AGA Gas, Inc.

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October 29, 2003

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fisher Lane, Room 1061
Rockville, Maryland 20852

RE: Draft Guidance for Industry on the Current Good Manufacturing Practices (cGMP) for Medical Gases – Docket No. 03D-0165

Dear Sir or Madam:

AGA Gas, Inc., a Member of Linde Gas, is a leading manufacturer and supplier of Medical, Industrial and Specialty Gases. AGA Gas, Inc., a Member of Linde Gas, 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and supplier of medical gases, the company has an interest and has included for submission, comments to the "Draft Guidance for Industry on the Current Good Manufacturing Practices for Medical Gases," Docket 03D–0165.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 on pages 24005 and 24006.

As part of this submission, AGA would like to include the comments as presented by the Compressed Gas Association (CGA) and the Gases and Welding Distributors Association (GAWDA). In addition, AGA would like to provide the following comments:

Draft Guidance
Production Record Review line number 1314:
The Agency recommends that the release of a drug product from an air separation plant or unit (ASU) not be performed by a third-party consignee (usually known as a transporter or a trucking company). That is, the third-party consignee receiving the product would not sign as the ASU's QCU to release the product.

Comment:
We agree with the agency in that what the industry refers to as spot haulers or spot contract drivers cannot be part of the firms QC unit for the review and release of medical products. However, if a firm has a dedicated contractor used to deliver products to

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medical facilities, they could be part of the firms Quality Control Unit provided the contract employees are:

- Trained in CGMP's
- Trained in reviewing the associated forms and records for accuracy, completeness and compliance.
- Given the authority and responsibility to review and approve the release of the lot or trailer
- Contract between the manufacturing firm and the dedicated contractor stating the responsibilities and
- The capability of the manufacturing firm to maintain the rights to hire or release these contracted employees.

The dedicated contractor is a firm specifically hauling for the manufacturing firm in that these employees are no different than the manufacturing firm's actual employees. The only real difference is where the employee receives his actual paycheck.

AGA would like the agency to clarify and include dedicated contract drivers as an acceptable means of reviewing the necessary records for accuracy, completeness and compliance for the release of bulk medical products in cryogenic trailers provided the provisions discussed above are met.

Draft Guidance
Quality control Unit Line 113:
We 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.

Comment:
The medical gas industry employs cross utilization of personnel in quality control and in the production process. These individuals receive CGMP training specific to their job functions that emphasizes the need to comply with all applicable regulations and that when performing the function of the Quality Control Unit, it is separate from that of the daily production role.
AGA recommends that industry be permitted to continue the cross utilization of personnel and that the guidance not recommend a separate independent QCU.

Draft Guidance
Calculation of Yield Line 627:
Actual yields and percentages 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
(§ 211.103).

FDA recognizes that accurate inventory records and reconciliation of use are difficult to maintain for liquefied gases. Normal losses of gas occur through vaporization, the filling process, and venting and could reach 10 percent or more. The FDA does not expect the reconciliation to be 100 percent accurate. A manufacturer's procedures for reconciling the use of medical gases can include allowances for normal storage and operating losses. The procedures would include provisions for further investigation when unexplained discrepancies occur, such as losses beyond established normal levels.

Comment:
In regards to Air Separation Unit, oxygen and nitrogen are manufactured by separating air into its natural components by the air liquefaction process. This is a scientific process based on the laws of thermodynamics in which through a distillation column, air is cryogenically separated into its natural components of oxygen and nitrogen. A requirement of the manufacturing process is to vent final product back to the atmosphere in gaseous form to provide column stability and enhances process efficiencies. In addition, the oxygen and nitrogen are stored at cryogenic temperatures in a liquid state. Thus, it is normal for this finished pharmaceutical product to vent continuously due to heat convection into the storage container and to maintain pressures. It is important that this product vent as it enables the process to maintain the low temperatures and prevent potentially dangerous high-pressure build-up in the storage containers.

Once manufactured at an air separation facility, medical gases are already in pharmaceutical form and require no additional work other than performing a transfilling operation. By contrast, the pharmaceutical industry combines ingredients to manufacture the drug product.

At a cylinder transfill operation, incoming bulk product is typically received in cryogenic liquid form and again stored in bulk storage tanks. This liquid product is then converted to a gaseous state for the filling of high-pressure cylinders. This process inherently has losses associated with it and they occur during normal transfill operations. In addition, the product is used to purge lines and cylinders as an integral part of the fill process.

In both the ASU and cylinder fill operations discussed above, the amount of losses varies widely from facility to facility, depending on the type of equipment used in the manufacturing process. The losses can even vary considerably within the same facility, due to changes in ambient conditions and in production demands.

AGA recommends the agency consider exempting the industry from this requirement.

Draft Guidance
Expiration Dating Line 778:
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 described in § 211.166 (§ 211.137(a)).

Expiration dates must be related to any storage conditions stated on the label, as determined by stability studies described in § 211.166 (§ 211.137(b)).

Expiration dates must appear on the labeling in accordance with the requirements of § 201.17 (§ 211.137(d)).

Comment:
AGA believes that medical gases should be exempted from expiration dating based upon the original data submitted by the CGA and our own manufacturing experience, AGA has determined that medical oxygen and medical nitrogen do not degrade. In addition, since medical gases are contained in a pressure vessel and are not exposed to ambient conditions, other than temperature, they cannot degrade chemically or allow the introduction of contaminants.

Draft Guidance
Stability Testing line 1134:
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 ('211.166(a)):

Reliable, meaningful, and specific test methods (§ 211.166(a)(3))

Testing of the medical gas in the same container-closure system as that in which the medical gas is marketed (§ 211.166(a)(4))

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 ('211.166(b)).

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.

Comment:
As with expiration dating and the data submitted from CGA to the agency, AGA believes the industry should be exempted from stability testing. Medical Gases have been proven to be stable over time, thus, negating the requirement to perform stability studies.

If the agency is concerned about leakage rates from cylinders, provided the appropriate leak tests are done during and at the conclusion of the fill, this should eliminate leakage from the actual cylinder.

Conclusion:
AGA Gas, Inc., a member of Linde Gas, appreciates the opportunity to comment on this proposed draft guidance and respectfully request Agency's consideration of our comments and those submitted from the Compressed Gas Association (CGA) and the Gases and Welding Distributors Association (GAWDA).

Respectfully submitted,

Michael Skrjanc
Regional Manager,
SEQ (Safety, Environmental and Quality)