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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: **Docket No. 03D-0165: Draft Guidance for Industry on the Current Good Manufacturing Practices for Medical Gases**

Dear Sir or Madam:

Air Products Healthcare provides the following commented related to the "Draft Guidance for Industry on the Current Good Manufacturing Practices for Medical Gases," Docket 03D-0165. The Notice of Availability for comment appeared in the Federal Register on May 6, 2003 at pages 24005 and 24006.

Air Products Healthcare, a wholly-owned subsidiary of Air Products, Inc., provides comprehensive home healthcare services, including respiratory care services, home medical equipment, rehabilitation and assistive technology, and infusion therapy services to over 100,000 Medicare and other government and private payors' beneficiaries. Our 51 locations covering primarily the New England, Northeast and Mid-Atlantic regions, provide medical gases to respiratory patients at their residences. We, therefore, limit our comments to those issues within this draft guidance that impact the manufacture and/or distribution of medical gases provided to our patients at their residences.

We believe that our comments will provide the agency with meaningful information, and that incorporating our proposed changes will assist the industry with clear guidance. In addition, as a member of company of the American Association for Homecare (AAHomecare), we concur with the comments regarding this guidance that were submitted by AAHomecare, and we will refer to their letter and Attachment I in our comments.

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Accredited by JCAHO

We have three general concerns:

1. "Recommendation" Phraseology – We believe that the use of the phrase "the agency recommends" throughout the document has a tendency of conferring greater authority to the agency-recommended practice. Although the boxed introduction in the document indicates that alternative approaches may be used for compliance, our use of an alternative approach in a state inspection, for example, may prove to be very onerous. Using this phraseology may limit the use of safe and acceptable alternatives to comply with the regulations. During the August 21, 2003 meeting between the agency and AAHomecare, the agency indicated that when an agency-recommended practice was included in a company's standard operating policies, the company would be in violation of CGMP if they did not follow their own SOP (the recommended practice becomes required practice for that company). We agree with this statement, but this will cause the agency-recommended practice (without proper rulemaking process) to become CGMP for the industry, when alternative, and perhaps better, practices may be acceptable.

   In addition, there were occasions during that August 21st meeting when the agency indicated that if we did not follow a recommended practice (e.g., the recommended content of complaint records), we would need to prove to the agency how our alternate practice meets the intent of the guidance, not just the regulation.

   The agency also indicated that guidance documents will now use the words "the agency recommends" as opposed to "should," "could," etc. per the Office of Chief Counsel. Through copy of this letter to Mr. Daniel Troy, Chief Counsel, we respectfully request that the agency reconsider this policy. We propose the use of the words "a firm may comply by..." or one method for complying with this regulation is to...," as a substitute for the "agency recommends" throughout the guidance.

   As described in the comments submitted by AAHomecare, we also propose that an introduction be incorporated into the guidance, similar to the information included in the 1989 Compressed Medical Gases Guideline. The introduction stated: "This guideline described practices and procedures for compressed medical gas (CMG) fillers...that constitute acceptable means of complying with certain sections of the current good manufacturing practice (CGMP) regulations for drug products (21 CFR Parts 210 and 211)."

2. Paraphrasing of Regulations – We are concerned by the significant amount of paraphrasing of the CGMP regulations throughout the draft guidance. We believe that the use of paraphrasing blurs the differences between what is regulation and what is guidance. We suggest that where regulations are presented in the guidance, that these regulations reflect the actual wording used in those regulations. We also believe that the regulations and guidance be organizationally separated and clearly defined in the document.

The use of paraphrasing may inadvertently have the effect of eliminating or adding requirements without regulatory basis. Although the regulatory citations are not in quotation marks, they are named immediately following each paraphrased passage within parentheses, giving the impression that the citation is a direct quote. Also, substituting the word "must" for the word "shall" when paraphrasing a regulation in the guidance document appears to confer greater regulatory authority to the guidance than stated in the regulations.

In many instances, where regulation is included in the draft guidance, the words "medical gases" have been substituted for the words "drug product." With this type of substitution, regulations that may not be directly applicable to medical gases now appear to be explicitly applicable to medical gases. The "medical gas" for "drug product" word substitution makes it appear that the operation cited in the guidance is in fact applicable to medical gases, or perhaps only to medical gases. We ask that the agency either simply cites the regulation as published in the CFR, or paraphrase to reflect only operations applicable to medical gases, and not those applicable to typical traditional pharmaceuticals.

Our comments on this paraphrasing issue are similar to those presented in the letter and Attachment I submitted by AAHomecare. As described in AAHomecare's information, we ask that the agency consider reversing or limiting the paraphrasing, and to also segregate the regulations from the guidance to enhance clarity of the document.

3. Citation of Historical Incidents – We are also concerned about the citation of historical incidents where medical gas mix-ups and other scenarios have occurred causing death, with inferences that these incidents were a result of a failure of the industry's manufacturers or distributors to follow or comply with CGMP. Many of these incidents were not directly related to manufacturer CGMP non-compliance, but rather to users circumventing the existing safety systems or not reading the product label.

