PRAXAIR

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

Re: Comment to Docket No. 03D-0165—Draft Guidance for Industry on Current Good Manufacturing Practice for Medical Gases, 68 Fed. Reg. 24005 (May 6, 2003)

Dear Sir or Madam:

Praxair, Inc. ("Praxair") appreciates the opportunity to comment on the U.S. Food and Drug Administration's ("FDA's") Draft Guidance for Industry on the Current Good Manufacturing Practice for Medical Gases ("the draft Guidance"), issued in the Federal Register on May 6, 2003.

Praxair is a major, nationwide supplier of medical gases, including oxygen, nitrogen, carbon dioxide, helium, nitrous oxide, and medical air. Praxair is proud of its safety record with respect to medical gases, and is fully committed to assuring that it has the necessary quality staff and technologies to maintain this standard of excellence.

As an industry leader, Praxair has been a full and active participant in the ongoing FDA/industry interactions to define and develop current good manufacturing practice ("cGMP") requirements for medical gases, including those concerning air separation unit ("ASU") validation and general medical gas cGMPs over the last two years. In responding to this draft Guidance, Praxair has worked closely alongside other Compressed Gas Association ("CGA") and Gases and Welding Distributors Association ("GAWDA") members to develop the joint CGA/GAWDA comments, that were filed on October 23, 2003. Praxair is fully supportive of industry's comments, and incorporates them by reference into these comments on the draft Guidance.

Through its participation in the industry effort, Praxair recognized that the broad scope and vertical integration of its medical gas operations—encompassing the full range of ASU, transfilling, and distribution operations—has provided certain supplemental insights that should be shared as additional comments on the draft Guidance. These comments seek to amplify certain of the issues raised in the CGA/GAWDA submission, and to address issues related to but not specifically addressed by the industry, which we believe should be further considered by the Agency.

As with the industry's comments, in addition to providing specific technical recommendations, Praxair also has several general recommendations with respect to the substance and format of the draft Guidance. A number of these general comments, as you will note, were raised in CGA's July 21, 2003 letter to David Horowitz; discussed

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with FDA at the meeting with industry on July 31, 2003; and reemphasized in the recent CGA/GAWDA submission. Given the importance of these themes to industry, Praxair respectfully requests that there be formal notice-and-comment responses to the issues we have raised.

I. General Recommendations

A. Substantive Recommendations

1. **"Best Practices" Recommendations:** At the July 31 meeting, the Agency stated that certain of the more costly and troubling Guidance recommendations (e.g., dedicated equipment and segregation) were "best practices" and would not be enforced. Elsewhere in the document, there are a variety of other "best practices" commentaries (e.g., with respect to training, and ideal organizational functions for Quality Control Units). Praxair has two concerns with this "best practices" approach to guidance. The first relates to cGMP philosophy and focus; the second relates to enforcement implications, once the Guidance is finalized.

   As FDA knows, the general pharmaceutical cGMPs are constructed to provide "the minimum good manufacturing practice for preparation of drug products,"[1/] and, as such, they avoid recommendations that are optimal or best practices. This "minimum threshold" theme is also echoed in a number of more specific cGMP guidances that implement and further interpret Part 211. We request, therefore, that the medical gas Guidance likewise reflect this premise.

   "Best practices" are particularly of concern in light of the long and complicated history of industry interactions with FDA inspectional personnel. Because medical gases are a unique segment of the drug industry, and dissimilar from conventional drugs in many respects, FDA field personnel invariably over the years have relied heavily on available FDA documents, without regard to their legal status, to guide inspection outcomes. Praxair continues to be concerned that, once the draft Guidance is finalized, enforcement will proceed based on the "best practice" recommendations of the Guidance, and discount reasonable alternatives that firms may have in place.

   For these reasons, any subsequent version(s) of the Guidance should avoid aspirational recommendations. The Guidance instead should acknowledge current industry standards and approaches, to the extent those standards and approaches are viewed by FDA as adequate and consistent with a minimum cGMP framework.

1/ 21 C.F.R. § 211.1(a).

