AIR LIQUIDE

2240 '03 OCT 28 A8:59

October 27, 2003

**Walter A. Mason, Ph.D.**
VICE PRESIDENT
QUALITY AND REGULATORY

U.S. Public Health Service
Food and Drug Administration
Dockets Management Branch (HFA-305)
Room 1061
5630 Fishers Lane
Rockville, Maryland 20855

Reference: Docket No. 03D-0165
Current Good Manufacturing Practices for Medical Gases *Draft Guidance*

Dear Sir or Madam:

Air Liquide America L.P. (ALA) incorporates, by reference, all Comments submitted by the Compressed Gas Association (CGA). In addition, included in this letter are numerous Comments to the referenced Guidance document. These Comments are organized into three (3) parts: Part I addresses General Concepts; Part II describes what Air Liquide considers to be useful Clarification; Part III discusses Specific Content of the Guidance. Where feasible, and for brevity, I have consolidated remarks on Draft Guidance concepts that are similar. Links are provided for Comments to the Draft Guidance line number(s), as published.

## I. GENERAL CONCEPTS

ALA is impressed with the amount of time and effort that FDA expended in developing the Guidance. The medical gas industry, Air Liquide included, views the Guidance as a document of paramount importance. Therefore, ALA thoroughly reviewed the Guidance and appreciates the opportunity to share with the FDA how the Guidance appears from ALA's perspective as a member of the regulated community.

A As an initial matter, ALA is requesting clarification from the FDA regarding the reason that Guidance does not address patient or product risk as a basis for FDA's current thinking on the topic of cGMP guidance for medical gases. This discrepancy makes it appear that the document was developed without consideration of the FDA's new risk-based approach as outlined August 21, 2002 in FDA's initiative *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach.* Air Liquide endorses the major goals of FDA's risk-based initiative and expects the Guidance to be based on, and develop from, the following initiatives.

03D-0165 C 26

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- The most up-to-date concepts of risk management and quality systems are incorporated, while continuing to ensure product quality
- The latest scientific advances in pharmaceutical manufacturing and technology are encouraged
- The submission review program and the inspection program operate in a coordinated and synergistic manner
- Regulation and manufacturing standards are applied consistently
- Innovation in the pharmaceutical manufacturing sector is encouraged in program Management
- FDA resources are used most effectively and efficiently to address the most significant health risks

Air Liquide America, as part of the Compressed Gas Association, has on several occasions, presented a risk-based validation model for medical Oxygen that substantiates the low risk associated with that validation process. ALA looks forward to clarification from FDA on how the Guidance is linked to FDA's risk-based initiative.

B Additionally, the Guidance states that in 1999, the Institute of Medicine (IOM) reported that an estimated 7,000 deaths were attributed to medication errors in 1993. However, neither the data on which IOM relied (NAICS 325412 and 325414) nor the Guidance states how many of the 1993 medication errors were made in dispensing medical gases. This omission is significant! When comparing the IOM estimate of 7000 deaths in 1993 to one "near miss" involving medical gases, a reasonable person must conclude that the risk of injury due to medical gases is very small.

We reviewed the NAICS data to try to determine the type of products involved in medication mix-ups. The data clearly indicates the following: 1) either the incidence of medication errors involving medical gas products was too low to be significant 2) the omission was an oversight, or 3) that the risk from harm attributable to medical gases is so low that it is not statistically meaningful.

Based upon these compelling data, Air Liquide America suggests that many of the concepts and recommendations in the Guidance, as per the examples above, are unnecessarily burdensome based on the risk posed.

C Air Liquide America is also concerned that the Draft Guidance expands the intended scope of the current good manufacturing practice (cGMP) regulations beyond their meaning or applicability to finished pharmaceuticals. By recommending or defining certain practices that do not reflect a regulation or current industry practice, the Guidance provides both industry and its field force with an interpretation that may result in confusing, unnecessary, redundant or extraneous requirements for medical gas manufacturers. For example:

1. Line: 113 to 114; Recommends that the QCU perform more than a testing function

Comment: 21 CFR 205, 210, 211 do not require that testing of product be a QCU function. The Guidance, thus, seems to expand the scope of the regulations. Air Liquide America requests that FDA remove this section, or that it be rewritten to more accurately representing the intent of the regulations.

2. Line: 119 to 120; Identification of QCU individuals

Comment: Air Liquide proposes that the Guidance be amended to state," All individuals who are part of the QCU may be identified..." This provides flexibility in the method of identification.

3. Line: 124 to 125, GMP training for OCU

Comment: The phrase "quality assurance training" in the Guidance is not a term common to the industry. Also, the Guidance suggests that GMP training be given "on a continuing basis." This is clearly beyond the scope of 211.25.

4. Line: 234 to 237; Recommends that 21 CFR 205(50) security requirements apply to an employee's home.

   Comment: Section 205(50) clearly applies to wholesale drug facilities, not an employee residence. While we do agree that delivery trucks should be secured, the Guidance appears to expand the scope of the regulations to an extent that personal privacy may be impinged.

