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U.S. Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

COMMENT: Docket No. 03D-0165: Draft Guidance for Industry on Current Good Manufacturing Practice for Medical Gases; 68 Federal Register 24005, May 6, 2003

Dear Sir or Madam:

The Compressed Gas Association (CGA), CGA's member companies, and the Gases and Welding Distributors Association (GAWDA) appreciate the opportunity to comment on the Draft Guidance for Industry on Current Good Manufacturing Practice for Medical Gases ("the draft Guidance"), which the U.S. Food and Drug Administration issued on May 6, 2003.

The medical gas industry constitutes over half of all registered drug manufacturers. CGA, founded in 1913, is dedicated to the development and promotion of safety standards and safe practices in the industrial and medical gas industry. CGA represents over 150 member companies in all facets of the industry—manufacturers, distributors, suppliers, and transporters of gases, cryogenic liquids, and related products and services. Through the committee system, CGA creates technical specifications, safety standards, training and educational materials, and works with government agencies to formulate responsible regulations and standards and to promote compliance with these regulations.

GAWDA, founded in 1946, is dedicated to the safe operations and economic vitality of independent distributors of industrial and medical gases and equipment. It represents over 800 member companies and provides them with compliance assistance and guidance directly through internal consultants. It is also very active in providing training and educational materials that promote safe operations and cGMP compliance. GAWDA participates actively with the CGA and its activities to create and promote responsible regulations and standards for the industry.

We appreciate the Agency's efforts to create a guidance document aimed at medical gas production and distribution. We note its cooperative step of meeting with the affected industry on July 31, 2003. Documenting the Agency's recommendations for applying drug cGMPs to the medical gas industry is helpful to guide not only industry but FDA's field personnel as well. These comments express our concern about both specific recommendations and eight overarching themes, which cut across the document's various sections. Although many of these themes were discussed with the Agency at the meeting on July 31, 2003, they remain central to our concerns with the draft Guidance and to our recommendations for its modification and implementation. We look forward to working with FDA collaboratively to develop an appropriate final Guidance.

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First, the draft Guidance appears to expand the intended scope of the current good manufacturing practice regulations as they apply to medical gases. (See, e.g., comments 2, 3, 6, 9 29, 31, 40, 42, 46, 50, 51, 54, 58.) FDA stated at the July 2003 stakeholders meeting that certain of the Guidance recommendations were "best practices" and would not be enforced. This "best practices" approach to guidance raises significant concerns. Because the cGMPs are, by definition, the "minimum" requirements for drug preparation, see 21 CFR § 211.1(a), the issuance of optimal or "best practice" preferences by FDA could lead to confusion in an enforcement setting. Medical gases are a unique segment of the drug industry, and dissimilar from conventional drugs in many respects. FDA field personnel have invariably relied heavily on available FDA documents, without regard to their legal status, to guide inspection outcomes. Understandably, there is concern that enforcement will proceed based on the "best practice" recommendations of the Guidance, and discount reasonable alternatives that firms may have in place. Although the medical gas industry appreciates FDA's verbal assurances regarding the non-binding nature of the Guidance, whether in draft or final form, concerns remain that indirectly the Guidance will have a binding effect once introduced to the field. The final document should, therefore, emphasize that firms may use alternative approaches that satisfy the regulatory requirements of the applicable cGMP regulation.

Second, the draft Guidance should reflect the risk-based principles recently enunciated in FDA's 21st Century GMP Initiative. (See, e.g., comments 26, 28, 34, 41, 44, 45, 47, 57, 62.) FDA relies on the few known patient incidents involving medical gases to justify many of the Guidance recommendations. This reliance is misplaced and disproportionate. It casts the medical gas industry's overall safety record in an unfairly negative light. For example, the medical gas industry is unaware of any patient deaths or injuries caused by the bulk manufacturing process. In the areas of transfilling and distribution, almost[1] all of the rare incidents that led to patient harm resulted from errors made downstream from the manufacturer, when the medical gases were outside the manufacturer's control, i.e., end users, such as hospitals and nursing homes, committed these errors. While regrettable, medication errors involving medical gases have been extremely rare over the years, particularly if compared to the number of medication errors involving traditional finished pharmaceuticals.

Clearly, industry and FDA share the goal to eliminate or minimize the risk of medical gas mix-ups. But in view of the overall safety record of the industry, any final Guidance should acknowledge that risk-based alternatives are acceptable. Manufacturers should not be discouraged from developing risk-based rationales to justify approaches less burdensome than those recommended by the Agency.

Third, many of the recommendations in the draft Guidance lack clarity in context or scope. It is often not apparent whether a given recommendation applies to all -- or only some -- points in the manufacturing/distribution chain for medical gases. (See, e.g., comments 1, 7, 18, 46, 58.) Fourth, the draft Guidance often does not employ the terms, definitions, and technical consensus standards developed and utilized by the industry. We suggest that that industry terms, definitions, and standards be used wherever possible. (See, e.g., comments 12, 18, 19, 20, 22, 23, 63, 64.)

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1 CGA is aware of only two exceptions in the past twenty years.

Fifth, throughout the draft Guidance the Agency paraphrases the regulations by replacing the term "drug product" with the term "medical gases," and then cites the regulation as though the excerpt is a direct quote from the regulations. Medical gases and traditional finished pharmaceuticals are distinctly different. Blurring this distinction by paraphrasing the regulations is misleading. When the Agency references the regulations, we request use of the term "drug product."

Sixth, the draft Guidance builds a wall of distinction between industrial and medical gases that does not reflect industry practice. (See, e.g., comments 8, 9, 12, 13, 17, 21, 51, 63.) For example, oxygen or nitrogen produced under a cGMP-compliant system *can* meet the USP/NF standard required for a medical application. If the oxygen or nitrogen produced under that cGMP-compliant system (and its vessel) are qualified for medical use prior to leaving the manufacturing facility, then that product may be delivered to any customer or market that can accept those specifications. In these circumstances, an industrial gas is not meaningfully distinct from a medical gas. Thus, common industry practice is to deliver such a product to both medical and industrial customers without cleaning the vessel between deliveries. We believe this practice satisfies the cGMP requirements, so we request that the Guidance confirm its acceptability.

Seventh, the Agency has recognized that, in certain respects, the medical gas industry differs from the traditional pharmaceutical industry. We believe certain recommendations in the draft Guidance do not apply to our industry in the sense specified by our comments below. Similarly, we believe certain cGMP regulations apply to our industry only in a limited context, as detailed by our comments below. (See, e.g., comments 4, 11, 15, 28, 29, 30, 37, 48, 49.)