2. **The Absence of Meaningful Risk-Based Analysis:** Several concerns with risk-based principles have been raised by the draft Guidance and subsequent FDA commentary on risk-based themes.

   a. First, in FDA's minutes of the July 31 meeting with industry, the Agency appears to be rejecting risk-based principles in connection with this draft. Specifically, FDA has suggested that "risk-based analysis is the firm's responsibility and not the Agency's." This perspective is not in keeping with FDA's recent cGMP policy of focusing regulation on critical areas that are likely to achieve the greatest public health impact—a tenet of FDA's "A Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century" initiative.[2/] Praxair also has field application concerns with this perspective. Specifically, without Guidance acknowledgement that risk-based approaches are acceptable, manufacturers will be reticent to develop risk-based rationales to justify approaches other than those recommended in the Guidance.

   b. Notwithstanding its suggested rejection of the application of risk-based principles to the draft Guidance, FDA has attempted, in a number of instances, to correlate patient risks with Guidance recommendations. The most prominent example of this is the medical gas mix-ups attachment and related references throughout the document to serious patient consequences. Praxair respectfully notes that historical facts do not support an assumption that these patient incidents justify many of the Guidance recommendations.

      In the areas of bulk medical gas production and home health care, for example, the medical gas industry is unaware of any patient death or injury as a result of the bulk manufacturing process or home health care operations. In the area of medical gas transfilling and distribution, the rare incidents that have led to patient harm have resulted, in virtually all instances, from improper actions taken downstream from medical gas manufacturer/distributor operations, i.e., by end users such as hospitals and nursing homes. These few adverse incidents over the years have been rare as compared to other traditional drug products. As noted in the Agency's recent proposed rule on safety reporting, there may be as many as 98,000 fatalities per year due to medication errors from more traditional drug products. By contrast, in the past 20 years, and millions of uses

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2/ See FDA, FDA Unveils New Initiative To Enhance Pharmaceutical Good Manufacturing Practices, http://www.fda.gov/bbs/topics/ NEWS/2002/NEW00829.html> (Aug. 21, 2002).

annually of medical gas products, FDA has only identified a small handful of fatalities—virtually all related to mix-ups or misuse of equipment at point-of-use, rather than point of manufacture.

To address root cause concerns relating to these adverse events, there has been intensive FDA and industry effort over the past two years to mitigate end-use risks. For nearly four years, there have been no reported fatalities involving medical gas products, suggesting that these collaborative interactions have been productive.

Without reference to this history, the draft Guidance creates the impression that the medical gas industry is singularly responsible for the reported injuries and fatalities over the past 20 years. This type of emphasis on adverse events will create unnecessary litigation exposure concerns because it tends to convey that the medical gas industry is both dangerous and careless. Praxair, as with the rest of industry, is proud of its safety record, and the success of collaborative efforts with FDA to further reduce mix-up events.

Because Praxair believes that a number of the new substantive proposals in the draft Guidance could not be justified based on risk principles, Praxair respectfully requests that FDA comment formally on the record how the industry's safety record and related efforts have been factored into the Guidance recommendations.

3. **The Absence of Economic Impact Analysis:** FDA took the position in the July 31 meeting that economic impact analysis is not necessary for this Guidance document, because it is "not like the promulgation of a regulation." Although Praxair is gratified with FDA's statement's regarding the non-binding nature of the Guidance document, it is still concerned that the Guidance nevertheless will have practical binding effect, once introduced to the field. If FDA's Guidance leads Praxair and others in industry to believe that the Agency will take action unless manufacturers comply with the terms of the document, industry standards necessarily will change. As standards necessarily change, the document for all practical purposes will have the force and effect of a substantive rule,[3/] regardless of language to the contrary.[4/] Praxair continues to believe that formal rulemaking may be a more equitable and appropriate means to develop medical gas cGMPs, and respectfully requests that the Agency formally reconsider this recommendation. In the alternative, even if FDA proceeds with guidance

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3/ Appalachian Power Co. v EPA, 208 F.3d 1015 (D.C. Cir. 2000). See also Croplife America v. EPA, 329 F.3d 876 (D.C. Cir. 2003); General Electric Co. v. EPA, 290 F.3d 377 (D.C. Cir. 2002).