   While we understand that the agency is seeking to use this document as a training tool, we believe that this is not the appropriate venue for citation of historical incidents. We suggest that either the Federal Register notice introduction to this guidance or the FDA Medical Gases website may be more appropriate for the background justification. We propose that, if the agency strongly believes that some incidents should be included in the document, then those could be provided in general terms, as opposed to the specific cases currently included in the draft guidance. If it is considered necessary to include these incidents, then we propose that the most appropriate place in the document would be at lines 65 through 75.

We are also concerned about the following specific issues that impact our company and our industry:

1. Issues related to the need to conduct Stability Studies, applying Expiration Dates and checking Cylinder Pressure for Backup Cylinders in Patients' Homes –

   A. Stability Studies/Expiration Dating – As described in the AAHomecare comments, we recommend that all medical gases, especially oxygen, be exempt from the expiration dating requirements. It is our understanding, based on discussion with agency personnel, that there is no concern that common medical gases, such as oxygen, have actual "stability" problems. It is also our understanding that the agency's primary concern is maintaining the pressure in unopened high-pressure cylinders. (See AAHomecare Attachment I – Item numbers 71, 72, 93, 94, 96 and 103). We agree with the comments on these issues submitted by AAHomecare that the original "stability" study data from CGA allows for plausible explanations for why some of the stability study cylinders did not have the "expected" amount of product contained within them.

   In addition, if the agency does not concur with our request to exempt medical gases from expiration dating requirements, we ask that all medical liquid oxygen be exempted, due to normal evaporation rates with cryogenic containers. During a seminar on October 8, 2003, the agency indicated that there was an expectation that cryogenic liquids would not be required to bear an expiration date.

   If the agency does not concur with either of these recommendations, then we recommend that the wording in the guidance reflect the wording in "Fresh Air 2000," allowing enforcement discretion on this issue, and to also allow the industry a sufficient amount of time (a minimum of five years from the date of publication of the final guidance) to comply with this change.

   B. Checking Cylinder Pressure in Patients' Homes –

   We recommend deletion of lines 794-799 stating that "...companies, especially home care companies and durable medical equipment suppliers, establish and follow a written plan to periodically verify the pressure (i.e, net content) of each high-pressure cylinder stored at a patient's home and that the results be documented." We believe that this recommendation is impractical, burdensome and offers no additional safety to the patient, and may, in fact, create an unsafe condition.

   Many homecare patients have cylinders stored in various locations, such as at relatives' homes, making it impossible for a firm like Air Products Healthcare to check all cylinders that might be delivered and left over a period of time. Even if this were possible, the data obtained would provide only a snapshot at the time the cylinders were checked. In addition, the recommended practice would require our company to remove the seals on post-valves of cylinders, which is how many patients traditionally ascertain if the cylinder has been used (has a seal indicates "full," no seal implies "empty"). Requiring our employees to break

or remove seals to check cylinder pressure may lead to confusion for our patients, and thereby in itself create an unsafe situation. There is also the possibility that the cylinders' valves would not be closed properly each time, causing the contents to "leak" out.

Typically, patients utilizing oxygen concentrators as their stationary system and high-pressure cylinders for portable use will have additional back-up emergency cylinders as well. Homecare companies, such as Air Products Healthcare, usually have 24-hour, 365-day on-call emergency services available, in the unlikely event that a back-up cylinder was found to be empty and required replacement for whatever reason.

For these reasons, and the others listed in Item #72 in the AAHomecare response, we support the deletion of the lines indicated above regarding checking of patients' cylinders in the home.

2. Calculating Theoretical and Actual Yields (Lines 626-639 of document) –

   We recommend that the current wording be deleted, and the following statement be substituted for current wording in lines 628-631 of the document: "Actual yields and percentages of theoretical yield do not need to be calculated for medical gases, as this provides no additional process control."

   Attempting to maintain accurate inventory records and reconciliation for liquefied gases would be difficult, due to normal losses of gas that occurs through vaporization, filling processes and venting. Efforts to calculate yield would provide no additional controls for these processes.

3. Issues associated with or potentially impacting curbside filling –

   A. Lines 61-62 of document: We recommend deletion of these lines, as finished product testing is not always required when a medical gas is moved from one container to another, such as when liquid oxygen units are filled at a patient's home from a previously qualified supply.

   B. Lines 558-560, and 568-569: We recommend quoting the regulations as published in the CFR, or change lines 568-569 to read: "Each component must be added to the batch by one person and verified by a second person either (a) at the time of addition, (b) after manufacturing operations have been completed but prior to distribution, or (c) after distribution if product is filled at the customer site." We do not believe that it would be fiscally sound to have a second person verify the liquid oxygen (each component) filled into a patient's vessel curbside by a driver technician (one person). This has been regarded as acceptable because oxygen is the only component involved and due to the unique circumstances of meeting the needs of our home oxygen patients (lines 568-569). Also, the filling of high-pressure cylinders is not observed by a "second"

person, rather the documentation is reviewed by a second individual (Quality Control Unit) after all manufacturing operations are completed.