Finally, there are sections in the document that offer industry no guidance at all. (See, e.g., comments 14, 16, 25, 31, 56, 60.) We request that these sections be removed from any final Guidance. The most egregious example is the "Attachment: Medical Gas Mix-Ups," which is also inflammatory, as we explain in comment 60.

As these eight themes run through the draft Guidance, they also run through the rationale for many of our comments. The following sections, to the extent feasible, track the draft Guidance and provide specific comments on a section-by-section/line-by-line basis.

Comments Relating to Statutory and Regulatory Requirements

1. In lines 59-62, the draft Guidance states: "Manufacturers of medical gases must follow the requirements in the cGMP regulations to comply with section 501(a)(2)(B). For example, each time a medical gas is filled into another container, finished product testing must be performed in accordance with § 211.165(a)."

The phrase "filled into another container" should be replaced with "released for distribution." Otherwise, this sentence could be interpreted to recommend testing the product once a delivery is made to a customer's tank installation, such as at a hospital. Industry is not equipped to conduct such post-delivery testing, which would be unnecessarily costly and provide no benefit. If FDA intends for industry to perform such testing, its economic consequences would be so substantial as to warrant risk-based analysis and further dialogue between industry and FDA. Under current industry practice, the supplier conducts finished-product testing prior to its release for distribution. This current practice comports with the way cGMPs are applied to the rest of the drug industry.

Comments Relating to Organization and Personnel

2. In lines 116-117, the draft Guidance states: "The corporate QCU would be responsible for reviewing and approving all written procedures, even those written by each individual location's organizational units."

CGA and GAWDA suggest deleting this sentence. It implies that *a local* QCU should not have the authority to approve relevant local procedures. We believe that a local QCU has such authority under current regulations. The Agency's recommendation should focus on a QCU's qualifications; it should not focus on a QCU's relative position in the company's hierarchy, about which the regulations say nothing, to curtail a QCU's authority. This recommendation expands cGMP expectations beyond regulatory requirements.

3. In lines 533-534, the draft Guidance states: "The Agency recommends that the corporate QCU not allow the local QCU to establish and implement written procedures that have not been reviewed and approved by the corporate QCU."

CGA and GAWDA suggest deleting this recommendation. Consistent with our reasoning in comment 2, we believe the regulations allow a local QCU to establish and implement written procedures. Consequently, we also believe that a properly trained QCU, authorized to oversee QCU functions at a specific site, should be allowed the latitude to establish and implement procedures that are unique to that site.

4. In lines 120-121, the draft Guidance states: "In a well-structured and well-defined corporate structure, the QCU would be included as a separate unit."

CGA and GAWDA suggest deleting this sentence. Almost all firms -- if not all -- in the medical gas industry rely on the same personnel to fulfill both operational and QCU functions. FDA has confirmed through meetings with industry that this practice of cross-utilizing human resources is acceptable and consistent with cGMP standards. We are concerned that this sentence implies the opposite and thus may confuse those interpreting the document in the field.

5. In lines 1322-1324, the draft Guidance states: "For swap agreements, the manufacturer having its trailers filled would be responsible for and would have its own QCU review and approve the cleaning of any trailers that have contained industrial product, prior to filling with a medical gas."

This sentence should be deleted. Alternatively, we suggest that FDA clarify that trailers may be cleaned and qualified within *another* supplier's quality system, as long as the manufacturer has previously approved that other system. If a manufacturer has qualified another supplier's cleaning process and receives associated documentation, then we believe such cleaning satisfies the cGMP regulation.

Comments Relating to Buildings and Facilities

6. In lines 205-207, the draft Guidance states: "The Agency recommends that buildings be maintained in good physical condition, kept clean, and have a sufficient number of areas for organized sequential operations, such as a well-defined filling area and a well-defined quarantine area."

CGA and GAWDA believe that the regulation is satisfied by the use of areas clearly marked by signage and of separation procedures that enable trained employees to differentiate among various types of containers. We suggest stating that methods other than spatial quarantine - such as color-coding, labeling, tagging, and signage - may satisfy the regulation. Industry uses these other methods to identify the various categories of containers and finished products. We believe that employees who are properly trained in the above methods can adequately differentiate cylinders by status and type. In other portions of this draft Guidance, FDA recognizes satisfactory alternatives to physical separation (e.g., such as labeling and color training for delivery truck drivers) and should do likewise here.

7. In lines 207-209, the draft Guidance states: "The Agency also recommends the creation of quarantine areas to separate incoming medical gases, high-pressure cylinders, cryogenic containers, manufacturing equipment, rejected containers and closures, and the finished product."

CGA and GAWDA suggest deleting this recommendation. Current industry practice is to identify incoming high-pressure cylinders and cryogenic containers in a common staging area until they are ready to be refilled; they are then separated and qualified for use prior to filling. We believe that this practice, reinforced by proper training and procedures, satisfies the applicable regulation.

Alternatively, we suggest that the recommendation be modified such that only rejected containers and closures should be quarantined, and that finished products should be separated. It is not necessary to have separate areas for incoming medical gases, high-pressure cylinders, cryogenic containers, and manufacturing equipment. The compressed gas industry typically reuses their container closures. When cylinders are brought in, they are placed in a common staging area

At a minimum, the "manufacturing equipment" and "finished product" categories should be deleted from this recommendation. Because FDA has already provided guidance on receipt of bulk gases, industry interprets the recommendation's use of the term "incoming medical gases" to apply only to high-pressure and cryogenic cylinders. The term "manufacturing equipment" does not apply to the quarantine context; manufacturing equipment is normally qualified for use, not quarantined. Finished products should be segregated, but need not be quarantined, if they have been approved for release.

8. In lines 210-211, the draft Guidance states: "No matter how large your operation, we recommend you avoid storing industrial gases and medical gases in close proximity to each other."

CGA and GAWDA believe that adequate segregation can be achieved through the proper use of signage, procedures, and training. The term "close proximity" is subject to various interpretations. With proper signage, procedures and training, a manufacturer can design a storage system that satisfies the regulation by preventing mix-ups of finished medical products, regardless of their precise proximity. Trained employees who handle cylinders are able to differentiate cylinders by status and type.

9. In lines 213-214, the draft Guidance states: "We also recommend that delivery vehicles have well-defined, separate areas for medical gases and industrial gases to prevent mix-ups from occurring."

This recommendation should be deleted. It appears to be outside the intended scope of the regulation. Moreover, segregated areas on delivery trucks may threaten loading safety and conflict with Department of Transportation regulations. We believe that proper training for drivers is a far better method to assure appropriate deliveries of medical gas.

10. In lines 234-237, the draft Guidance states: "The security requirements of § 205.50(b) apply to all facilities used for medical gas distribution. FDA interprets this regulation to include all facilities where loaded medical gas delivery trucks are parked prior to making deliveries, including at an employee's home when a loaded medical gas delivery truck is driven there and parked overnight for early morning runs."

