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November 3, 2003

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Re: **Docket No. 03D–0165: Draft Guidance for Industry on the Current Good Manufacturing Practices for Medical Gases**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

Lincare offers the following comments for the "Draft Guidance for Industry on the Current Good Manufacturing Practices for Medical Gases", Docket 03D–0165.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 (pp. 24005, 24006).

Lincare is a home respiratory company that principally provides medical oxygen to patients in their homes. Accordingly, we limit our comments to medical oxygen manufactured for and used in the home care setting. We currently have over 440 locations registered as medical oxygen manufacturers, and have serious interest in the outcome of the CGMP guidance document for medical gases.

In the past, it seemed that the proposed guidance document's predecessor, the "Fresh Air" series, became a standard for use in inspecting medical gas manufacturing firms. Consequently, the industry, in many cases, aligned its practices with the expectations advanced in the "Fresh Air" guidance document. This being the case, any changes to the positions held in "Fresh Air", including the development of the proposed guidance document, have great impact on our industry organizationally, methodologically, materially and economically. As such, we are hopeful that the agency, in the development of "Fresh Air" into an official guidance, will consider and, where appropriate, incorporate the information presented by AA Homecare's response, as well as the response in this letter.

Our representatives, as members of AA Homecare's medical gases committee, attended a meeting with FDA's Pamela Schweikert, Duane Sylvia and Paul Haynie on August 21, 2003, in order to further inform our response to the Federal Register posting of the guidance document. We appreciate the agency's willingness to work with the industry through AA Homecare's medical gases committee, which has expended a great amount of time and effort in analyzing the

industry while retaining, and, we hope, enhancing, the safety of homecare patients. Lincare supports AA Homecare's proposed changes, both in its response letter and in its 53-page attachment, which echo our own concerns. Herein, we will highlight, and, in some cases, expand upon the recommended changes that we find to be especially important.

AA Homecare's Concern 1 – Recommendation phraseology:

Throughout the proposed guidance document, the phrase, "the agency recommends", is used to introduce explanations of how to comply with the stated regulations. While the boxed introduction on page 1 allows for alternative approaches, the weight of the words, "the agency recommends", repeated throughout the document, implies that the agency is less likely to accept alternative means of compliance than may be the case. The 1989 "Compressed Medical Gases Guideline" contained introductory language that could be useful in the proposed guidance's introduction, and could be used thematically throughout the text, such as the following passage:

> "This guideline describes 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)".

Further, the 1989 guidance, throughout the text, did not "recommend", but named "acceptable methods" of compliance. For example, it used phrases such as:

- "An acceptable method of assuring..."
- "FDA considers it acceptable to continue to use..."
- "Acceptable procedures ...in such circumstances would include..."

The 1989 guidance's wording is preferable because it still conveys an acceptable method without imposing the potential burden of meeting a "recommendation" that may not be the only method for compliance and may not be required by the regulation. Coming from the agency, the word "recommend" connotes greater authority than we believe is intended for the guidance document.

AA Homecare's Concern 2 – Paraphrasing of Regulations

CGMP regulations are often paraphrased in the proposed guidance, rather than exactly quoted, even though the regulation numbers appear parenthetically, immediately following the paraphrased quotation of the regulations. For example, the guidance frequently replaces the word "shall" (as is used in the regulations) with the word "must". The word "must" is known to be stronger than the word "shall", so the guidance appears to claim greater authority than do the regulations. We see no purpose in misquoting the applicable regulations, which already contain carefully considered language, and propose that the applicable regulations be accurately quoted.

Throughout the proposed guidance, the "guidance" and the regulations are blurred, in that the regulations are interwoven with the guidance throughout the text. For example, in lines 1463-1474, the agency recommends that complaint records include certain information. The ensuing list contains the requirements of § 211.198, but adds new elements to complaint records, such as the address of the complainant, the date the complaint is received, the initial action taken, including dates and the identity of the person taking the action, and the date the response was sent to the complainant. It might be argued that guidance is segregated from the regulations because the list containing the added language is preceded by "the agency recommends", however the segregation of the "recommendation" from the regulations could be made more clear: in the proposed guidance, the list of requirements for complaint records is both preceded and followed by passages containing paraphrased quotations of the regulations, which are named parenthetically. A more desirable approach would be to use the format used in the 1989 guidance, where the applicable regulations were quoted under a "requirements" heading and the guidance was quoted under a "guidance" heading. Organizational separation and clear identification of regulations and guidance would provide a more accurate portrayal of what is required, contrasted with what is recommended.