5. Line: 259 to 260; Cleaning of medical equipment.

   Comment: The Guidance indicates that equipment should be cleaned "if exposed to a contaminant." Air Liquide believes that equipment used in the medical gas industry can only be contaminated internally. Thus, the Guidance appears to be overly restrictive.

   We propose the wording be amended to state, " Equipment used in the manufacture of medical gas (e.g., manifolds, pigtails, valve assemblies, hoses, and gauges) should be cleaned by qualified individuals prior to initial use and if contaminated internally."

6. Line: 300 to 304; Check valves

   Comment: The Guidance links check valves directly to prevention of backflow of foreign product or contaminants into supply systems. In addition, while Air Liquide agrees that check valves may be used for this purpose, this is not their primary purpose.

Air Liquide recommends the Guidance state, "Medical gas manufacturers using check valves may comply with 211.63 by ensuring the check valves prevent back flow, or that they prevent over-pressure of the system, and they have been properly installed."

7. Line: 580 to 581; Overfilled cylinders

   Comment: Although there may be a concern with liquefied compressed gases, the Department of Transportation regulations require a pressure relief device. In addition, 21 CFR 211 does not address container safety. Therefore, this guidance is redundant and expands the scope of the FDA regulations.

   Air Liquide recommends this line be removed from Guidance.

8. Line: 739-741; Net contents

   Comment: There is no regulation prohibiting the use of a tag or sticker on the container that states the net quantity contents information.

9. Line: 792 to 797; Verify pressure in high-pressure cylinders at patients' home

   Comment: Equipment such as high-pressure cylinders, whether placed in homes, hospitals, or in emergency vehicles do not normally have a method for identifying continuous net contents or pressure. When filled, these cylinders are checked for leaks. Thus, initial pressure is verified.

   At-will entry into homes or domiciles goes above what the health care provider is entitled to by virtue of its agreement with the patient and hence, monitoring is not feasible. Additionally, the costs of performing such monitoring will be extraordinary. Air Liquide proposes that this provision of the Guidance be deleted.

D. Finally, our final general Comments involve sections of the Guidance document that do not provide any guidance, but appear to be anecdotes of medical gas mix-ups. The Attachment to the Guidance, lines 1704 to 1796, is the most prominent of these.

   Another example of this is in lines 683 to 685, which begins, "In light of recent deaths..." Clearly, this type of statement is meant to express feeling rather than provide guidance. This type of dialogue neither adds value, nor provides guidance.

   Comment: ALA request that FDA review its draft Guidance document for other sections that provide no guidance and that they be removed.

## II. CLARIFICATION

A. The majority of the Guidance recommendations do not clearly specify whether they apply to all, or only some, points in the chain of medical gas distribution.

   Comment: ALA recommends that there be discreet, specific sections to clarify the requirements in different contexts. This is particularly important to small businesses.

B. The context and scope of many recommendations are unclear. It is often not apparent whether a given recommendation applies to all – or only some – points in the medical gas supply chain, such as bulk production, distribution, transfilling operations, and home use.

Comment: To help clarify the scope of the recommendations' applicability, ALA recommend that the Guidance incorporate the terms, definitions, and technical consensus standards developed and utilized by the industry and the Compressed Gases Association (CGA).

## III. SPECIFIC CONTENT

The following comments are indexed to specific line numbers as they appear in the Draft cGMP Guidance for Industry published May 15, 2003.

A. Line: 21; Footnote 2 defines the term manufacturer.

Comment: ALA agrees that persons who distribute medical gases that they fill, transfill, cascade or transfer are manufacturers. Additionally, ALA believes that distributors of bulk-liquid medical gases must be registered as manufacturers as this activity involves mixing. However, the definition of *manufacturer* appears to include persons whose sole business is distribution of medical gases, but who perform none of the other, above described activities.

With pharmaceuticals, biological products and medical devices there are companies registered as distributors that just distribute products. In the medical gas industry, there are also companies or divisions of companies whose sole business is product distribution. The Guidance should make a distinction between these two types of companies. Air Liquide suggests that the Guidance should more closely follow the definitions in 21 CFR 201.1(b) and 203.10(dd). In both of these sections, it is clear that while manufacturers may also be distributors, there are distributors who are not manufacturers.

Air Liquide recommends that in order to clarify the distinction between a product manufacturer and a person whose sole business is product distribution, footnote 2 should be modified to state, "For purposes of this document, the term *manufacturer* includes fillers, transfillers, cascaders, and transferors that distribute medical gases that they process, pack or label."

Line 21 should then be amended to read, "...The recommendations should help manufacturers[2], fillers, and distributors[3] comply with CGMP..." This adds footnote 3 defining distributor. Footnote 3 then would state, "For purposes of this document, the term *distributor* includes manufacturers who sell, deliver, or offer to deliver medical gases as their primary business, but do not manufacture medical gases."