CGA and GAWDA suggest deleting these two sentences. We believe this recommendation is better addressed to the states, whose licensing schemes regulate wholesale drug distributors, than to industry. Alternatively, we ask the Agency to clarify whether a manufacturer may satisfy the regulation by adequately instructing drivers to secure their delivery trucks if parked overnight.

Comments Relating to Equipment

11. In lines 250-252, the draft Guidance states: "Equipment must be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the medical gas beyond the official or other established requirements."

CGA and GAWDA recommend clarifying that the sanitization aspect of this regulation does not apply to the medical gases industry because of our unique manufacturing process: our systems are both closed and dedicated by product. Current industry practice is to clean the equipment only at initial use or if exposed to a contaminant, based on fitness-for-use criteria that ready the equipment for specific gas applications. CGA and GAWDA request that FDA confirm the adequacy of these industry criteria and practices, which are well-established and documented in industry publications. See, G-4.1, Cleaning Equipment for Oxygen Service; G-4.4, Industrial Practices for Gaseous Oxygen Transmission and Distribution Piping Systems; see generally, Handbook of Compressed Gases, (4th ed.; Ch. 11: "Cleaning Components, Equipment, and Systems for Oxygen Service").

12. In lines 259-260, the draft Guidance states: "We recommend that equipment used in the manufacture of medical gas (e.g., manifolds, pigtails, valve assemblies, hoses and gauges) be cleaned at initial use and if exposed to a contaminant."

CGA and GAWDA request clarification of the circumstances under which the Agency would not consider an industrial gas to be a "contaminant." We believe that an industrial gas manufactured at a regulated drug site under a quality system that meets USP specifications should not be deemed a contaminant. We are unaware of any valid scientific basis that would support a contrary view.

We believe that the applicable regulation is satisfied by current industry practice: use a single manifold for the production of gas, both industrial and medical, as long as the production process satisfies the cGMP standards. This practice is consistent with the Agency's recommendation in its 1989 Compressed Medical Gases Guideline. Please clarify whether the Agency still considers this practice acceptable.

13. In lines 267-271, the draft Guidance states: "We recommend that storage tanks (especially those installed at a health care facility, nursing home, or hospital), tractor trailers, rail cars, high-pressure cylinders, and cryogenic containers prior to the introduction of a medical gas be cleaned in the following circumstances: when they previously contained industrial gases; when they are first received, whether new or used; and when they are or could be, contaminated."

CGA and GAWDA suggest deleting the phrase "when they previously contained industrial gases." A vessel delivering product that is subject to the firm's quality management system does not require cleaning before the introduction of a "medical" gas. In the case of oxygen, current industry practice is to ensure oxygen compatibility of the vessel prior to its introduction; in the case of other gases, the vessel also undergoes a pre-fill inspectional process. We rely on a Certificate of Analysis that a vessel is oxygen-ready or otherwise appropriately prepared for the relevant gas. We believe reliance on these certificates from third-party vendors is an acceptable alternative under the regulation.

We also suggest deleting the phrase "when they are or could be contaminated." If this phrase remains, it will cause confusion in the field. The draft Guidance does not clarify the circumstances under which industry should suspect that a container "could be contaminated." For example, it is unclear whether all industrial gases would be deemed "contaminants." If so, we contend that this position lacks any scientific merit.

Comments Relating to Components, Containers, and Closures

14. In lines 350-352, the draft Guidance states: "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 (§ 211.82(a)).

We suggest deleting this sentence. This excerpt paraphrases the regulation but is not accompanied by any guidance. Moreover, we believe the concept of "labeling as to contents" does not apply to the medical gas industry. To the extent the regulation does apply to our industry, we interpret it only to require that firms qualify containers prior to use.

15. In lines 352-353, the draft Guidance states: "Containers and closures must be stored under quarantine until they have been tested or examined, as appropriate (§ 211.82(b))."

We suggest deleting this sentence. This excerpt paraphrases the regulation but is not accompanied by any guidance. Moreover, the aspect of "stor[ing]" all containers until they have been tested or examined in a quarantined area does not appear to apply to the medical gas industry because the containers are tested prior to filling anyway.

To the extent the regulation does apply to our industry, we interpret it only to require firms to inspect containers prior to filling. (See comments 6, 8.) To the extent FDA believes this regulation does apply, we suggest FDA exempt bulk trailers from this regulation, except for new trailers, which would be kept from service until appropriately commissioned.

16. In lines 375-377, the draft Guidance states: "In addition, we advise medical gas manufacturers to determine valve assembly compatibility prior to installation on a high pressure cylinder and during the lifetime of the valve."

After the word "determine," CGA and GAWDA suggest adding the following phrase: "or verify that suppliers can demonstrate acceptable compatibility for." Suppliers are required to supply materials that meet established specifications for compatibility. We believe that a manufacturer can satisfy the regulation without conducting its own determination by relying on a supplier's determination of compatibility.

17. In lines 379-380, the draft Guidance states: "To avoid the possibility of contamination, we recommend that all high-pressure cylinders and cryogenic containers used for medical gases be dedicated to medical use only."

This sentence implies that industrial gases may contaminate medical gases. As explained in comment 13, CGA and GAWDA reject as scientifically unsound the view that all industrial gases are contaminants. Consequently, we believe that the regulations do not require dedication of equipment to medical gases. FDA confirmed at its meeting with CGA and GAWDA on July 31, 2003 that medical gas equipment need not be dedicated as long as the equipment undergoes validated cleaning procedures when being converted to medical use. The final Guidance should state that existing cleaning and change-of-grade practices are an acceptable alternative to the dedication of equipment.

In practice, the medical gas industry uses the same vessels to store and transport product for both medical and industrial applications. We rely on procedural safeguards to ensure that products conform to USP/NF standards in medical applications. Throughout the draft Guidance, however, the Agency distinguishes between medical gases and industrial gases. The distinction's mistaken premise is that an industrial-grade gas produced under a unified quality-management system cannot meet the USP/NF standard required in a medical application. It can—and therefore bridges the document's unrealistic distinction between industrial and medical gases.

18. In lines 402-403, the draft Guidance states: "We recommend that cylinders containing liquid be inverted and drained."

CGA and GAWDA suggest narrowing the scope of this recommendation. Only post-valve type cylinders containing oxygen USP should be inverted and drained because they are used in an environment where liquid reflux is possible.

19. In lines 430-431, the draft Guidance states: "The following colors are used by the medical gas industry in the United States to aid in identifying a medical gas. We recommend manufacturers use them."