The proposed guidance could be a more effective teaching tool if organized like the 1989 guidance. In its current form, the proposed guidance more closely resembles a talk-paper, rather than a stand-alone written teaching tool, in that the organizational units of "regulation" and "guidance" are blurred because there are no headings to announce which language is regulation and which is guidance. Part of a talk-paper's organizational effectiveness lies in the multiple elements of the presentation (i.e., projected slides, handouts, and the speaker's vocal cues, gestures and timing). These elements are not present in a written guidance; therefore using headings to differentiate guidance from regulations would be very beneficial.

AA Homecare's 'Specific Issues'

Please see AA Homecare's Attachment 1, which contains 117 "items" proposing changes to the proposed guidance document. We would like to accent some of those proposed items here, but also support the items as they stand in the AA Homcare letter and attachment. The following issues in the draft guidance are of specific concern given their impact on our industry and their uncertain value in enhancing the safety of our patients. The items below are numbered to coincide with the "item" numbering system in AA Homecare's response. Because the "recommendation phraseology" and the "paraphrasing of regulations" are addressed above, the following comments will be limited to other specific issues of special importance. **Please note that the following item numbers reflect AA Homecare's Attachment 1, but the page and line numbers coincide with the PDF version of the proposed guidance posted on the internet.**

Item 2, page 2, lines 61-62:
The current wording does not allow for the filling of medical oxygen at a customer's residence without further testing. Filling 'curbside' without further testing is industry standard when there

is documentation of the testing of the source vessel on a certificate of analysis (COA), as is recognized later in the proposed guidance.

Item 8, page 3, lines 119-120:
The proposed guidance recommends that QCU individuals be identified in a firm's operating procedures, however we believe it more practical for QCU personnel assignments to be kept in a local file and/or posted on a wall, because our many registered locations use the same set of operating procedures issued by the corporate office.

Item 17, page 5, lines 216-217:
The proposed guidance recommends 360-degree wrap-around labels to identify medical gases in large cryogenic containers (LCCs), but does not recognize that some LCCs are permanently mounted to vehicles. We believe that labeling visible to the filler as he/she is working the controls is adequate in such cases, because permanently mounted vessels are always situated in the same position, rather than being turned around as happens with LCCs that are not permanently mounted to a vehicle.

Item 20, page 6, lines 234-237:
The proposed guidance states that § 205.50(b) applies to all facilities used for medical gas distribution, however § 205.50(b) applies to wholesale distribution and some medical gas distributors are not wholesalers. The proposed guidance also extends security requirements to delivery vehicles parked at employees' homes for early morning runs, but § 205.50(b) refers only to "facilities", not to delivery vehicles. Many State licensing laws do not specify that security alarms are required for delivery vehicles, but only speak to security of "facilities".

Item 23, page 6, lines 261-262:
The proposed guidance recommends the use of protective end caps to prevent contamination of hoses used to fill cryogenic containers. This is sensible for fill hoses with open ends, however some fill hoses have attached to them special fill heads that already do not allow contamination due to insects, dirt, debris, etc. End caps would be redundant and inappropriate for such equipment.

Item 24, page 7, lines 267-271:
The proposed guidance recommends that containers, such as high-pressure cylinders and cryogenic containers, be cleaned when they are first received, whether new or used. When new, these containers are cleaned for their particular service prior to shipment by the device manufacturer. To require that they be cleaned again upon receipt (other than exterior cleaning) by the receiving firm would involve de-valving cylinders and removing poppet valves from cryogenic containers, then introducing cleaning agents, removing the cleaning agents and re-inserting the valves. We believe this is beyond the scope of operations in most homecare firms, except perhaps at their specialized repair facilities, who would still have to ship the cleaned equipment to their field offices, who would again have to "receive" the equipment. The potential for error in the cleaning process and/or error in re-valving such equipment at small field offices

not equipped for internal cleaning of cylinders and cryogenic containers is real, and we strongly suggest accepting AA Homecare's proposed re-wording of this passage.

Additionally, some equipment manufacturers sell new medical gas cylinders that are already filled and labeled as a finished drug product. To then empty the new cylinder to clean it and refill it would be redundant.

In the homecare environment, used equipment, such as cylinders and cryogenic containers, is continually recirculated through the homecare company for refilling. To again clean such equipment internally at the time of each receipt would be burdensome and could entail unnecessary risk. Also, high- pressure cylinders are examined and odor tested by the filler prior to each fill.

Item 33, page 9, lines 390-391:
The proposed guidance allows for ultrasonic testing of steel cylinders, but ultrasonic testing of *aluminum* cylinders is also permissible.