These changes would provide clarity for both FDA field staff and for distributors and manufacturers.

B. Line: 61 to 62; Finished product testing

Comment: The Guidance states that each time a medical gas is filled into another container, finished product testing must be performed in accordance with 211.165(a). Finished dosage form pharmaceutical products that are repackaged do not require finished product testing before release. This guidance is inconsistent with industry standards for drugs.

This concept is also inconsistent with other examples in the guidance, such as that for liquid-to-liquid filling of oxygen units filled at patients' home, lines 980 to 1003.

Air Liquide recommends that this guidance section be deleted.

C. Line: 103 to 105; QCU responsibility

Comment: Air Liquide agrees that where a contract exists between parties whereby a contractor company manufactures, processes or packages drugs for the contracting firm, the contracting firm is responsible for releasing the product. However, additional guidance needs to be developed to explain the responsibilities of a manufacturer who purchases finished, bulk liquid medical gases from another manufacturer, and the original manufacturer.

In this case, it is clear that a manufacturer that purchases bulk medical gases and obtains a certificate of analysis for the load, does not need to have its QC Unit release the product. This release is the responsibility of the firm that manufactured the product.

These concepts are consistent with the Commissioner's Comments in the March 28, 1979 final rule for cGMPs for Drugs [Docket No. 75N-0339]. This is also in concert with current medical gas industry practice, and with normal sales and distribution practices for the pharmaceutical industry.

Air Liquide recommends that this clarification be incorporated into the Guidance.

D. Line: 119 to 122; Organization of QCU

Comment: Air Liquide agrees that the QCU must be a separate unit from those other units engaged in sales, marketing, manufacturing and distribution. Further, this QCU responsibility needs to be centralized. This is especially true in large organizations that have distributed business units or profit centers. Having a centralized, independent QCU ensures that all quality assurance and quality control functions, including consumer complaints, corrective actions, product review and release, and adherence to procedures, are consistently focused for management review.

Also, Air Liquide recommends that the following text be added after line 122: "*Persons performing manufacturing, processing, or packaging operations, should not be assigned QCU responsibilities for activities they directly perform or supervise.*"

ALA also agrees that while small, independently owned companies may have individuals performing both operations and quality functions, independence of the QCU function must be stated in procedures. In the case of small companies, ALA recommends adding the following to line 122, "Periodic, independent assessments of quality and manufacturing operations by outside consultants should be performed in order to verify quality system program integrity."

E. Line: 207 to 211; Creation of quarantine areas

Comment: The recommendation implies that industry would need to create six (6) quarantine areas. This is not a requirement in pharmaceutical manufacturing. Air Liquide does agree that quarantine areas or a quarantine process is needed for unapproved finished product, unapproved containers and closures, and for rejected materials and products. However, the process of on-line quarantine has been a proven, acceptable practice in the industry for quarantine of finished product prior to QCU release.

Air Liquide supports the quarantine areas proposed in the Guidance. However, ALA recommend that the Guidance be amended by inserting the following at section IV, A, line 210, "High-pressure and cryogenic cylinders may be quarantined on the production line, as long as their status is readily identified."

F. Line: 213 to 220; Segregation of medical from industrial gases on delivery vehicles

Comment: Accepted industry practices involve vehicle safety and Transportation Department requirements, unique label identifiers, and specialized dispensing equipment for all gases, including different medical gases. The recommendation to have well-defined, separate areas for medical gases and industrial gases in delivery vehicles is burdensome and may be unsafe. The loading of delivery vehicles is governed by the United States Department of Transportation.

ALA understands the concern about preventing the delivery of an industrial gas to a medical customer; however, this concern can be addressed through other mechanisms. Some that have been proposed in the guidance to industry include cylinder color codes for medical gases and 360 labeling for VGL's. There are other options available through bar codes with handheld units and cylinder markers that would be more effective in preventing inadvertent delivery.

Another option not in the guidance would be to use labels for medical gases that are distinctively different from industrial gases. This would also require coordination with the DOT for label approval.

Air Liquide requests that the recommendation for physical separation be omitted from the Guidance.

G. Line: 216 to 217; 360-degree labeling

Comment: 360-degree labeling is not appropriate for permanently mounted cryogenic vessels. Air Liquide recommends that the Guidance be amended to state, " A 360-degree wrap-around label may be used to identify gases in large, portable cryogenic vessels. Permanently mounted vessels should be appropriately marked for their usage."

H. Line: 224 to 226, Security

Comment: The Compressed Gas Association is currently working with the American Chemical Council in the development of security guidelines for the industry. These include Site Security Guidelines, Transportation Security Guidelines and Customer Qualified Security. The areas used to manufacture bulk medical gases are reasonably secure.