CGA and GAWDA agree. The final Guidance should incorporate by reference CGA C-9 (Standard Color Marking of Compressed Gas Containers Intended for Medical Use -- 1998).

20. In lines 439-440, the draft Guidance states: "Blends of medical gases use a combination of the corresponding color for each component gas. For example, oxygen and carbon dioxide would be green and gray."

CGA and GAWDA suggest incorporating by reference CGA C-9.

21. In line 472-473, the draft Guidance states: "To avoid the possibility of industrial contaminants, we recommend that large cryogenic containers used to contain medical gases be dedicated to medical service only."

While dedication of large cryogenic containers is one method to avoid contaminants, the Part 211 regulations do not require dedication of equipment to medical gases. FDA confirmed at its meeting with CGA and GAWDA on July 31, 2003 that medical gas equipment need not be dedicated as long as the equipment undergoes validated cleaning procedures when being converted to medical use. CGA and GAWDA believe that existing cleaning and change-of-grade practices are acceptable alternatives to the dedication of equipment. Moreover, as we have discussed with FDA, there is no reason to believe that industrial liquid is any less pure than medical liquid, as both types usually come from the same qualified air separation plant.

22. In lines 487-488, the draft Guidance states: "These labels are designed to repeat the drug name (e.g., Medical Oxygen) in the appropriate color around the entire container."

CGA and GAWDA suggest that FDA should further consult with industry before recommending specific wording on the 360° tape identification. At a minimum, we suggest omitting the adjective "medical" from the product name. Prefixing each gas name with the word "medical" will dilute, not sharpen, the name's distinctiveness. Moreover, the name of the gas will be less visible from all angles, because it will have to share space with the word "medical."

Also, we suggest the Agency clarify that conforming to the industry standard as set forth in SB-26 (Safety Bulletin: Cylinder Connections on Portable Liquid Cryogenic Cylinders -- 2001) satisfies the applicable requirement. This safety bulletin allows appropriate flexibility in the use of 360° identification tape. In addition, the industry has established complementary standards: C-6 Standards for Visual Inspection of Steel Compressed Gas Cylinders; C-6.1 Standards for Visual Inspection of Aluminum Compressed Gas Cylinders; C-6.2 Guidelines for Visual Inspection and Re-qualification of Fiber Reinforced High Pressure Cylinders, C-6.3 Guidelines for Visual Inspection and Re-qualification of Low-pressure Aluminum Compressed Gas Cylinders. See generally, Handbook of Compressed Gases (4th ed.; Ch. 10: "Compressed Gas Cylinders, Marking, Labeling, Visual Inspection, Periodic Qualification, Filling and Disposition").

23. In lines 481-483, the draft Guidance states: "An inspection of the inlet and outlet connections for any signs of damage, oil or grease and to ensure that they are the correct fittings for the corresponding medical gas. Permanently attach all connections or fittings to the container."

CGA and GAWDA suggest clarifying that adherence to CGA SB-26 (Safety Bulletin: Cylinder Connections on Portable Liquid Cryogenic Cylinders -- 2001) is acceptable.

24. In lines 496-502, the draft Guidance reads: "We recommend that the following prefill inspections be performed on permanently mounted cryogenic containers: ... An inspection of the product label."

CGA and GAWDA suggest deleting this phrase. Permanently mounted cryogenic containers are not patient vessels. Because they are not final-use containers, they need not bear a product label, although we agree that they should bear some identification.

25. In lines 506-509, the draft Guidance states: "Containers and closures must be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the QCU in accordance with § 211.84 as necessary (e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the medical gas container or closure) (§ 211.87)."

CGA and GAWDA suggest deleting this sentence. It paraphrases the regulation but offers no guidance. Alternatively, we suggest clarifying how this regulation applies to medical gas containers. Current industry practice is to inspect cylinders and containers during the pre-inspection stage of the pre-fill process, in accordance with a manufacturer's standard operating procedures and DOT regulatory requirements. These cylinders and containers are neither tested for identity, strength, quality, and purity, nor processed through the QCU.

Comments Relating to Production and Process Controls

26. In lines 541-543, the draft Guidance states: "We recommend that a manufacturer or individual, especially a manufacturer filling multiple gases, have data on file demonstrating the amount of vacuum evacuation required to remove all contaminants from high-pressure cylinders."

CGA and GAWDA suggest deleting this sentence. Contrary to this recommendation's implication, a vacuum evacuation is not intended to remove *all* contaminants from high-pressure cylinders. The vacuum step is intended to reduce any residual product (remaining in the cylinder after venting) down to a level that will not adversely affect the assay. We believe that current industry practice, consistent with the 1989 Guidance document, removes contaminants in an acceptable manner: pulling a vacuum to 25 or more inches (adjusted for altitude) and conducting a pre-fill odor test. Alternatively, a double purge method to 200 psi is likewise acceptable.

27. In lines 543-545, the draft Guidance states: "We also recommend that the manufacturer have data demonstrating that each different gas it fills would be removed by the established vacuum evacuation limit."

CGA and GAWDA suggest deleting this sentence. Compressed gases have built-in safeguards that traditional pharmaceuticals lack to ensure that only the proper gas enters the proper container. The fact that other gases happen to be filled at the same site does not necessarily increase the chances that a gas could enter the wrong cylinder. For example, if oxygen is filled at one end of the plant and nitrogen at the other, mix-ups are no more likely than if they were filled at separate sites, as long as the two gases use separate manifolds. If multiple gases are filled using the same manifold, then the process can still be qualified to ensure that the proper gas enters the proper container.

28. In lines 568-569, the draft Guidance states: "Each component must be added to the batch by one person and verified by a second person (§ 211.101(d))."

CGA and GAWDA believe that confirmation by a second person is appropriate only if the testing protocol does not verify that the proper components were added, and that any improper components were not added. We suggest clarifying that this regulation applies differently to medical gases than to traditional pharmaceuticals. Verification by a second person should be required only if the testing protocol fails to verify that the proper components were added or that improper components were not added. We believe testing is an acceptable alternative to visual verification of component addition. Unlike a traditional pharmaceutical, oxygen consists of a single component rather than multiple chemicals blended into a single drug. Even if the product is a gas mixture (consisting of two or three component gases), industry practice is to identify each gas through finished product testing. The final review, conducted by a second person, includes a verification of the analytical results.

29. In lines 628-631, the draft Guidance states: "Actual yields 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 (§211.103)."

CGA and GAWDA request that medical gases be exempted from this regulation. The Agency has previously acknowledged the validity of the industries' argument to exempt medical gases from the requirement for calculation of yields and reconciliation. The requirements for yield calculations should not apply to medical gases because the atmospheric-gas-separation and cylinder-filling processes are unique.