C. Lines 670-673 and 682-683: We propose adding a sentence to this section that states, "Visual verification of labeling by a second individual does not apply to filling cryogenic home vessels at a patient's residence (curbside fills)." Although it is industry practice to apply labels by hand, it is not industry practice in all instances to have labeling performed by one person, and then independently verified by a second person. While we understand the regulatory requirement, this cannot be accomplished, nor is it industry standard, for labeling of cryogenic home vessels filled at a patient's residence.

D. Line 811: We recommend the addition of the following sentences regarding the quarantine of medical gases before release by the QCU – "Home care companies filling cryogenic vessels at the customer site are exempt from the requirement for QCU release prior to distribution. Documentation associated with this activity must be reviewed by the QCU within a reasonable period of time after distribution."

This exemption for home care companies is required due to conducting filling at the patient's residence. Current industry practice is to have the QCU review the documentation associated with the filling of vessels at the patient's home within a reasonable period of time.

4. Issues with Quality Control Unit Organization and Responsibilities, Personnel Qualifications and Responsibilities and Consultants:

A. Lines 113-114: We recommend that the wording be changed as follows – "A firm may comply by having the QCU's function be independent of the production process being reviewed." The current wording includes the use of the term "quality assurance," which is not defined. In addition, historically, the industry has utilized manufacturing personnel to perform testing of the product, in compliance with law and regulation, and has utilized "QCU" for record review and approval, including test results. Independence on the QCU has meant that the individual performing the QCU function at the time of the performance is independent of the actual process being reviewed. As we believe that multitasking is imperative to optimize efficiency at our locations, we are recommending the change in wording.

B. Lines 119-120: We propose changing the current wording to "All individuals who are part of the QCU may be identified in writing in a manufacturer's operating procedures or other document." This would allow the QCU member to be identified through alternate mechanisms, rather than addressing this issue in our SOPs.

C. In addition, we concur with the statements presented in the AAHomecare Attachment I for item numbers 6-12, 14-16, 24, 49, 52, 74 and 86.

5. Issues related to Facility Organization, Warehousing and Distribution and Security (Related to 21 CFR Part 205 – State Licensing of Wholesale Prescription Drug Distributors):

   We are in agreement with Item numbers 18-20, 73-78 from AAHomecare's Attachment I regarding these issues.

6. Issues related to Equipment Cleaning and Maintenance:

   We concur with AAHomecare's Item numbers 21-24, 88 and 98. The proposed changes reflect our industry practices more accurately, and would permit clarification of the current wording.

7. Issues related to Process Equipment Control, Calibration and Validation, including Evacuation issues, Computer Validation issues and 21 CFR Part 11 compliance:

   We believe that the comments submitted by AAHomecare for item numbers 25-27, 29, 42, 50, 51, 78, 83, 95 and 109 accurately reflect our opinions on these issues. In particular, we recommend consideration of the rationale for Item #50 (lines 541-545) vacuum evacuation to a minimum of 25 inches of mercury at sea level during high-pressure cylinder transfilling processes. In addition, we feel that the installation of pressure gauges at the end of a manifold is not required, as described in the rationale for Item #51 in AAHomecare's Attachment I.

8. Issues related to the Control of Components, Containers and Closures: We agree with the numerous AAHomecare Items listed in their Attachment I, including numbers 30-39, 43-48, 57, 58 and 113. These proposed changes would provide further guidance for the industry.

9. The following indicate the remainder of issues by topic and references to Item numbers from the AAHomecare Attachment I:

   A. Production and Process Controls – Items 53-58, 111.
   B. Product Labels/Labeling and other product identification items – 17, 40, 41, 46, 47, 53, 60, 61, 63-70, 77 and 117.
   C. Laboratory Controls and Test Method Validation: Items 79, 80, 82-85, 89, 91, 92, 104, 112 and 115.
   D. Records and Reports: Items 94, 97, 98-102, 104, 105, 107 and 112.
   E. Glossary, Terminology and minor editorial comments – 1, 44, 87, 106, 111-117.

We believe that the information in this letter, in conjunction with the 117 items identified and reviewed in the letter and attachment submitted by AAHomecare, provide appropriate rationale for the agency to modify the proposed guidance document.

If the agency does not concur with our proposed changes, we request that the agency meets with the American Association for Homecare prior to the final issuance of the guidance to further discuss our concerns, issues and recommendations, as well as the impact on the health benefits to our patients and our company.

We appreciate the opportunity to comment on this proposed draft guidance. If there are any questions regarding our issues, concerns or proposals, please do not hesitate to contact me at 1-888-243-3456, ext. 226.

Thank you for your consideration.

Sincerely,

Bob Cucuel
President and Chief Executive Officer
Air Products Healthcare

CC: Paul Haynie, Consumer Safety Officer, CDER, Office of Compliance
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