4/ See Appalachian Power Co., 208 F.3d at 1023.

development, Praxair believes that significant and costly changes in industry standards will be inevitable and, thus, must be scrutinized and justified through economic analysis protections.[5/]

Given the importance of this theme to Praxair and industry generally, Praxair respectfully requests that FDA formally respond on the record to this concern.

4. **Adoption of Recognized CGA Technical Standards and Terms:** The draft Guidance references and recommends the adoption of a number of standards and terms that are different than current industry consensus standards and adopted terms. Consistent with Office of Management and Budget Circular A-119, and Section 12 of the National Technology Transfer and Advancement Act of 1995,[6/] the federal government, including FDA, is directed to use whenever possible standards developed by private consensus organizations. Accordingly, similar to references to the United States Pharmacopeia, Praxair respectfully requests that FDA incorporate into the Guidance the terms, definitions, and technical consensus standards developed and utilized by the medical gas industry, as referenced in CGA/GAWDA's and these comments. Praxair believes that the adoption of industry terms and definitions would reduce confusion with the draft Guidance recommendations, and would help to clarify certain FDA positions.

5. **Scope of Recommendations:** In some areas, the draft Guidance appears to expand the intended scope of the cGMP regulations (e.g., references to medical device applications for Nitrogen NF; recommendations for distribution records beyond the scope of 21 C.F.R. § 211.196; and discussion of securing delivery trucks at employees' homes). The absence of a formal rulemaking record with respect to these types of recommendations would deny the industry its procedural rights under the Administrative Procedures Act ("APA").

6. **Acknowledgement of the Unique Characteristics of Medical Gases:** In various areas throughout the draft Guidance, there is inadequate accounting for the recognized differences between traditional finished pharmaceuticals and medical gases. Examples include discussions of: retesting containers for "purity" and "identity;" "component" testing of liquid medical gases; dedication of

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5/ See Executive Order 12866, 58 Fed. Reg. 51735, 51741 (Sept. 30, 1993) (requiring agencies to provide OMB, for each significant regulatory action, the draft text and a description of the need for the regulatory action, and an assessment of the potential costs and benefits). See also 5 U.S.C. § 601-612 (Regulatory Flexibility Act); Public Law 104-4 (Unfunded Mandates Reform Act).

6/ See Office of Management and Budget Circular No. A-119, Revised (Feb. 10, 1998); National Technology Transfer and Advancement Act of 1995, P.L. 104-113, 110 Stat. 776 (104th Cong. 1996) (codified in part at 15 U.S.C. § 272).

labeling lines to different "strengths" of medical gases; and medical gases as "active ingredients." The Agency has, in a number of places, mechanically applied standard drug cGMP regulations to medical gases (e.g., replaced the term "drug products" with "medical gases" in quoting the regulations), and, in so doing, has not considered the unique characteristics of these products and their production process. Praxair recommends, therefore, that there be a more affirmative evaluation and discussion of the unique characteristics of medical gases, to avoid the imposition of confusing and potentially unnecessary cGMP burdens.

7. **Additional Comment Processes/Protections**: Finally, in light of the significant economic and resource consequences of many of the recommendations, if formal rulemaking is not pursued, Praxair requests additional procedural protections relating to the draft Guidance. As previously requested by Congress several years ago, in addition to allowing extensive industry input and interaction, and other good guidance protections, FDA should affirmatively respond in writing to all industry comments. This would best be accomplished by issuing FDA's specific responses to industry concerns in the Federal Register.

B. Style/Format Recommendations

1. **Applicability of Recommendations To Various Aspects of the Supply Chain**: It is often not apparent whether a given recommendation applies to all—or only some—points in the medical gas supply chain, such as bulk production, distribution, transfilling operations, and home use. Because most medical gas manufacturing facilities are only involved in one of these functions, it would be extremely helpful to consolidate the recommendations under these headings. This organization would benefit industry and FDA inspectors, and help avoid compliance confusion. Accordingly, Praxair requests that FDA separately enumerate its recommendations for these different medical gas activities.