Item 34, page 9, lines 397-399:
The proposed guidance recommends that cylinders failing prefill inspections be removed from service until their suitability has been determined by the QCU. However, the person who determines a cylinder's suitability may not always be a member of the QCU. For example, if a cylinder were removed because its hydrostatic test date was due, the hydrostatic tester would determine the cylinder's suitability, not necessarily the QCU person of the firm that sent the cylinder for requalification. The firm's QCU would have the overall responsibility of assuring that a process is in place to assure valid requalifications.

Item 44, page 11, lines 475-477:
Line 475 is the heading of Prefill Inspection section 4, called "Prefill Inspections of Large Cryogenic Containers". We suggest changing the heading to "Prefill Inspections of Large Cryogenic Containers *not Permanently Mounted in a Vehicle*" so that it can not appear that that the inspections of LCCs permanently mounted in a vehicle are subject to both sections 4 and 5. We believe that they are only intended to be subject to section 5.

Item 46, page 11, lines 487-488:
The proposed guidance recommends that LCCs be labeled with 360-degreee wrap-around labeling stating "Medical Oxygen". The current official name of the product is "Oxygen, USP", so we believe that existing labeling stating "Oxygen, USP", should be considered adequate. A firm should provide training so its employees know that Oxygen, USP, is medical oxygen.

Item 47, page 12, line 502:
The proposed guidance, under "Prefill Inspections for Permanently Mounted Cryogenic Containers", lists an inspection of the product label. We recommend that "product label" be replaced with "product identification" or "product marking", instead of "product label" because

permanently mounted LCCs are not end-use containers. Currently, in industry, some product suppliers will not place their 'drug labels' on permanently mounted LCCs, because wording on their drug labels does not apply to some features of permanently mounted vessels, which are not end-use containers.

Item 50, page 13, lines 541-545:
The proposed guidance recommends that a manufacturer (especially of multiple gases) have data on file demonstrating the amount of vacuum evacuation required to remove all contaminants from high-pressure cylinders. However, the industry standard has long been that a vacuum be pulled to negative 25 psi (at sea level), and we aware of no negative outcome from this practice. AA Homecare's Attachment 1 provides an excellent mathematical analysis, proving that the current industry standard should be considered acceptable and should be continued.

Item 53, page 13, lines 571-575:
The proposed guidance recommends that all high-pressure cylinders and cryogenic containers be filled according to the net content statement indicated on the label. We understand this to mean that grocery-store type shoulder-stickers, which currently show the lot number and the statement of contents, would no longer be allowed (see proposed guidance page 17, lines 732-733), and that the statement of contents would have to be on the drug label, itself. This would necessitate another mass relabeling of medical gas containers, which was only recently completed to accommodate the "Rx ONLY" relabeling initiative that was accomplished under the deadline of February 19, 2003. We ask that another relabeling burden not be placed on the industry at this time, because the labor, time and expense of replacing literally millions of large, very sticky, cylinder labels is great. We understand that the agency is concerned that shoulder stickers may fall off, however our practice is to not deliver containers whose shoulder stickers have fallen off and, if they do fall off, to move to shoulder stickers that have better adhesives. If the agency rules that the contents statement must be on the drug label and not on a supplemental sticker, we ask to be given the same amount of time to complete the project as we were given for the recent relabeling (5 years).

The proposed guidance states that the net content statement can be the same as the fill pressure or the service pressure. On high-pressure cylinders, the maximum service pressure is stamped into the shoulder of the cylinder, and industry practice is to fill high-pressure cylinders as closely as possible to the maximum service pressure, without going over, so the container is essentially already marked as to contents by psig, when full.

On home cryogenic containers (HCCs), the net contents are typically listed on the device manufacturer's label, so requiring it on the filler's drug label would be redundant. The standard practice in industry is to fill HCCs until full, which is typically defined in device manufacturers' instructions as 'when liquid product begins to flow from the vent valve'.

Item 55, page 14, lines 587-588:
The proposed guidance indicates that the temperature and pressure of high-pressure cylinders should be recorded on the batch production record before the filling is complete. We believe that recording the temperature and pressure should be allowed *after* the filling is complete. This is current industry practice, because fillers monitor the temperature and pressure and must have their hands free to close supply valves at the correct time, otherwise overfilling could occur.

Item 57, page 14, lines 597-598:
The proposed guidance states that it is critical not to overfill aluminum cylinders. AA Homecare's proposed wording is more complete, in that it addresses the fact that, "no overfill allowance is made for aluminum or composite cylinders, which should not be stamped with a "+" symbol".