I. Line: 379 to 380, Dedicated Equipment and Containers

Comment: The draft Guidance recommends that: "All high-pressure cylinders and cryogenic containers used for medical gases be dedicated to medical use only." However, it is normal industry practice to use the same equipment for manufacturing multiple products.

Air Liquide believes that where product uniqueness is such that dedicated equipment is needed, or where cleaning procedures cannot be adequately developed, then the Guidance recommendation is appropriate. However, where product similarities exist, and adequate cleaning procedures exist, dedicated equipment should not be an issue.

Air Liquide recommends that this section of the Guidance be modified to state that, "Adequate cleaning procedures are acceptable in lieu of dedicated equipment and containers."

J. Line: 587 to 588; Temperature and pressure readings

Comment: The Guidance recommends that temperature and pressure should be recorded "before the filling is complete." This line should be changed to, "Upon completion of the fill, the temperature and pressure reading would be recorded on the batch production record." This would reflect industry practice, which is to wait until an activity is completed before filling out records.

K. Line 597 to 598; Overfill of aluminum cylinders

Comment: The Guidance recommends that aluminum cylinders not be overfilled. Air Liquide proposes this be amended to state, " No overfill allowance is made for aluminum cylinders. Aluminum cylinders must not be stamped with a plus."

L. Line: 625 to 638; Calculation of yield

Comment: On November 22, 1994, CGA filed a Citizen's Petition, 94P-0426/CP1 (Attachment A), requesting an exemption from 21 CFR 211.103 and 21 CFR 211.184 (c). In 1995, the FDA responded to this Petition and appeared to agree with CGA's position in its internal memorandum on Calculation of Yield, dated May 11, 1995 (Attachment B) and in its posting to the current CDER website under Human Drug Notes, dated June 1997 (Attachment C).

Air Liquide requests that the Guidance provide medical gas manufacturers with an exemption from this provision based on: 1) the low risk associated with medical gases, 2) the fact that air liquefaction is a non-reactive separation process, and 3) the fact that FDA tacitly agrees with CGA's Citizen Petition.

M. Line: 774 to 786, and 1136 to 1144; Stability Testing/Expiration Dating

Comment: On March 6, 1979, the CGA filed a Citizen's Petition, 79P-0067/CP (Attachment D) requesting an exemption from 21 CFR 211.137, Expiration Dating. CGA submitted information that indicated that medical gases do not degrade or produce degradation byproducts.

Historically, FDA has not raised concerns about the stability of medical gases, either in its publications or through policy development. By not requiring the application of expiration dates on medical gas products, FDA appears to have tacitly assented to CGA's position.

Based upon the low risk associated with medical gases, and considering the FDA's historical compliance attitude concerning these products, Air Liquide America believes that the Guidance should specifically exempt medical gas manufacturers from the requirements for expiration dating. ALA therefore encourages FDA to grant the Citizen's Petitions referenced above.

N. Line: 845 to 846; handheld computer validation

Comment: The Guidance recommends that handheld computer devices or computers used during distribution operations be validated. Air Liquide believes that there is value in assuring that handheld computers operate, and that if such use is impacted under 21 CFR 11, then validation of the system in which handhelds are used would require validation. However, validation as a concept cannot, and should not, be applied to a discreet function, part, component, operation, or activity.

Air Liquide recommends that lines 845-846 be deleted since validation of processes and equipment maintenance are addressed both in the regulations, and in other sections of the Guidance.

O Line: 949 to 957; Analytical method for standards

Comment: All of the recommendations are good with the exception of line 955 – Analytical methodology. Manufacturers of gas standards do not typically supply this type information. Hence, inspectors may find our industry in noncompliance while our suppliers have no requirement to supply this type information.

We recommend deleting line 955.

Thank you for your attention in this matter. Should you have questions or require additional information, please contact Harold Jones, Director, CGA-FDA Liaison, at the address below, or call 713-402-2157.

Sincerely,

Walter A. Mason, Ph.D.

Attachments (4)

**ATTACHMENT A**

**CITIZENS PETITION, 94P-0426/CP1**

COMPRESSED GAS ASSOCIATION, INC.
1725 JEFFERSON DAVIS HWY. ■ ARLINGTON, VA 22202-4102 ■ (703)412-0900 ■ FAX (703)412-0128

November 22, 1994



Department of Health and Human Services
Food and Drug Administration
Dockets Management Branch
5600 Fishers Lane
Rockville, Maryland 20857-0001

CITIZEN'S PETITION

The Compressed Gas Association, through its Medical Gases Committee, representing approximately 37 major medical gas manufacturing and Home Respiratory companies, submits this petition in accordance with Section 10.25 of Title 21 Code of Federal Regulations.

A. Action Requested

The Compressed Gas Association respectfully requests that the Food and Drug Administration amend 21 CFR parts 211.103 and 211.184(c) as follows to exempt medical gas manufacturers and repackagers from reconciliation of incoming bulk products to finished medical gases. We submit that calculation of yield provides no protection to the consuming public and does not provide meaningful information to medical gas manufacturers. The industry has other safeguards that adequately meet the concerns that the reconciliation is intended to address.

