DONALD B. WHITE
President

PETER C. STOREY
Vice President, C.O.O.

ELIZABETH WOOLRICH
Vice President, Clinical Services

ARLETTA SAMULAK
Director of Finance

PATIENT MANAGEMENT CENTERS

BUFFALO
ALBANY
AMHERST
FINGER LAKES/ ROCHESTER
JAMESTOWN
OLEAN
PLATTSBURGH
SYRACUSE
WATERTOWN

SERVICES

Home Oxygen
Respiratory Therapy
Non-Invasive Ventilation
Respiratory Medications Pharmacy
Home Medical Equipment
Home Infusion Therapy
Sleep Apnea Treatment
Enteral Nutrition
COPD, CHF & OSA Disease Awareness Programs

FULLY ACCREDITED

Associated HEALTHCARE

2003 NOV -5 10:14

October 31, 2003

Dept of Health and Human Services
Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 30D-0165
Draft Guidance for Industry on the Current Good Manufacturing Practices for Medical Gases

Associated Healthcare Systems, Inc. is an independent Home Medical Equipment provider with 9 locations throughout Upstate New York. We provide compressed oxygen cylinders and liquid oxygen to our customers. Our corporate location provides compressed oxygen cylinders to four locations while the others obtain their cylinders from local suppliers.

We have certainly benefited from your "Fresh Air" guidance in the past. However, we feel the current *draft guidance* contains serious regulatory burdens for our company and the industry that do not ensure, nor improve, patient safety should it be adopted in its current form.

Our objections to portions of the Draft Guidance are as follows:

INTRODUCTION

Page 1, footnote #2: For the purposes of this document, the term *manufacturer* includes fillers, transfillers, cascaders, distributors, and transferors of medical gases.

This definition of 'manufacturer' expands to include more than organizations which are moving medical gases from one container to another. This definition would require every respiratory medical equipment provider to register, even when they simply obtain pre-filled oxygen containers from a supplier, warehouse it and then deliver it to a patient. Although the term "distributor' is later defined in the glossary, including it within the definition of 'manufacturer' has conflicting definitions with far reaching implications. We are requesting that the

03D-0165 C39

85 Woodridge Drive ▪ Buffalo, NY 14228 ▪ Phone: 716-564-4500 ▪ Fax: 716-564-4511
www.AssociatedHealthcare.com

terms 'distributors' and 'transferers' be dropped from the definition of manufacturer in the footnote on the first page.

RESPONSIBILITIES OF THE QUALITY CONTROL UNIT

Page 3, line 112: ..recommend that the QCU perform more than a testing function, be independent of the production process, and have *both quality assurance and* quality control responsibilities.
And line 124:... including quality assurance training.

Manufacturing quality assurance training is not relevant for the individual(s) who will be responsible for approving or rejecting any oxygen which is going to be distributed to patients. It either meets the requirements of USP or it doesn't. QA training is not as important as understanding their duties as members of the QCU. Compliance with the company's own written protocol is the issue. We request that the requirement for *quality assurance training* in addition to defined quality control responsibilities be dropped from the guidance document.

Line 169: We recommend that an individual responsible for performing an odor test not have an ailment (e.g. a cold or allergies) that would adversely affect his or her sense of smell. Likewise, employees responsible for performing the inspection for the standardized colors should be able to distinguish colors.

We are concerned that this directive will lead to additional required documentation on each batch production record where the filler or other member of the QCU verify that that the individual transfilling the oxygen is without symptoms of a respiratory infection or allergy; and the existence of records of a color-blind test be administered to staff who will be reviewing labels. We request that this additional documentation requirement be deleted from the guidance document.

SECURITY

Line 227: All facilities used for medical gas distribution must be secure from unauthorized entry.
Line 230: Entry into areas where medical gases are held must be limited to authorized personnel.
Line 238: A manufacturer could use an alarm system to secure the building and keep loading docks secure rather than open and easily accessible.