Item 58, page 14, lines 611-613:
The proposed guidance states that, when filling high-pressure cylinders, the second leak test should be performed "after all valves have been closed". While true, it is even truer that the second leak test should be performed after the valves are closed and after the cylinders have been removed from the manifold. To perform the second leak test with cylinders still attached to the manifold would not help in determining that the cylinder valve has been fully closed because any leaks would be channeled into the manifold and would, consequently, not be apparent until removal from the manifold.

Item 59, page 15, lines 626-639:
The proposed guidance would require that actual yields and theoretical yields be determined at the conclusion of each appropriate phase of manufacturing, processing, packing, or holding of medical gases. Until now, the industry has been exempt from this regulation for the good reasons listed in AA Homecare's Attachment 1, and we ask that the exemption be continued because we are aware of no negative consequences due to the current practice and we see no likelihood of further positive results that would occur in the quality of care for our patients. While it may be that, for reasons of security, medical gases such as nitrous oxide should be subject to the calculation of yield rule, our interest is in Oxygen, USP, and we believe that Oxygen, USP, should continue to be held as exempt.

Item 65, page 17, lines 732-733:
The proposed guidance recommends that cryogenic home containers filled on site or by a third party in advance for future delivery be given a lot number. We feel that AA Homecare's proposed wording more completely reflects the possible circumstances that can arise when filling a cryogenic home container 'on site', in that a distinction is made between containers filled for stock and containers filled for a specific patient for near-immediate delivery. In any event, the container should be assigned a source lot number on the batch production record and the patient's paperwork, but not necessarily its own, *unique*, lot number on a lot tag if the container's destination is known (akin to curb-side filling). We find that assigning unique lot numbers under

this circumstance would unnecessarily complicate paperwork by lengthening the chain of traceability, making errors more possible.

Item 66, page 17, lines 739-741 (also see Item 53, page 13, lines 571-575):
The proposed guidance recommends that the net contents on medical gas cylinders and cryogenic containers not be on a removable tag, a certificate of analysis or a small separate sticker. For the reasons stated earlier relative to Item 53, and for the reasons presented by AA Homecare's Item 66, we ask that the recommendation be deleted.

Item 68, page 18, lines 757-758:
The proposed guidance recommends the use of a 360-degree wrap-around label to identify medical gases in large cryogenic containers. This does not reflect the unique labeling circumstances of permanently mounted LCCs (please see the earlier commentary on Item 17, regarding page 5, lines 216-217). Additionally, AA Homecare's proposed change, "A 360-degree wrap-around label may be used as an additional means to identify gases in large cryogenic containers that are not permanently or semi-permanently mounted in vehicles", more accurately reflects other guidance documents on this subject (see the FDA Public Health Advisory flier, "Medical Gas Mix-ups Can Cause Death and Serious Injury", and the "FDA Public Health Advisory: Potential for Injury from Medical Gas Misconnections of Cryogenic Vessels", and the FDA Public Health Advisory, "Guidance for Hospitals, Nursing Homes, and Other Health Care Facilities").

Item 71, pages 18 and 26-27, lines 776-788 and lines 1136-1156:
The proposed guidance seeks to disallow the current exemption of medical gases from expiration dating. We request that the exemption of medical oxygen be continued for the stated reasons in AA Homecare's Attachment 1 (items 71 and 72). If the agency does go forward with requiring expiration dating of medical oxygen, we ask that sufficient time be allowed for the industry to conduct joint stability studies. While the lone stability study performed years ago may have yielded some negative results as to cylinders holding product over time, we feel the fault may have been in the study, rather than the stability of the containers.

We ask that liquid medical oxygen continue to be exempt, because its normal evaporation rate precludes the establishment of any meaningful expiration period. Also, when filling cryogenic containers at a patient's residence, it is a standard practice to not empty the previous lot from the container prior to filling, resulting in a batch that takes on the lot number of the newest refill. Although it receives a new lot number, a percentage of the previous lot remains. If the previous lot were to 'expire', the only way to assure that no percentage of the previous lot remains would be to vent the current lot, as well. This would be impractical and inadvisable, as releasing liquid oxygen in large quantities increases risk (1 measure of liquid oxygen = 860 measures of gaseous oxygen).