Current Wording:

211.103 Calculation of yield.

Actual yield and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.

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Proposed Wording:

211.103 Calculation of yield.

Actual yield and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person. Yield calculations for compressed medical gases need not be determined.

Current Wording:

211.184 Component, drug product container, closure, and labeling records.

These records shall include the following:

(c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.

Proposed Wording:

211.184 Component, drug product container, closure, and labeling records.

These records shall include the following:

(c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure. Reconciliation records are not required for compressed medical gases.

B. Statement of Grounds

For 211.103:

In short, the CGA is requesting this exemption for the following reasons:

1. Identity, strength, quality, purity and quantity of medical gases is assured through means other than reconciliation.

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2. Because of the unique properties of compressed medical gases and manufacturing processes, available data does not provide meaningful criteria to meet the purpose of 211.103.

Rationale

1. Other methods used to ensure specific requirements are:

**A. Identity:**

Medical gases are manufactured by transfilling from a bulk source to a smaller portable container, by compression of atmospheric air or the mixture of two or more gases. Only dedicated filling systems are used with unique fittings and container closures to preclude the filling of the wrong gas. A representative sample of single gases is tested in accordance with CMG Guidelines. Mixtures of two or more components are individually analyzed in accordance with CMG Guidelines.

**B. Strength:**

* Bulk components are qualified in accordance with the CMG Guideline and stored in dedicated supply tanks or cylinders.
* Single gases are produced by simple transfer of product without chemical alteration.
* Gas mixtures are produced by combining two or more single gases without chemical alteration.
* A representative sample of single gases is tested in accordance with CMG Guidelines.
* Each container of mixed gas is tested in accordance with CMG Guidelines.

**C. Quality:**

In addition to the above points, each container receives pre-fill, in-process and post-fill checks appropriate to the container.

**D. Purity:**

In addition to the above points, purity is assured by closed systems maintained under pressure that prevent introduction of contaminants during the manufacturing process.

**E. Quantity:**

Quantity is assured by pressure-temperature measurements, weight of individual containers or volume limiting mechanisms.

2. The unique properties of compressed medical gases and manufacturing process that prevent establishment of meaningful criteria for reconciliation are:

A. It is common for a compressed medical gas producer to manufacture both industrial and medical gases in the same facility. Containers and transfilling equipment are the same for both. The yield calculations, therefore, cannot be linked specifically to medical production. Medical gas manufacturing is differentiated by increased procedure compliance, documentation and labeling.

B. Product losses, affecting yields, are inevitable while handling compressed gas products. Losses for a given facility can vary from less than 10% to over 50% depending upon daily activity. The reasons for these losses include cool-down of pumps, activation of pressure relief devices and vaporization during fill of cryogenic liquid containers. Factors affecting loss rates include storage tank temperature and pressure, receiving container temperature and pressure, length of cool down and ambient air temperature. For example, filling an empty, warm cryogenic container may result in losses greater than 50% of the final fill volume. Filling an empty cold cryogenic container could result in losses less than 5%. Temperature of the container cannot be determined at the time of the fill.

Heat gain into bulk storage containers of cryogenic liquids will cause the pressure in the tanks to rise possibly resulting in activation of the pressure relief device. When this occurs, product vents to atmosphere. These events do not always occur during periods when facility is occupied and they are therefore not recorded. The quantity discharged during the event may vary and the frequency of occurrence is dependent upon frequency of bulk product delivery and other tank management factors.

C. Useful data cannot be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging or holding of the drug product. Measurements covering several manufacturing cycles are needed to provide data that is within the sensitivity of tank measurement devices that are standard within the industry.

For 211.184(c)

1. We believe that the component reconciliation record requirement is based on 211.103, yield calculations, therefore these records would not be required if CMG's are exempted from 211.103.

## C. Environmental Impact

The Petitioner is of the opinion that this request qualifies for the "categorical exclusion" under 25.24 of the Code. Adoption of this proposed change will not result in the production or distribution of any substance and, therefore, will not result in introduction of any substance into the environment.

D. Economic Input

Not required unless requested by the Commission following review of this petition.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Signature:

Name of Petitioner: Carl T. Johnson, President

Compressed Gas Association, Inc.