Due to the uniqueness of the medical gases, calculation of yield provides no benefit and would be very difficult to perform. In particular:

- 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 1st and 2nd Laws of thermodynamics in which through a distillation column, air is cryogenically separated into its natural components of oxygen and nitrogen. With this process, there is no practicable means of reconciling the incoming air with the resultant oxygen and nitrogen components due to losses of product in the manufacturing process. A requirement of the manufacturing process is to vent final product 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.

- In a cylinder transfill operation, incoming bulk product, which when received is a finished pharmaceutical, is typically 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 fill lines and cylinders as an integral part of the fill process.

- The utility of yield calculations depends on the concept of a chemical reaction occurring during a phase of the pharmaceutical process in which by-products, isomers, or residual starting materials can be determined. The air liquefaction process has no such chemical reaction. There are no by-products or other reaction intermediates that can form during the manufacture, processing, or filling of the separated atmospheric gas constituents. It is not possible to accurately determine the amount of "starting material," i.e., incoming air or purified gas for filling, relative to the final products due to the intrinsic manufacturing losses mentioned previously. A calculation of the relative amounts of products distilled or filled compared to starting materials is only a measure of the efficiency of the distillation or filling process, an economic measure, and is independent of product quality.

- 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.

In the first two 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 production demands.

Medical gases are unique in that product losses occur due to the extremely cold manufacturing and storage temperatures. Thus it is nearly impossible to provide any accurate reconciliation figures which would provide any benefit or enhance product safety. Oxygen and nitrogen are in their final dosage form of $\geq$ 99.0%, respectively, and there is no real danger of producing a product of a different dosage form.

Comments Relating to Packaging and Labeling Controls

30. In lines 675-676, the draft Guidance states: "Upon receipt from the printer, labels would be counted to verify the quantity received and would be examined to ensure correctness when compared against the master label."

CGA and GAWDA suggest deleting this sentence. Alternatively, FDA should clarify that a visual inspection is an acceptable alternative to quantitative reconciliation. Unlike traditional pharmaceuticals, managing a visual inspection process is feasible for medical gases because of the industry's small batch size and its minimal type and size variations. Labels are typically ordered in bulk, sometimes hundreds of thousands at one time. We see no benefit to rolling labels off the spool to count them because labels are reconciled when issued to the filler for application. This reconciliation is conducted to 100%. Under §211.125(c), labeling reconciliation is *waived* for cut or roll labeling when a 100-percent examination for correct labeling is performed according to §211.122(g)(2). By analogy, we believe that the industry practice of performing a 100% reconciliation for our hand-applied labeling satisfies §211.122 (g)(3).

31. In lines 678-680, the draft Guidance states: "We recommend that labels be locked in a secure area with access limited to authorized personnel. Different medical gas labels would be stored separately. We recommend that industrial labels be stored in a separate area."

CGA and GAWDA suggest deleting this recommendation because it does not apply to our industry. Storing different medical labels separately would not improve safety because each container is visually inspected anyway after labeling operations. We also believe that the regulations allow different medical labels to be stored within the same storage cabinet, as long as measures are taken to prevent mix-ups.

32. In lines 683-685, the draft Guidance states: "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."

CGA and GAWDA respectfully request that statement be deleted. It provides no guidance. Most of the few deaths involving medical gases were caused by end-user errors. These end users either misused the product and/or circumvented built-in safeguards.

33. In lines 729-731, the draft Guidance states: "In addition, we recommend each large cryogenic container containing liquid oxygen for delivery to patients at home, whether

portable or permanently mounted in a van or a truck, be considered a lot and be assigned a unique lot number."

CGA and GAWDA suggest modifying the recommendation to capture the following distinction. Liquid oxygen cylinders that are top-filled (i.e., the new liquid is added on top of the residual product) should each be analyzed and receive a unique lot number. By contrast, portable cryogenic cylinders that are blown down and evacuated prior to fill need not each receive a unique lot number. A group of this latter category of cylinders, if filled sequentially in an uninterrupted filling cycle, should receive the same lot number (as other liquefied gases do); only one cylinder from each such lot needs analysis. The filling process for CO_2 and N_2O are likewise amenable to this lot-numbering scheme.

34. In line 571-572, the draft Guidance states: "The Agency recommends that all . . . be filled according to the net content statement indicated on the label in accordance with section 502(b)(2) of the act." And in lines 739-741, the draft Guidance states: "We recommend that the net contents appear on the body label or shoulder label and not on (1) a removable tag, (2) a certificate of analysis, or (3) a small separate sticker."

CGA and GAWDA suggest deleting these two sentences. We believe that using a small separate sticker, certificate of analysis, or removable tag that is applied to the drug product container satisfies the requirements of Section 502 (b)(2) of the FD&C Act. Long-standing industry practice is to indicate the net contents on a separate sticker. We believe adding the net contents to the product label would vastly complicate the labeling process and, thus, increase the likelihood that labels would be misapplied.

35. In lines 750-751, the draft Guidance states: "FDA would not prohibit the sale of medical oxygen with this labeling to emergency medical services (see Glossary for definition of an EMS) without a prescription."

CGA and GAWDA suggest removing the phrase "to emergency medical services." Medical oxygen should be available for emergency use to populations other than those served by EMS.

36. In lines 753-755, the draft Guidance states: "We recommend the labeling for large permanently mounted containers, trailers, and rail cars bear a statement consisting of 'Name of the Medical Gas, Refrigerated Liquid USP or NF,' such as 'Oxygen Refrigerated Liquid USP.'"

We believe that "large permanently mounted containers" refers to containers used in transportation and not to stationary tanks. Therefore, we request that the Agency delete this recommendation. The Department of Transportation addresses the issues of placarding these units for transportation.

37. In lines 780-782, the draft Guidance states: "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))."

CGA and GAWDA request that the Agency exempt medical gases from the regulation for expiration dating. The Agency has previously agreed with industry to exercise enforcement

discretion by not requiring an expiration date for compressed medical gases. We believe that, unlike some traditional pharmaceuticals, medical gas products do not degrade over time.

CGA and GAWDA suggest (1) deleting the paraphrased requirements in lines 780-788 and (2) explaining that, in the context of medical gases, stability pertains only to leakage. At the July 31, 2003 meeting, the Agency and industry agreed to meet and decide on the type and quantity of data required to resolve this issue. CGA and GAWDA request a temporary exemption from expiration dating until these meetings have been held and the data agreed upon have been presented. Also in line 1197, FDA should replace "stability studies" with "data regarding leakage rate." The term "stability studies" can be confusing in this context.

38. In lines 794-799, the draft Guidance states: "The Agency recommends that high-pressure cylinders stored for long periods of time, such as those provided to patients as a backup to their oxygen concentrator, be monitored to ensure they contain the correct net contents (i.e., pressure). 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."