Item 72, page 18, lines 794-799:
The proposed guidance recommends that homecare companies check each high-pressure cylinder stored for long periods of time in patients' homes to monitor and verify the pressure (net content). This would entail removing the protective tape or cap that patients customarily use as an indicator of which cylinders are full, then attaching a regulator, opening the valve and re-closing the valve. The result would likely be patients' confusion of empty cylinders for full cylinders, and would be much worse than the industry not having new stability studies finalized. As well, contaminants could more easily pass into the valve's port during storage following the removal of the protective tape or cap. We believe it inadvisable to interfere with a finished drug product in our patients' possession. In the industry, it is common practice to check that one of a patient's back-up cylinders, typically the one that already has a regulator attached and has already been opened, has adequate contents, and this act is documented. But it is not industry practice to remove the seal of each cylinder and attach a regulator to double-check the contents. We submit that the industry is already providing a viable solution for the unlikely event of cylinder leakage, in that multiple back-up cylinders are provided for patients who need them and on-call personnel make daytime and after-hours deliveries if their patients need cylinders due to emergencies, such as power failures. We support the thorough AA Homecare rationale (item 72) for not adding this impractical and potentially unsafe interference with a finished drug product in the patient's home.

Item 74, page 19, line 811:
The proposed guidance states the regulation for the quarantine of medical gases before release by the QCU. While this statement falls under "warehousing procedures", we suggest adding a clarification to exempt home care companies from QCU reviews prior to release if they are filling liquid medical oxygen at their patients' residences, because it is not possible for a QCU person to ride along with each delivery person.

Item 77, page 19, lines 840-845:
The proposed guidance recommends the use of a 360-degree wrap-around label to identify medical gases in large cryogenic containers. We request a notation in the guidance recognizing that permanently mounted LCCs are not subject to the recommendation of 360-degree wrap around labeling. Please see item 68 for related comments.

Item 86, page 23, lines 995-996:
The proposed guidance recommends that employees responsible for witnessing their supplier's testing of incoming liquid oxygen should be trained in the supplier's analytical methodology and that the employee's company document the training. We agree that the employee's company should maintain the training records, however the supplier who conducts the training usually documents the training, and the trainee's company just maintains the record.

Item 91, page 26, lines 1125-1126:
The guidance recommends that test methods alternative to the official USP test method be compared against the official testing methodology. We agree, but the guidance also lists hand-

held analyzers as subject to comparison. With medical oxygen, hand-held analyzers only check for identification and are not used to prove purity, so they are not comparable with the official testing methodology.

Item 93, page 26-27, lines 1134-1156:
The proposed guidance requires stability testing of medical gases. For reasons given with item 71, we suggest that medical oxygen be exempted from stability testing.

Item 96, page 27, line 1197:
The proposed guidance requires stability testing, which we suggest deleting based on the rationale in item 71.

Item 102, page 30, line 1289:
The proposed guidance recommends that batch production and control records have the signature of the individual who checked the entries for accuracy and completeness. We ask that the guidance reflect § 211.188(b)(11), which requires *identification* of the persons performing and directly supervising or checking each significant step in the operation.

Item 103, page 31, lines 1368-1369:
The proposed guidance requires stability testing, which we suggest deleting based on the rationale in item 71.

Item 105, page 33, lines 1422-1423:
The proposed guidance recommends that a certificate of analysis for a liquid supply of medical gases contain the specific model number of the analyzer used, however we suggest that only the test method used to perform the analysis be included, and not the specific model. Some liquid oxygen suppliers' COAs show only the test method, i.e., paramagnetic analysis. Their internal production records would contain proof of the specific model number used to conduct testing.

Item 112, page 43, lines 1817-1818:
The proposed guidance defines a certificate of analysis as a single document. Although we agree that a single document is easier to handle than multiple documents, it is also possible to keep multiple documents on file. We suggest replacing the phrase "a single document" with the word "documentation".

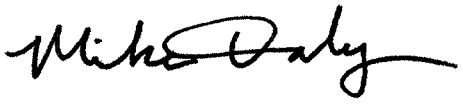
Item 113, page 43, lines 1826-1830:
The proposed guidance defines cryogenic containers, however we suggest further differentiation of the various types of cryogenic containers. Please see AA Homecare's item 113 for an example.

Item 115, page 43, lines 1844-1845:
The proposed guidance defines hand-held oxygen analyzers and lists several types of hand-held analyzers, but excludes other types. Several manufacturers make ultrasonic hand-held analyzers,

but they are not listed in the definition. Other technologies may be developed during the lifetime of this document, therefore we suggest a definition such as, "Oxygen analyzers used for ID testing Oxygen USP and/or for testing the output of oxygen concentrators: they do not have the required accuracy for determining potency".

We hope the above suggestions for the proposed guidance document can contribute to its overall effectiveness. Lincare appreciates the opportunity to comment. Thank you for your consideration of our concerns.

Sincerely,



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