Mailing Address: 1725 Jefferson Davis Highway, Suite 1004

Arlington, Virginia 22202

Telephone Number: 703/412-0900

Please Note: The primary CGA point of contact for this item is:

Mr. Lee Elwell
Staff Manager
Medical Gases Committee (Docket 92-75)
Compressed Gas Association
703/412-0900, extension 720

Carl T. Johnson
President

**ATTACHMENT B**

**LETTER DATED MAY 11 1995 FROM MR. DUANE SYLVIA, FDA**

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DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

# Memorandum

Docket 92-75

Date: May 11, 1995

From: Sterile Drugs Branch, HFD-322
Division of Manufacturing and Product Quality

Subject: Citizen's Petition 94P-0426/CP 1

To: Director
Division of Regulatory Affairs, HFD-360

We have reviewed the November 22, 1994, Compressed Gas Association Inc.'s (CGA) Citizen's Petition 94P-0426/CP 1 requesting an exemption from Title 21, *Code of Federal Regulations*, Sections 211.103 Calculation of yield, and 211.184 Component, drug product container, closure, and labeling records for the medical gases industry. We concur with the CGA's request for exemption from Section 211.103, and Section 211.184 (c).

The CGA's rationale for the product losses experienced during the manufacture of both medical and industrial gases is reasonable and valid. The reconciliation of medical gases is quite difficult to determine, if not impossible, considering that industrial gases are filled concurrently, and thus play a major part in the losses. See page 4, Item B. under Rationale for more specific details. Therefore, we feel the citizen's petition has merit and should be granted.

If you should have any questions, please feel free to call me at 594-0095.

Duane S. Sylvia

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**ATTACHMENT C**

**"GAS WHAT" POLICY QUESTION ON MEDICAL GASES**

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# GAS WHAT?

Docket 92-75

## Policy Questions on Medical Gases

Reprinted from: *Human Drug CGMP Notes*
Duane Sylvia, FDA

**Human Drug CGMP Notes (June 1997)**

1) What is the current policy on gas product yield reconciliation? I understand the Compressed Gas Association filed a citizens petition requesting exemption from this requirement.

Reference: 21 CFR 211.103, Calculation of yield; 211.184(c), Component, drug product container, closure, and labeling records.

The Compressed Gas Association filed a citizens petition requesting that medical gases be exempt from the requirements for yield reconciliation. On May 11, 1995, the agency concurred with the CGA based on the amounts of product loss through evaporation from storage tanks, large cryogenic dewars, the filling operations, and the filling of large amounts of industrial product from the same storage tanks.

The agency will publish a notice in the Federal Register proposing to amend the CGMP regulations accordingly. The notice will include an interim enforcement policy that will apply the exemption. However, existing requirements remain in effect until the notice is published.

2) Must batch production records for compressed medical gases contain copies or specimens of all labeling used, or are alternative measures acceptable? What regulatory follow up would be appropriate if labeling/copies are required but lacking?

Reference: 21 CFR 211.188(b)(8), Batch production and control records.

Batch production records for compressed medical gases must contain copies or specimens of all labeling used, per 21 CFR 211.188(b)(8). Photographs or photocopies of large labeling that would be awkward to physically append to the records may be used in place of original labeling. It's important to have labeling, or accurate copies thereof, to enable investigations and problem resolution in the event of mix ups. Although additional labeling controls may contribute to preventing mix-ups, such controls are not substitutes for including labeling specimens or copies in the batch

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**ATTACHMENT D**

CITIZENS PETITION, 79P-0067/CP

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

March 6, 1979

Compressed Gas Association, Inc.
500 Fifth Avenue
New York, N.Y. 10036

Attn: J.C. Crawford

This is to acknowledge receipt of your submission:

RE: EXPIRATION DATING ON MEDICAL GASES DATE: FEBRUARY 21, 1979

[X] It has been accepted for filing and assigned a docket number. Please refer to this number in any future correspondence with the Agency.

DOCKET NO: 79P-0067/CP DATE OF FILING: March 6, 1979

[ ] We are returning your submission. It has not been accepted for filing at this time because it does not comply with the following sections of the Food and Drug Administration's Administrative Practices and Procedures regulations.

(See enclosure for referenced sections.)

[ ] Other:

Please feel free to contact us if we can be of further assistance.

Sincerely yours,

Jean Houston

Jean Houston
Hearing Clerk
Public Records and Documents Center

FLH 2009 (9-75)

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GAS
500 FIFTH AVENUE · NEW YORK, N.Y. 10036 · (212) 354-1130

February 21, 1979

Hearing Clerk
Food and Drug Administration
Department of Health, Education and Welfare
Room 4 - 65
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

Citizen Petition

The Compressed Gas Association submits this petition pursuant to:

Part 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals. 211.137 Expiration Dating

of the Federal Food, Drug and Cosmetic Act as found in the Federal Register Vol. 43, No. 190 - Friday, September 29, 1978, to request the Commissioner of Food and Drugs to revoke the requirement of expiration dating on medical gases.

A. Action Requested

The present wording is as follows:

211.137 Expiration Dating

(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in PP 211.166.

(b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in PP 211.166.

(c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products.

(d) Expiration dates shall appear on labeling in accordance with the requirements of PP 201.17 of this chapter.

(e) Not applicable to medical gases.