This recommendation should be deleted because it is simply impractical in many instances. Many people purchase oxygen cylinders at the retail counter. Resolution of the stability-testing issue will resolve this issue as well.

39. CGA and GAWDA believe that Liquid oxygen, USP, and liquid nitrogen, NF, filled into cryogenic containers should be exempt from stability testing for the following reasons:

- Cryogenic liquid containers are specifically designed to hold liquid oxygen and liquid nitrogen. These containers are designed with an inner and outer tank and insulation material between the tanks. This insulation helps prevent heat loss. However, without any external refrigeration there is an inherent loss of the products described as normal evaporation rate (NER). The NER is required to maintain a safe operating pressure by relieving the pressure in the container through a pressure relief device (PRD). If the container is not used for long periods of time, the pressure will build in the container and the product will be vented through the PRD to atmosphere to maintain a safe operating pressure. Most applications require a usage rate that is equal to or higher than the container's normal evaporation rate (NER). During normal operation the container will typically be used quickly (e.g. within a few weeks) due to the application requirements.

In conclusion, due to the design of cryogenic containers for immediate use in high flow applications and the normal evaporation rate associated with periods of no product withdrawal from the containers, stability testing and expiration dating are not applicable nor do they provide any additional product safety.

Comments Relating to Holding and Distribution

40. In lines 814-818, the draft Guidance states: "The Agency recommends that separate areas be designed for the following: (1) empty containers, (2) full containers, (3) in-process containers, (4) different types of medical gases, (5) rejected containers and closures, (6) medical gases that have been released, and (7) medical gases that have not been released.

We also recommend that industrial gases, containers, and equipment be stored separately from medical gases, containers, and equipment."

These recommendations should be amended to clarify as acceptable alternative control systems that utilize proper signage, procedures, and training to enable employees who handle cylinders to differentiate among them by status and type. As discussed in the introductory section of these comments, recommendation of "best practices" is beyond the scope of the cGMP requirement as set forth in 21 CFR §211.1(a).

41. In lines 820-821, the draft Guidance states: "We recommend medical gas containers be stored under protective covering and not be subject to temperature extremes."

This recommendation should be deleted. This recommendation would apply to hospital reserves, cylinders stored at fill plants, and other manifolds, all of which are typically not under a covering. Compressed gas containers are designed to be stored outdoors and exposed to the elements. Outdoor storage does not affect the quality or attributes of the product. Current industry practice is to use protective cylinder caps or valve outlet covers. We believe this form of protection and outdoor storage are acceptable conditions of storage under the regulations.

42. In lines 837-840, the draft Guidance states: "The Agency recommends that delivery vehicles have well-defined, separate areas for medical gases and industrial gases to prevent mix-ups from occurring. For example, medical and industrial gases can be separated physically in the delivery truck, or a manufacturer can use a unique identifier to distinguish medical gases from industrial gases."

CGA and GAWDA believe this recommendation should be modified to remove the concept of "well-defined, separate areas" in vehicles. A load separation on non-dedicated trucks is not feasible because a balanced load distribution is required for safe operation of the transport vehicle. Proper weight balancing (of empty and full cylinders) is essential for safe transportation, as set forth in Department of Transportation regulations. This will often require close proximity of different types of gases, or grouping cylinders by weight. We believe that proper labeling of cylinders, color, tape, or other means -- in conjunction with training of delivery personnel -- is equivalent to spatial segregation. These alternatives thus conform to the regulations and better serve the Agency's goal of preventing mix-ups.

Comments Relating to Laboratory Controls

43. In lines 1014-1016, the draft Guidance states: "If a new shipment of oxygen is combined in a storage tank with a previously received, tested, and approved lot, we recommend that the manufacturer test the combined product and approve it before use."

To clarify this recommendation, CGA and GAWDA suggest changing "use" to "release" and adding "e.g., testing of the storage tank or testing one cylinder from the first manifold filling sequence."

44. In lines 1016-1019, the draft Guidance states: "If the storage tank is located on the company's premises and is used to fill vehicle-mounted containers or cryogenic home containers, the Agency recommends an identity and strength test be performed by sampling from the storage tank after each oxygen delivery and prior to the filling of any cryogenic containers."

CGA and GAWDA suggest deleting the following words: ". . . after each oxygen delivery and . . ." This would clarify that it is not necessary to test the storage tank after each delivery of oxygen if no cryogenic containers have been filled in the meantime. Testing need only occur prior to the filling of any cryogenic containers.

45. In line 1061, the draft Guidance states: "Each filled large cryogenic container would be tested prior to release."

CGA and GAWDA suggest adding the following sentence: "One acceptable alternative is to vent and evacuate a series of large cryogenic cylinders and then analyze one cylinder from each uninterrupted filling sequence prior to release." Current industry practice for filling liquefied gases is (1) to vent and evacuate these containers and then, after filling, (2) to analyze only one cylinder from each uninterrupted filling sequence. This method coincides with the first-fill testing concept in comment 43.

46. In line 1064, the draft Guidance states: "A valid COA would be provided with each cryogenic container."

CGA and GAWDA suggest deleting this recommendation. Providing a COA to a customer is not a cGMP requirement. COAs are not typically provided except upon request and therefore should be optional.

47. In lines 1085-1086, the draft Guidance states: "In addition, an identity test for the other gas would be performed on one cylinder from the manifold filling sequence."

CGA and GAWDA suggest deleting this recommendation. Alternatively, we suggest modifying it to encourage either (1) an independent verification process step or (2) final product testing to assure proper mixture components. If a second gas in a two-component mixture is verified by a second party during the filling process, we believe further testing for identity is unnecessary. Likewise, if the equipment is dedicated to the two components, testing the identity of the second gas is unnecessary. If appropriate process controls are in place, these checks are redundant.

Comments Relating to Records and Reports

48. In lines 1169-1171, the draft Guidance states: "Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of medical gas must be retained for at least 1 year after the expiration date of the batch (§ 211.180(a))."

CGA and GAWDA suggest clarifying that this regulation does not apply to medical gases for which no expiration date is required. Pending resolution of the stability/expiration issues discussed in comments 37 and 39, we suggest that the regulation be applied to medical gases in the following manner: records must be retained for three (3) years after a product is released for distribution. This interpretation would parallel the regulation for OTC drugs without expiration dates (See § 211.137(h)).

49. In lines 1215-1216, the draft Guidance states: "Equipment cleaning and use logs can be maintained for trailers, rail cars, and storage tanks, especially those installed at a health care facility or a hospital."