2. **Editorial Comments Offered in the Draft Guidance:** As a general matter, Praxair believes that, consistent with good guidance principles, this Guidance document should be stated as concisely as possible, and avoid non-constructive dialogue. The Agency should be particularly attentive to striking all references that offer no guidance in and of themselves, because they will only confuse interpretation and application in the field. For example:

   a. The commentary on medical gas mix-ups is inappropriate for inclusion in the Guidance document because it offers no guidance to industry, and neither accurately portrays nor places in context the historical mix-up events (see Draft Guidance at 37-38 (Section XV) and 40-42 (Attachment: Medical Gas Mix-Ups)). As noted above, there is no reasoned connection between many of the cited cGMP violations and patient deaths/injuries.

As revealed in the medical gas mix-ups attachment, the rare incidents that have led to deaths or injuries, have resulted in almost every instance, from improper actions taken downstream from medical gas manufacturer/distributor operations. This type of emphasis on adverse events will create unnecessary litigation exposure concerns because it tends to convey the impression that the medical gas industry is both dangerous and careless. Inclusion of the medical gas mix-up commentary is also inappropriate given the industry's safety record, and its successful efforts in working with FDA on these issues in recent years.

b. There are Guidance references to FDA enforcement options in the event of noncompliance, which Praxair requests likewise be deleted. In particular, at pages 2-3 of the draft Guidance, there is an extensive discussion about the courses of action FDA can take in the event of a cGMP violation.[7/] FDA then proceeds to emphasize that it has issued numerous Warning Letters and, on many occasions, has successfully pursued seizure actions, injunctions, prosecutions, civil contempt actions, and inspectional warrants to enforce the cGMP regulations as they apply to medical gases."[8/] References to enforcement in this context are unhelpful because: (1) no guidance is provided; (2) it establishes unhelpful overtones for FDA-industry relations; and (3) it undermines the FDA's verbal assurances that this Guidance conveys only recommendations.

c. Virtually every section in this Guidance quotes specific cGMP regulations. The discussions of specific cGMP regulations add significant text, while offering no additional value or guidance to industry. To the extent the document simply recites the regulations, Praxair recommends that those references be removed.

d. Finally, the draft Guidance includes detailed restatements of external standards (e.g., USP standards). It is ordinarily the case that FDA will simply cite to external standards, and not attempt to interpret them in detail, for several reasons. First, standards are subject to change over time.

7/ The draft Guidance states the following: "FDA can take several courses of action when a CGMP violation is found: (1) issue a warning letter; (2) seize gas-related products (including storage tanks, high-pressure cylinders, vehicles containing permanently mounted large cryogenic containers, tankers, and/or cryogenic home containers on the company's premises and trucks); (3) seek an injunction; and/or (4) initiate prosecution. FDA may also recommend disapproval of certain government contracts with the manufacturer. FDA can also notify the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration) of the violation. This may affect Medicare reimbursement for that company's products." Draft Guidance at 2-3.

8/ Id.

Second, there is a risk that standards will be described imprecisely, as has occurred in this draft (e.g., the current USP/NF monograph requires 99.0%, not 99.5%, oxygen). We therefore recommend that all attempts to restate the standards be removed, as they unnecessarily introduce ambiguity and confusion.

These more overarching concerns represent the bases for many of Praxair's specific comments on the draft Guidance recommendations. As with the CGA/GAWDA submission, Praxair's specific comments are organized and referenced by section and line in the draft Guidance.

II. Specific Recommendations

A. Comments Relating to Statutory and Regulatory Requirements

1. In lines 77-78, the draft Guidance states: "The Attachment, Medical Gas Mix-Ups, describes in detail some of the adverse events that the Agency has investigated, including mix-ups that have resulted in serious injury or death."

Praxair requests that this and all related commentary on adverse events from mix-ups be deleted for the reasons set forth above in Sections I.A.2.b. and I.B.2.a.