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(f) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

In view of the Commissioner's General Comments 356 and 360 as found in the Federal Register Part II of September 29, 1978, we wish to make the following statements of clarification and request that the medical gases carbon dioxide, cyclopropane, helium, nitrogen, nitrous oxide and mixtures of these gases be exempted from expiration dating.

B. Statement of Grounds

The Good Manufacturing Practices Comments published in the Federal Register Vol. 43, No. 190, Friday, September 29, 1978, state in 360 "The Commissioner sees no justification at this time for exempting compressed medical gases from the requirements of expiration dating." The medical gas industry wishes to state again its conviction that medical gases should be exempted.

At one time the FDA stated that medical gases were subject to expiration dating as this is a requirement of the US Pharmacopeia. However, a closer look at the USP definitions and requirements reveals that the gases, with the possible exception of oxygen, are "drug substances" rather than "dosage forms". See page 1, last paragraph of "Official" and "Official Articles" and page 3 "Added Substances---". The medical gases are not administered as they are released from the cylinder, but are mixed by the anesthesiologist, who compounds the proper mixture for each patient. Page 9, "Expiration Date" requires an expiration dating of dosage forms only.

Medical gases are pure, chemically stable, elements or compounds, carbon dioxide, cyclopropane, helium, nitrogen, nitrous oxide and oxygen. They do not deteriorate, inter-react with the dry steel container, or change in purity, quality, strength or characteristics over periods of ten or twenty years. It is generally known that some gases, such as carbon monoxide, hydrogen, nitric oxide and nitrogen dioxide do react in steel cylinders. These gases in small parts per million concentrations, especially in the presence of oxygen and moisture, will disappear such that they cannot be held successfully as calibration standards. These unstable gases are the same gases which are potential contaminants in the medical gases. Thus, the quality of medical gases improves if any change does occur. We therefore believe that there is no logical justification for imposing an expiration date.

It is noteworthy that these same gases, carbon dioxide, helium, nitrogen, nitrous oxide and oxygen, and mixtures of these gases have been supplied industrially in similar steel cylinders for many years for precise laboratory applications in which specifications are generally more demanding than USP. Yet there is no evidence that any of these gases deteriorated, lost purity or quality due to age or adverse storage conditions, even though held for well over five years.

Comment 356 states "The Commissioner believes that expiration dating will be more than marginally beneficial to consumers even for drugs that are unusually stable. First, it will reinforce pharmacist and consumer confidence in the



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product and thus will avoid unnecessary disposal and replacement of old but not outdated drug products". The industry believes that in the case of medical gases, the opposite is true. The pharmacists and hospitals have demonstrated their faith in the stabilities of these gases by continuing to keep standby and backup cylinders for many years. The appearance of a three or five year expiration dating will destroy this faith. "My God! I wonder if this $CO_2$ cylinder I have been drawing from for the last twenty years is still good, if this new stuff is only good for three." There should be no hesitancy on the part of the doctor or hospital to use gas which has been filled ten or twenty years earlier.

It may seem strange that the industry should request exemption from expiration dating as such dating would cause the return, blow off and refill of cylinders reaching expiration. We are anxious to see cylinders which are in dead storage and serving no purpose returned to active service. Most cylinders of medical gas are used up in a few days, and the average return of empties to the supplier is three or four months. But there are many cases where relatively small quantities of gas, possibly 5 ml., are needed for treatment or research. Tissue freezing machines use small quantities of $CO_2$ or N2O and the cylinders may be used infrequently. Although O2 and N2O are piped from bulk supply in many larger hospitals, the anesthesia machines have small standby cylinders attached which are used in emergency breakdown only.

Nursery and transport incubators, transport stretchers and crash carts in hospital corridors carry back-up cylinders which are seldom used, but are vital in an emergency. Gases, particularly oxygen, are held for emergency use in homes and offices. Emergency squads at fire houses or beaches may have long unused cylinders. The steel cylinders are often purchased by the user because they will be in the user's possession indefinitely.

Expiration dating provides no element of protection from loss of safety, identity, strength, nor purity for the patient. There is no advantage, but probably a disadvantage to patient, doctor and institution to require return for refill of a perfectly good cylinder of gas. In this day of malpractice suits and over sensitivity to matters that are not clearly understood, it is a disservice to imply fault by applying an illogical expiration date.

Outdated gases cannot just be tossed out, as the high pressure steel containers are of several times the value of the gas contents. Furthermore, the return of a full (or empty) cylinder involves considerable shipping cost due to weight (15 pounds to 150 pounds per cylinder) with complex and unaccustomed paper work for the customer, as he normally ships back empty steel. The industry cannot give credit for outdated gas returned.

The Commissioner has made the point that packages containing unquestioned stable products should be dated and removed from stock after several years because cartons, labeling and general appearance become shoddy. Cylinders without labels or with illegible labels should not be used,but should be returned promptly to the supplier. But cylinders maintain as good an appearance as when delivered for years if kept in reasonable storage.

