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February 9, 2005

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

Re: **Docket No. 2004D-0443: Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, Availability**

Dear Sir or Madam:

Linde Gas LLC is a leading manufacturer and supplier of Medical, Industrial and Specialty Gases. Linde Gas LLC is located in over 50 countries with the Corporate Headquarters for the United States regional office located in Cleveland, Ohio.

As a manufacturer and supplier of medical gases, the company has an interest in "*Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*," Docket No. 2004D-0443. The Notice of Availability for comment on the referenced draft guidance appeared in the Federal Register on October 4, 2004 at page 59256, and would like to make the following comments and will limit its comments to those issues affecting the manufacture and/or distribution of medical gases provided to our customers. .

We appreciate the goal and scope of the guidance as stated in sections B and C of the draft guidance, and agree with the philosophy described in both the CGMP regulations and quality systems that quality must be built into the product. However, contrary to lines 538 and 539 of the draft guidance that state that the "...language...has been tailored to the pharmaceutical manufacturing environment," it does not appear it has been tailored to account for the uniqueness of the many aspects of the medical gas segment of pharmaceutical manufacturing. Throughout the guidance, the terms "robust" and "modern" are associated with the words "quality system," and in line 353 it states, "Implementing a robust quality system can help ensure compliance with regulations." Although it is not explicitly stated in the guidance, that failure to implement the recommendations, as described in this guidance, may prohibit one's ability to comply. We recommend that the words "robust" and "modern" be dropped for the guidance document. The use of the word "current" may be an acceptable alternative word.

2004D-0443

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Linde would like to offer the following comments related to two areas of the draft guidance, (1) The Quality Unit, and (2) Audits.

Quality Unit; Pages 5 and 6 Lines 200 through 238

In response to the Docket No. 03D-0165: "Draft Guidance for Industry on the Current Good Manufacturing Practices for Medical Gases". Linde Gas and The Compressed Gas Association in which Linde is an active member, provided comments regarding the structure of the Quality Unit which Linde believes are appropriate for the agency's consideration in this guidance.

The Medical Gases draft guidance recommended "...that the Quality Control Unit perform more than a testing function, be independent of the production process, and have both quality assurance and quality control responsibilities." We proposed that the Medical Gas guidance be modified to, "A firm may comply with CGMP's by having the Quality Control Unit's function be independent of the production process being reviewed." Our proposed change was based on the medical gas industry's long standing practice of utilizing qualified manufacturing personnel to perform testing of in-process and final product to ensure established specifications have been met (the quality control function), and utilizing the "QCU" for among other things record review and approval (the quality assurance function), including review and approval of test results. This practice has historically been accepted provided there are appropriate controls and safeguards to prevent conflict of interest situations (i.e. individuals are not permitted to review their own work.) We propose that lines 204 through 212 of the draft QS Guidance be modified to reflect a similar option.

Lines 234 through 238 of the draft QS Guidance appear to key on the "independence" of the Quality Unit. These lines also discuss the Quality Unit in "small operations". The Medical Gases draft guidance indicates, "In a well-structured and well-defined corporate structure, the QCU would be included as a separate unit", and further stated, "A small medical gas manufacturer can designate a single individual as the QCU." Historically, independence of the QCU in the medical gases arena has meant that the individual performing the QCU (QA) function at the time of its performance is independent of the manufacturing and quality control process he or she is reviewing. Regarding the size of the QCU, we proposed that the Medical Gases draft Guidance state, "The size and complexity of a Quality Control Unit varies greatly with the size of the operation and tasks assigned. (Medical gas) manufacturers may operate one or more locations where a single qualified individual may be appropriately designated as the QCU at each location. Other locations may require more than one qualified QCU individual." We believe that the size of the manufacturer should not dictate the setup of the QCU. We believe the QCU must be adequately staffed with personnel qualified to perform its operations, and while performing these operations, independence must be maintained. We propose that lines 234 through 238 of the draft QS Guidance be similarly modified.

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We appreciate the Agency's consideration of our comments. If you have any questions, please do not hesitate to contact me at (216)-642-6790

Sincerely,

A handwritten signature in black ink, appearing to read "Michael E. Skrjanc".

Michael E. Skrjanc  
Regional Manager, SEQ  
Linde Gas LLC