2. In lines 80-90, the draft Guidance states: "FDA can take several courses of action when a CGMP violation is found: (1) issue a warning letter; (2) seize gas-related products (including storage tanks, high-pressure cylinders, vehicles containing permanently mounted large cryogenic containers, tankers, and/or cryogenic home containers on the company's premises and trucks); (3) seek an injunction; and/or (4) initiate prosecution. FDA may also recommend disapproval of certain government contracts with the manufacturer. FDA can also notify the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration) of the violation. This may affect Medicare reimbursement for that company's products. FDA has issued numerous warning letters and on many occasions has successfully pursued seizure actions, injunctions, prosecutions, civil contempt actions, and inspectional warrants to enforce the CGMP regulations as they apply to medical gases."

Praxair recommends that this paragraph be deleted for the reasons stated above in Section I.B.2.b.

B. Comments Relating to Organization and Personnel

3. In lines 114-116, the draft Guidance states: "Ideally, the QCU would participate in and have final responsibility for all functions that could affect product quality."

References to "ideal" practices should be deleted for the reasons stated above in Section I.A.1.

4. In lines 119-120, the draft Guidance states: "We recommend that all individuals who are part of the QCU be identified in the manufacturer's operating procedures."

Praxair recommends that the Guidance clarify that it is acceptable for operating procedures to provide the *means* of identification of individuals in the QCU. The use of individual names would require the revision of an operating procedure every time a new person was hired or when a person was moved from their position. Accordingly, the phrase "by function or title" should be added following the phrase "be identified."

5. In lines 121-122, the draft Guidance states: "A small medical gas manufacturer can designate a single individual as the QCU."

Praxair requests that this statement be clarified. Consistent with FDA's confirmation that medical firms can rely on the same staff to fulfill operational and quality control functions, with defined roles outlined and reinforced in standard operating procedures and training, a manufacturer should be able to designate a single individual as the QCU, regardless of its size. Acceptable practices should apply to both small and large operations alike.

6. In lines 124-125, the draft Guidance states: "We recommend that QCU individuals receive adequate CGMP training on a continuing basis, including quality assurance training."

Because "quality assurance" is not identified or defined in the cGMP regulations, Praxair recommends that the statement be replaced with the following: "We recommend that QCU individuals receive adequate cGMP training on a continuing basis."

7. In lines 139-141, the draft Guidance states: "FDA recommends that CGMP training not be conducted in one massive training session. Rather, it should be presented in smaller more manageable sessions held throughout the year, or at a minimum be held once a year."

These statements should be deleted because they provide overly prescriptive detail. Medical gas firms must have a process in place that ensures the adequacy and effectiveness of training, but there are numerous ways to accomplish this goal.

8. In lines 184-185, the draft Guidance states: "We recommend that consultants hired to provide assistance in achieving CGMP compliance have sufficient medical gas education, training, and/or experience."

Praxair recommends that the reference to "medical gas" in this context be deleted, to conform to cGMP principles. While cGMP principles require that qualified consultants have the requisite skills to perform assigned tasks, they do not require that consultants serving the medical gas industry have detailed experience with medical gas production. For example, it is not always relevant or necessary for computer validation consultants to have detailed experience with medical gases, in order to assist companies in achieving cGMP compliance in this area.

C. Comments Relating to Buildings and Facilities

9. In line 192, the draft Guidance states: "Medical gases are subject to the requirements in § 211.42 - Design and construction features."

Praxair recommends that FDA clarify that the production of bulk gases involves closed manufacturing systems not susceptible to contamination. Additionally, the following statement should be inserted after the above statement: "These recommendations for design and construction specifically pertain to medical gas transfilling operations."

10. 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."

Praxair agrees with CGA/GAWDA's comments concerning this statement—any additional safety measures need to be consistent with Department of Transportation requirements and other fundamental precautions for the safe handling of gas products. Additionally, Praxair notes FDA's July 31 meeting discussion concerning this issue, during which the Agency confirmed that it would need to proceed with APA rulemaking in order to require that medical and industrial gases be separated during the distribution process. The Agency stated that it has rejected this course of action because industry could comply voluntarily without the need for new rulemaking. Praxair respectfully requests that these Agency discussions and understandings be acknowledged in the Guidance.