Most Home Medical Equipment providers distribute beds, wheelchairs and other equipment along oxygen from a warehouse with a loading dock. Within that warehouse is the oxygen transfilling and storage area. United Parcel Service and 18-wheeled trucks make frequent daily deliveries and pick-ups at this same loading dock. As a general rule visitors to the warehouse are either met or escorted upon entry. Random and open access is not granted to the

public for liability reasons. To require limited access, security against unauthorized entry, and to institute the purchase, installation and use of an alarm system is punitive and excessive. To date, there have been no instances where patient safety has been compromised through this routine business activity. We request that these requirements be dropped from the guidance document.

EQUIPMENT

Line 248: Equipment must be cleaned, maintained, and sanitized at appropriate intervals…
Line 253: …and cleaning schedules..

Causing a home medical equipment provider to start periodically using trichloroethylene on a periodic basis for cleaning oxygen equipment is asking for trouble. Wiping down the external working surfaces of a transfill system and performing manufacturer's periodic maintenance to the system is logical, but introducing cleaning and sanitizing to any internal surfaces within the system which conducts medical oxygen is beyond the scope of most home medical equipment providers and more likely to cause contamination of the finished oxygen. Have there been instances where a patient has become ill from pathogens within the dry gas system? Doubtful.
We request that the requirements for periodic cleaning and sanitization be clarified to address exterior surfaces or if necessary, that the task of cleaning the inside of hoses be outsourced back to the manufacturer of the hose or local contractor.

EQUIPMENT CALIBRATION

Line 296: and that the calibrations be documented in a separate log.

Why in a separate log? In some instances, this documentation is combined on a multi-use form. As long as it is documented, that should fulfill the requirement. We request that the 'in a separate log' be dropped' from the guidance document.

COMPONENTS, CONTAINERS, AND CLOSURES

Line 348: Each medical gas container and closure, upon receipt and before acceptance, must be examined visually for appropriate labeling as to contents, container damage, and contamination. Containers and closure must be stored under quarantine until they have been tested or examined, as appropriate……

We believe this is intended to refer to a new shipment of medical gas from a supplier. However, there is room to misinterpret this to also include receipt of empty or partially empty oxygen containers which have been retrieved from a patient's home. These containers would normally be placed in the 'empty' area

rather than 'quarantine' area. Please clarify that this directive refers to receipt of a new shipment of oxygen from a supplier. Also, if the definition of 'manufacturer' in the footnote continues to include distributors, *all* home medical equipment providers receiving oxygen from their supplier but who do not manipulate or apply a label to the product would still be required to purchase an analyzer capable of performing a purity test for the incoming oxygen. This is expensive, burdensome and excessive.

Line 400: We recommend that cylinders containing liquid be inverted and drained.

We believe this is intended to refer to a compressed gas cylinder. We also believe that this could be misinterpreted to indicate the expectation that cryogenic oxygen vessels are routinely inverted and drained of any residual liquid oxygen prior to refilling. The risk of cryogenic burns and fire hazards (visions of large amounts of oxygen boiling away in a metal barrel) we are sure are unintended. Please clarify that you are referring to draining any contaminant liquid from a compressed gas cylinder.

CALCULATION OF YIELD

Line 624 through line 626: Actual yield and percentage of theoretical yield must be determined at the conclusion of each appropriate phase of manufacturing, processing, packing, or holding of medical gases. Such calculations must be performed by one person and independently verified by a second person.

The guidance goes on to concede that FDA recognizes that accurate inventory records and reconciliation of use are difficult to maintain for liquefied gases. We propose it is also difficult to maintain for compressed gases. This entire requirement does not pragmatically transfer from Title 21, CFR 210 & 211 which are designed specifically for drug products in traditional dosage forms. This exercise has no impact on patient safety or quality of product. This exercise is cumbersome. Please acknowledge that all of lines 622 through 635 are not relevant and delete from this guidance.

