NAICS Code	Industry Description	Small Business Threshold
325411	Medicinal and Botanical Manufacturing	1,000
325412	Pharmaceutical Preparation Manufacturing	1,300
325413	In-Vitro Diagnostic Substance Manufacturing	1,250
325414	Biological Product (except Diagnostic) Manufacturing	1,250

B. Description of the Potential Impacts of the Rule on Small Entities

We estimate the highest single year average cost per small entity by type of entity. Year one-and-a-half will have the highest single year average costs because many costs require a one-time investment, which occurs when compliance begins.[26] We assume that costs are spread evenly across all affected entities. These costs can be found in Table 33.

We measure the potential impacts of this final rule on small entities by the ratio of the establishment's expected rule-induced costs to estimated annual revenue. The most recent revenue data is from the 2017 Statistics of U.S. Businesses (SUSB) data from the U.S. Census (Ref. 9).

The 2020 ERG report (Ref. 2) identified small entities by mapping business from D&B proprietary database on basic information pertaining to businesses to the corresponding NAICS codes. D&B data mapped to 57 distinct NAICS codes.[27] However, for simplicity, we will use the Pharmaceutical and Medicine Manufacturing, NAICS code 325400 annual receipts.

[25] SBA 2023 size standards: https://www.sba.gov/sites/sbagov/files/2023-03/Table%20of%20Size%20Standards_Effective%20March%2017%2C%202023%20%281%29%20%281%29_0.pdf

[26] Reading and understanding the rule costs are not included in this table because they occur in year zero.

[27] All NAICS codes used in ERG report: 213112, 312140, 325120, 325998, 332313, 333992, 333249, 333999, 334514, 339113, 334510, 621910, 484220, 423440, 423450, 423830, 423840, 423990, 424210, 424690, 424720, 444190, 444130, 452319, 441310, 446110, 454110, 454310, 523120, 524114, 531120, 551112, 525910, 523130, 532283, 532490, 561320, 541519, 812990, 532120, 812219, 811310, 621111, 623110, 622110, 622310, 621511, 621610, 621498, 621999, 611310, 813920, 541330, 541380, 561110, 541611, 541690.

Table 33. Costs Per Small Entity by Entity Type

	Small Manufacturer	Small Downstream Entity Not Engaged in Homecare	Small Downstream Entity Engaged in Homecare
New Label for Oxygen Containers	$5,965.63	$5,965.63	$5,965.63
Full Compliance Quality Units	$371.83	$371.83	$371.83
Full Compliance Personnel Qualifications and Responsibilities	$295.29	$295.29	$295.29
Written Procedures for Personnel Qualifications and Responsibilities	$25.45	$25.45	$25.45
Rejected Containers Must Be Documented and Assessed	$132.27	$132.27	$132.27
Portable Cryogenic Containers Working Gauge Requirement	$2,505.91	$2,505.91	$2,505.91
CVM Adverse Events	$1.33	$1.33	$1.33
Submission of Certification Request	$0.00	$8.76	$8.76
Annual Report for Granted Certifications	$121.49	$0.00	$0.00
Total Cost			
Total Cost	$9,419.13	$9,306.48	$9,306.48

The ratio of highest single year costs to receipts is highest for small manufacturers with 0 to 4 employees (0.860 percent) while the average costs to receipts ratio rounds to 0.007 percent for all three entity types. These estimates can be found in Table 34.

Table 34. Percent of Single Year Highest Costs Relative to Annual Receipts for Compliant and Non-complaint Firms

Employment Size	Annual Receipts per Firm ($1,000)	Small Manufacturer	Small Downstream Entity Not Engaged in Homecare	Small Downstream Entity Engaged in Homecare
Total	128,896	0.007%	0.007%	0.007%
0-4	1,095	0.860%	0.850%	0.850%
5-9	2,983	0.316%	0.312%	0.312%
10-19	6,892	0.137%	0.135%	0.135%
<20	2,742	0.344%	0.339%	0.339%
20-99	16,161	0.058%	0.058%	0.058%
100-499	71,220	0.013%	0.013%	0.013%
<500	14,702	0.064%	0.063%	0.063%
500+	1,206,037	0.001%	0.001%	0.001%

Our analysis of the impact of the final rule on small entities suggests that small firms will not be significantly affected by the regulation. We do not estimate the impact of the rule on other small entities, such as non-profits or state and local governments, because we do not anticipate that the rule will affect these entities. We therefore certify that this regulation will not have a significant effect on small entities.

IV. References

The following references are cited in the analysis. FDA has verified the Web site addresses for the references displaying a URL, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.

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