CGA and GAWDA suggest deleting this sentence. This recommendation does not fit the realities of medical gas vessels. Current industry practice is to ready a vessel, according to specific procedures, for the product it will hold. Once in service, trailers, rail cars, and storage tanks are generally not cleaned unless they undergo a change of service, which is rare. Such rare cleaning is documented but not in "logs."

50. In lines 1316-1319, the draft Guidance states: "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."

CGA and GAWDA suggest deleting this paragraph. The recommendation discourages the contractual delegation of QCU operations and thus reaches beyond the regulation's scope. The cGMP regulations do not prohibit trained, contracted service personnel from performing QCU-related tasks, including the release function.

51. In Lines 1322-1324, the draft Guidance states: "For swap agreements, the manufacturer having its trailers filled would be responsible for and would have its own QCU review and approve the cleaning of any trailers that have contained industrial product, prior to filling with a medical gas."

CGA and GAWDA suggest deleting this recommendation. The regulation [cite] does not specify which party's QCU must conduct the review, as long as the personnel are qualified and trained. The required steps are the same. Through audit processes, one company should be able to rely on another's COA and QCU operations.

52. In line 1416, the draft Guidance lists recommended types of information including: "Supplier's name and complete address."

CGA and GAWDA suggest appending the following phrase after "address": "or sufficient information to trace that supplier." We believe that including a traceable lot number would achieve the same purpose.

53. In line 1421, the draft Guidance lists recommended types of information including: "Actual analytical results for full USP monograph testing, (e.g., 99.5 percent oxygen)."

CGA and GAWDA suggest changing the example to "99.0 percent oxygen" in order to accurately reflect the current USP requirement.

54. In lines 1422-1423, the draft Guidance lists recommended types of information including: "Test method used to perform the analysis. If an analyzer is used, the specific model number is indicated."

CGA and GAWDA suggest deleting this recommendation, which reaches beyond the scope of cGMP regulations. CGA and GAWDA see no reason to specify the instrument used for analysis.

55. In lines 1436-1437, the draft Guidance states: "Distribution records must contain the name and strength of the product and description of the dosage form, name and address of the consignee, and date and quantity shipped (§ 211.196)."

CGA and GAWDA suggest that the draft Guidance clarify that the requirements regarding "strength" and "dosage form" do not apply to medical gases. These concepts are meaningless in the medical gas context.

Comments Relating to Returned and Salvaged Drug Products

56. In lines 1515-1531, the draft Guidance states: "Medical gases are subject to the requirements in § 211.204 - Returned drug products. Returned medical gases must be identified as such and held (§ 211.204). If the conditions under which returned medical gases have been held, stored, or shipped before or during their return, or if the condition of the drug product, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the medical gas, the returned medical gas must be destroyed unless examination, testing, or other investigations prove the medical gas meets appropriate standards of safety, identity, strength, quality, or purity (§ 211.204). . . . Medical gases are subject to the requirements in § 211.208 - Drug product salvaging. Medical gases that have been subjected to improper storage conditions must not be salvaged and returned to the marketplace (§ 211.208)."

CGA and GAWDA suggest deleting these paraphrased regulations, because the section offers no guidance.

Comments Relating to Air Separation Plants or Units (ASU)

57. In lines 1542-1544, the draft Guidance states: "The Agency recommends that an ASU that receives deliveries of a drug product into its storage tanks from outside sources perform finished product testing on the incoming supply, prior to accepting the delivery. Appropriate COAs would be maintained."

CGA and GAWDA suggest modifying this paragraph so that it recommends the specified testing *only* if circumstances suggest that the pedigree of the product has been compromised or if the Certificate of Analysis (COA) is otherwise not valid for the lot delivered. The company receiving the delivery would make this determination, in accordance with its quality management system procedures. Otherwise, reliance on COAs for product pedigree is an acceptable method under the regulation. In general, then, a company should either conduct the specified testing or rely on a COA. It need not do both. By analogy, we suggest similarly modifying lines 1573 and 1577.

The Medical Gas industry uses COAs at various points in the distribution of medical gases to describe the "pedigree" of the product. These COAs establish the product's conformance to the applicable USP/NF standard. In various provisions of the draft Guidance, the Agency recommends using COAs *and* performing certain product testing. If the supplier provides a valid COA for the product, additional testing unnecessarily duplicates the quality analysis already completed on the same product.

Comments Relating to Storage Tank Installations at Health Care Facilities

58. In line 1550, the section heading reads: "Storage Tank Installations at Health Care Facilities."

Despite this heading, a portion of that section (lines 1565-1584) pertains instead to storage tank *filling*. CGA and GAWDA request clarification that this entire section applies only to storage tank installations and not "storage tank filling," which is an ongoing operation.

In addition, the two aspects in lines 1575 and 1576 should be replaced with "maintain installation records." In Line 1577, the words "first fill" should replace "each delivery."

59. In lines 1580-1584, the draft Guidance states: "If a third party is contracted to install a health care facility storage tank and associated equipment, the supplier of the medical gas would determine whether the system has been installed in accordance with CGMP. This determination would be made prior to introducing the medical gas into the supply system and would be fully documented. The supply firm would consider itself responsible for the actions of the third party installer."

CGA and GAWDA suggest deleting this recommendation. We believe that whichever party contracts with the third-party installer -- either the supplier or the health care facility -- should be responsible for the installation. The medical gas supplier should not be responsible for third parties hired by a health care facility.

Comments Relating to Medical Gas Mix-Ups and Attachment

60. In lines 64-78, 1589-1634, 1710-1800, the draft Guidance refers to alleged medical gas mix-ups related to deaths and injuries.

CGA and GAWDA suggest deleting lines 64-78 and 1589-1602 and deleting the entire Attachment (1710-1800). They offer no guidance and make inflammatory and false implications.

A guidance document should help manufacturers comply with cGMP regulations as they apply to medical gas production and distribution. The information provided in Section XV and the Attachment does not accomplish this objective. Furthermore, it is inflammatory. It casts our industry's safety record in an unfairly negative light. Most of the few mix-ups occurred downstream from the manufacturer, when the medical gases were outside the manufacturer's control. The Agency is already communicating accordingly with health care facilities about mix-ups.

Comments Relating to Carbon Dioxide and Helium Manufacturers and Wholesale Distributors

61. In lines 1641-1646, the draft Guidance states: "The Agency recommends that manufacturers perform process and computer systems validation and have a written agreement with the raw material manufacturer to be notified of any changes in the manufacturing process or the quality of the raw material. We also recommend that manufacturers perform an initial *fingerprinting* or characterization of the incoming raw material for any contaminants or impurities that could affect the quality, strength, purity, or identity of the finished drug product."

CGA and GAWDA suggest excluding helium from these two recommendations. The raw material used in the helium manufacturing process is consistent (produced only from natural gas wells); once liquefied, it contains no harmful constituents.