PACKAGING AND LABELING CONTROLS

Lines 666-669: It is industry practice to apply labels by hand, therefore, we recommend a second person verify the correctness of the label and document the verification.

Please clarify that this would NOT be required if only oxygen (one gas) is transfilled at the location. There is no chance that the wrong label is inadvertently applied to the container if the facility is only labeling one medical gas. Per earlier procedures, the labels have been received, checked against the master, and stored securely. This step of having a second person verify the correctness of the label and documenting this verification after application to the container would be unnecessary.

Lines 678-681: In light of recent deaths and injuries, this examination is critical to ensure that the correct label has been applied to a container of medical gas.

Reference to deaths and injuries do not belong in a guidance document. This line should be deleted. Besides, "recent" would be incorrect usage in a long term guidance document.

Line 694: ..must require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued if the discrepancies are outside narrow preset limits based on historical operating data.

Medical gas containers are not routinely re-labeled with each new fill. Labels are replaced when damaged and/or illegible. Language in the draft guidance implies calculations between volume of oxygen and quantity of labeling issued; with parameters set for what the normal limit is for this ratio. None of this is logical for the medical gas industry. We request the entire reference for evaluation of discrepancies be struck from this document.

EXPIRATION DATING

Lines 773 through 780: To ensure that a medical gas meets applicable standards of identity, strength, quality, and purity at the time of use, each container must bear an expiration date determined by appropriate stability testing. Expiration dates must be related to any storage conditions stated on the label, as determined by stability studies described....

Oxygen is not a new drug; it is an ***element*** . Basic high school chemistry tells you elements to not decompose or change composition over time. Compressed gaseous medical oxygen has been stored and provided to millions of patients in steel and aluminum tanks for at least 50 years without any instance of deterioration of the drug product. Re-instituting expiration dating is regressive and unnecessary. In order to effectively establish an expiration date for medical oxygen, it would also be necessary for each transfiller to research, understand, and establish scientific method for stability testing. Institution of expiration dating is both unnecessary and contrary to basic chemical science; **elements do not expire!**

Line 782: expiration dates must appear on the labeling....

Currently, Lot number labels with, or without, expiration dating are applied in addition to the to the drug label. The lot number label/tag must be removed with each fill whereas the drug label is replaced only when damaged or illegible. Why would expiration dating <u>ever</u> be applied to the drug label? The cost or replacing the drug label upon each refill because it contains an expiration date

is considered unnecessary and extravagant and should be removed from the guidance.
If expiration dating persists, please clarify that it is acceptable to have it appear on the lot number label/tag which is separate from the drug label.

Line 791 through 794: We recommend 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.

Home Medical Equipment providers have a vested interest in ensuring that patients have adequate backup supply oxygen in the case of a concentrator malfunction.
First, this is over-extending FDA's jurisdiction from establishing quality processes for medical gases to standards of care in the home.
Second, requiring documentation of the pressure in the patient's back up cylinder implies that portions of the patient file containing this information could be audited at the time of a FDA inspection since this information typically is documented on the company's delivery ticket or concentrator check form. This runs contrary to many HIPAA regulations for privacy of medical records.
Third, to monitor the pressure in each cylinder after it is filled would require the cylinder or the oxygen regulator to have a pressure gage attached. This would be a new and costly requirement imposed solely on the home care industry.

LABORATORY CONTROLS

Line 876-885: In the past, deaths and injuries have resulted from adulterated products that contained contaminants or impurities that were not detected. In one example, a carbon dioxide (CO2) manufacturer in Tennessee failed to include an analysis for hydrogen cyanide in its finished product testing. As a result, the manufacturer released several large liquid batches of medical CO2 that were contaminated with this deadly toxin. The source of this problem was the lack of an agreement between the supplier and the CO2 manufacturer requiring notification of any change in the manufacturing process. Fortunately, the problem was discovered before any injury occurred. Our investigation found the supplier of the raw material had changed the manufacturing process, which resulted in elevated hydrogen cyanide levels. Because testing for hydrogen cyanide was not performed, an adulterated drug product was released.