Medical gases are packaged in steel cylinders intended for refilling with no limit to years of service other than periodic hydrostatic retests for wall thickness and strength of the steel as required by the Department of Transportatic



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Such retests are required only for refilling. The gas contents of these stable gases may be retained and shipped interstate even though the cylinder itself may be overdue for the five or ten year retest.

If there is question as to leakage, the gases are under considerable pressure (up to 2200 pounds per square inch in the case of oxygen, nitrogen, and helium If the closure is not leak proof, the contents will be lost in a few days, not over a period equivalent to any expiration dating.

We urge exemption from expiration dating for these medical gases. They are an entirely different form of drug from those in capsules, tablets, powders, cartons or bottles. We do not believe the user will sense any inconsistency if these gases do not bear expiration dating like the other drugs in his supp

C. Environmental Impact

The discharge of outdated gas must be done by knowledgeable personnel in well ventilated areas free from hazards from spark or open flame, depending upon type of gas. The volume discharged would be insignificant in terms of environment.

Very truly yours,

J. C. Crawford

JCC:ssd

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TO: FEDERAL FOOD AND DRUG ADMINISTRATION
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PARK BUILDING ROOM 1-23
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FROM: COMPRESSED GAS ASSOCIATION'S MEDICAL GASES COMMITTEE

DATE: October 18, 1993

SUBJECT: Compressed Gas Association Citizen Petition
FDA Docket #79P-0067/CP

To Whom it May Concern:

This report is being submitted by the Compressed Gas Association's (CGA) Medical Gases Committee in support of CGA's Citizen Petition Docket #79P-0067/CP filed March 6, 1979 (a copy of which is provided as Enclosure I). This Citizen Petition was filed to exempt medical gases from the expiration dating requirement found in 21 CFR 211.137.

The medical gases listed in the table below were tested for stability by the following three CGA member companies: Air Products and Chemicals (AP), Airco/BOC (BOC), and Union Carbide Industrial Gases, Inc. (Linde) now called Praxair. The test data and the statistical analysis of the assay data for each gas is included in the attachments reference in the following table. Each company filled three cylinders of each gas as indicated by an X in the table below, and periodically conducted analysis of the contained product over a five to six year period. Test intervals were determined by each company and are indicated on the individual test data tables in the respective attachments to this report.

| ATTACHMENT | GAS | AP | BOC | LINDE |
|---|---|---|---|---|
| I | OXYGEN, USP | X | X | X |
| II | NITROGEN, NF | X | X | X |
| III | MEDICAL AIR, USP | X | X | X |
| IV | NITROUS OXIDE, USP | X | X | |
| V | CARBON DIOXIDE, USP | X | X | |
| VI | HELIUM, USP | X | X | X |
| VII | CARBON DIOXIDE/ OXYGEN MIXTURES | X | X | |
| VIII | HELIUM/OXYGEN MIXTURES | | X | |

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Dosage Form and Method of Administration

The dosage form and method of administration is gas/inhalation.

Specifications/Test Methodology

The purity (strength) of, and the maximum allowable contaminants contained in, each product are dictated by the current United States Pharmacopeia/National Formulary (USP/NF). The official USP/NF monographs and test methods (or validated alternate) were used during the study. At the time that the stability tests were initiated, there was no monograph for "Medical Air". There currently are no monographs for Carbon Dioxide/Oxygen mixtures or Helium/Oxygen mixtures. If alternate test methods were used by a member company, a description of the alternate method is provided in Enclosure III.

STATISTICAL ANALYSIS

The following formulas were used:

The arithmetic mean:

$$\bar{y}=\frac{(\Sigma y_i)}{n}$$

where $y_i$ = each obtained value, and
$n$ = the total number of values

The population standard deviation:

$$\sigma_y=\frac{\sqrt{\Sigma(y_i-\bar{y})^2}}{n}$$

The Slope:

$$a=\frac{n\Sigma xy-\Sigma x\Sigma y}{n\Sigma x^2-(\Sigma x)^2}$$

The Intercept:

$$b=\frac{\Sigma x^2\Sigma y-\Sigma x\Sigma xy}{n\Sigma x^2-(\Sigma x)^2}$$

y′ = the expected y value at x = 5 years (calculated in days)

y″ = the expected y value at x = 10 years (calculated in days)

using the linear regression slope formula: $y=ax+b$

CONCLUSION

Review of the data in the attachments indicates there is no product deterioration or instability over time for the products tested.

The Compressed Gas Association's Medical Gases Committee recommends that oxygen, nitrogen, medical air, nitrous oxide, carbon dioxide, helium and approved mixtures of these gases, be exempt from the expiration dating requirement specified in 21 CFR 211.137 and as requested in our petition docket 79P-0067/CP filed March 6, 1979.

Respectfully submitted,

Robert Danley

Robert Danley
Chairman CGA Medical Gases Committee

cc: Duane Sylvia
CGA docket file 86-11-6

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