62. In lines 1669-1670, the draft Guidance states: "The Agency recommends that all tankers or trailers used for the delivery of carbon dioxide be dedicated to medical use only."

CGA and GAWDA suggest deleting this recommendation or at least clarifying that validated cleaning procedures that qualify tankers or trailers are an acceptable alternative to dedication. FDA confirmed at its meeting with stakeholders on July 31, 2003 that medical gas

equipment need not be dedicated as long as the equipment undergoes validated cleaning procedures when converted to medical use.

Comments Relating to Terminology or Glossary

63. CGA and GAWDA suggest that the Agency modify its definitions and terms so that they mirror the definitions and terms standardized and understood by the industry. Examples include the following: "Certificate of Analysis," "Cryogenic containers," "Distributor," "Oxygen for environmental use," "Oxygen for industrial use," "Oxygen for aircraft use," and "USP/NF." We also suggest reconciling the substantive standards to those in other Guidance proposals.

We offer seven specific suggestions for modifying definitions and terms. First, in line 20, the term "transferring" is unclear. CGA and GAWDA suggest using instead industry terms such as transfilling or transporting.

Second, in footnote 2, please remove "distributors" and "transferers" or replace those terms with "distributors who transfill."

Third, the term "large cryogenic containers" is used in numerous places throughout the document. Instead, we suggest the Agency adopt a term that conforms to Department of Transportation 4L specifications.

Fourth, please remove term "Quality Assurance." Although widely recognized in the traditional segments of the drug industry, this term is not commonly used in medical gas operations.

Fifth, in line 603, please replace the term "safety plug" with "pressure relief device."

Sixth, throughout the document, whenever the term "label" is used, please add modifiers such as "drug" or "product" when those meanings are intended, in order to distinguish from other stickers placed on containers.

Seventh, please modify the definitions involving oxygen in the following manner: (1) in line 1857, delete the words "inhalation or," (2) in lines 1861-62, delete the second sentence in the definition of "oxygen for industrial use," and (3) add a definition of "oxygen for medical use -- oxygen that meets USP specifications and is intended for inhalation or therapeutic treatment of humans or animals."

Comment Relating to External Standards

64. CGA and GAWDA suggest that, wherever possible, the Agency utilize or reference CGA, USP, or other recognized external standards. The Medical Gas industry has well established standards that use unique terms/definitions that are well accepted and known to employees at all levels. Use of these industry standards will avoid the confusion and training requirements associated with new terms and standards. This practice would lend consistency to the terms in the draft Guidance. Referencing external standards boasts another advantage over fixing standards into the draft Guidance. These standards change, according to industry experience or new technology. Reliance on external references will prevent the draft Guidance from obsolescing or retarding the implementation of new technology. The draft Guidance should state that if the external standards change, the new standards would supercede any references in the guidance. We offer the following ten examples:

First, regarding lines 558-575, CGA and GAWDA suggest referencing the applicable standards from which the technical information was derived. Related industry standards documents include the following: CGA P-2 Characteristics and Safe Handling of Medical Gases; CGA V-1 Standard for Compressed Gas Cylinder Valve Outlet and Inlet Connections; CGA V-5 Diameter Index Safety System (Non-interchangeable Low Pressure Connections for Medical Gas Applications; CGA V-7.1 Standard Method for Determining Cylinder Valve Outlet Connections for Medical Gases; and CGA V-9 Standard for Compressed Cylinder Valves.

Second, regarding lines 602-617, CGA and GAWDA suggest referencing applicable industry standards from which the information was derived. Related industry standards documents include CGA P-15 Filling of Industrial and Medical Non-Flammable Compressed Gas Cylinders; CGA S-1.1 Pressure Relief Device Standards Part 1 Cylinder for Compressed Gases. Also, the Agency should acknowledge the acceptability of other existing methods for leakage detection, such as pressure hold options. In addition, we suggest that the section beginning at line 382 refer to P-15 (Filling of Industrial and Medical Nonflammable Compressed Gas Cylinders)

Third, regarding lines 873-879, the Guidance should acknowledge that if the external standard changes, that such changes would supercede the text in the guidance. Changes to the monograph could result in conflicts between the Guidance and the external standard.

Fourth, regarding lines 906-910, we suggest the Agency simply reference current USP.

Fifth, regarding lines 1068-1079, CGA and GAWDA suggest referencing the Handbook of Compressed Gases (4th ed.).

Sixth, regarding lines 231-232, the industry, through CGA, has adopted consensus standards for the storage and sale of nitrous oxide. (See SB-6 Nitrous Oxide Security and Control and CGA's Nitrous Oxide Sales and Security Recommended Guidelines.) The Agency should adopt these standards.

Seventh, regarding lines 247-248, CGA and GAWDA suggest referring to and adopting the current industry standards, developed through CGA and GAWDA. Applicable references include the following: CGA G-4.1, Cleaning Equipment for Oxygen Service; CGA G-4.4 Industrial Practices for Gaseous Oxygen Transmission and Distribution Piping Systems; and the Handbook of Compressed Gases (4th ed.; Ch. 11).

Eighth, regarding lines 481-83, the Agency should refer to CGA standards for guidance on how to determine the correct fitting. (See CGA's V-1: Standard for Compressed Gas Cylinder Valve Outlet and Inlet Connections.) For line 484, refer to the following: CGA C-6 Standards for Visual Inspection of Steel Cylinders; CGA C-6.1 Standards for Visual Inspection of Aluminum Cylinders; CGA C-6.2 Guidelines for Visual Inspection and Re-qualification of Fiber Reinforced High Pressure Cylinders; CGA C-6.3 Guidelines for Visual Inspection and Re-qualification of Low-Pressure Aluminum Compressed Gas Cylinders; and the Handbook of Compressed Gases (4th ed.; Ch. 10).

Ninth, regarding lines 753-755, CGA and GAWDA suggest the Agency refer to and reconcile applicable Department of Transportation and Federal Railroad Administration Standards. Also refer to CGA C-7 Guide to Preparation of Precautionary Labeling and Marking of Compressed Gas Cylinders.

Tenth, regarding lines 820-823, CGA and GAWDA suggest referring to CGA P-2 Characteristics and Safe Handling of Medical Gases and the Handbook of Compressed Gases (4th ed.).

We hope to receive FDA's response to our concerns very soon, and we welcome continuing our dialogue to resolve any differences.

Sincerely,

Carl T. Johnson
President
Compressed Gas Association

Henry W. Doyle, III
Executive Director
Gases and Welding Distributors Association

Cc: David Horowitz, Director, Office of Compliance, Center for Drug Evaluation and Research, FDA