Anecdotal references to mishaps, death and injury do not belong in guidance material. Per the definition for 'Guidance' in FDA Manual of Policies and Procedures, MAPP 4000.2: "guidance are prepared to establish clarity and consistency in FDA policies, regulatory activities, and inspection and enforcement procedures.... Guidance documents do *not* include: (6) other communications or actions taken by individuals at the FDA directed to individual persons or firms.
This entire section should be removed.

STABILITY TESTING

Line 1128 through 1147: Medical gases are subject to the requirements in § 211.166 – Stability Testing. There must be a written testing program designed to assess the stability characteristics of medical gases. The results of such stability testing must be used in determining appropriate storage conditions and expiration dates. The written program must be followed and must include

- **Reliable, meaningful, and specific test methods**
- **Testing of the medical gas in the same container-closure system as that in which the medical gas is marketed**
- **An adequate number of batches of each medical gas must be tested to determine an appropriate expiration date, and a record of such data must be maintained**

The Agency recommends that the testing program take into account the compatibility of the valve assembly, the acceptability of the valve packing and the valve seal used, the type of cylinder, and any other factor that can have an effect on the stability of the medical gas. Each medical gas would be tested for stability in the exact container closure system that it is marketed in, such as steel high-pressure cylinders, aluminum high-pressure cylinders, and cryogenic containers.

As stated earlier in response to lines 773 through 780, stability testing of oxygen the element is impractical for the medical equipment industry and unnecessary for the element oxygen. Once the purity test establishes the contents of a cylinder as Medical Grade USP 99.0% or above, the element oxygen does not decompose nor change composition as a chemical compound might.

Stability of "valves" and their ability to maintain pressure for specific periods is a DOT responsibility not within the prevue of the FDA. Please note the FDA (even the medical devices section) does not approve cylinders or valves, of any type for use in the gas industry. The valves are an integral part of the cylinder and are regulated by the DOT. The fact that a cylinder meets the DOT standards is all the law requires and not appropriate for redefinition in a FDA Guidance document.

The ability of a cylinder to maintain pressure is likewise a DOT responsibility; licensed and regulated by the DOT.

MEDICAL GAS MIXUPS

Line 1576 through 1623 do not belong in a guidance document. See previous comment referencing FDA Manual of Policies and Procedures, MAPP 4000.2 .

GLOSSARY

Line 1835: We recommend they be validated. (Hand held analyzers)

A Home Medical Equipment provider does not have the ability to 'validate' their oxygen analyzers. Hand held oxygen analyzers are used to verify identity only,

they are not used to verify purity of liquid or compressed oxygen because they have too wide a variance in accuracy - ± 3 percentage points.

Our Summary: This guidance document should not impose impractical requirements on the manufacturing process. If you examine the history of problems with medical gases, you will **not** find the problems to have occurred in the manufacturing process but rather in the delivery or dispensing processes.

Yield calculation, expiration dating, stability testing, quality assurance training, and other burdensome requirements for documentation will not improve the safety of the manufacturing process. Rather, they will serve as distractions, diluting attention from the steps in the process with real meaning. These unnecessary processes have not been enforced for a number of years and we challenge the FDA to cite one instance where they would have improved the quality of the product manufactured. Have these processes ever been cited as possible remedies to problems at the user end of the chain?

Medical Gases are uniquely different from the other drugs/medications the FDA oversees. In the past several years the FDA has recognized this difference and provided reasonable guidance which allowed manufacturers to focus on steps in the process which have a direct effect on the final product's suitability for medical use. Unnecessary steps do nothing to improve the process,

Adding unnecessary steps to the manufacturing process will only provide areas to field agents to examine, they will not improve safety.

Please consider the recommendations we made.

Sincerely,

Dennis E. Trach

Dennis E. Trach
Regulatory Compliance Manager