Praxair also notes that new labeling highlighting the medical vs. industrial status of gases, would create a new form of labeling confusion. That is to say, there is a risk that users over time would begin to focus on the "medical" designation and ignore the more significant risk, that relates to the *type* of gas used (e.g., oxygen vs. nitrogen).

Given the complexity of medical gas labeling issues, Praxair recommends that any significant decisions on these matters be deferred pending additional FDA/industry discussions. For example, Praxair recognizes that there are unique aspects of medical oxygen labeling, given the predominant use of this product in a multitude of health care settings, that may warrant further dialogue. Potentially, FDA and industry may want to

develop collaboratively a specific labeling system tailored to the realities of medical oxygen use (as opposed to addressing labeling for all medical gas products). FDA/industry development of such a system could further improve product safety.

Praxair stands prepared to work with FDA on these important issues. Any labeling system once developed, however, would continue to be secondary to the primary means of controlling mix-ups, which is to have properly trained personnel, knowledgeable about engineered safeguards and the need to carefully read all labels.

As additional industry-FDA discussions proceed on these issues, Praxair proposes that the above statement be replaced with the following interim recommendation: "We also recommend that the medical gas industry use a unique identifier for the grade of gas provided to medical applications, i.e., identify the gas with the official labeling, adopting the USP/NF designations (e.g., "Oxygen USP," "Nitrogen NF," "Carbon Dioxide USP," "Nitrous Oxide USP")."

11. In line 232, the draft Guidance states: "We recommend areas where nitrous oxide is held be especially secure."

The medical gas industry, through CGA, has established consensus standards for the storage and sale of nitrous oxide, and believes that FDA properly should refer to and adopt the current industry standards. Also, terms such as "especially secure" are unclear, may lead to ambiguous interpretation in the field, and should be avoided. Accordingly, Praxair recommends that above statement be replaced with the following: "We recommend areas where nitrous oxide is held conform to established consensus industry standards for the storage and sale of nitrous oxide (See SB-6 Security and Control of Nitrous Oxide. See also, P-2, Characteristics and Safe Handling of Medical Gases, section 4.3.1. See generally, Handbook of Compressed Gases, Fourth edition pp. 18-19)."

D. Comments Relating to Equipment

12. In lines 262-265, the draft Guidance states: "We also recommend that high-pressure cylinders exposed to the elements be provided with protective caps or some other protective device, applied to the valve opening to prevent contamination. See related clarifications in § 211.80(b)."

Prior to high-pressure cylinder use, inspections are made to the cylinders to ensure that there is no contamination to external surfaces. This industry practice historically has served as an adequate means of preventing contamination. Accordingly, Praxair recommends that the above statement be changed to the following: "Pre-fill inspections of high-pressure cylinders should provide an adequate means to prevent contamination."

13. In lines 275-276, the draft Guidance states: "Medical gases are subject to the requirements in § 211.68 - Automatic, mechanical, and electronic equipment."

FDA states later in the draft Guidance that ASU validation requirements will be addressed separately. The following clarification should therefore be added after the above sentence: "The applicability of these recommendations to bulk production activities at an Air Separation Plant will be addressed in a separate FDA guidance."

14. In lines 289-291, the draft Guidance states: "We recommend that vacuum gauges undergo two calibrations. The first calibration, performed daily, would ensure that the needle on the gauge returns to zero. This check can be performed with no vacuum present, and recorded on either a batch production record or a separate log."

The term "calibration" should be changed with respect to the requirement of the first check on the vacuum gauge. The current industry practice is to subject vacuum gauges to a daily performance check, rather than calibration. This is a visual check to assure the gauge needle is on zero, and is recorded on the daily fill log. The annual calibration is performed against a known standard verifying and, as necessary, adjusting the gauge accuracy to that known standard. This second activity would then be documented in a calibration-type record.

Consistent with industry practice, therefore, Praxair recommends that the foregoing statements be replaced with the following: "We recommend that vacuum gauges undergo a daily performance check to ensure that the needle on the gauge returns to zero. This check can be performed with no vacuum present, and recorded on either a batch production record or a separate log. In addition, at least annually, a calibration of each vacuum gauge should be performed against a known standard, verifying and, as necessary, adjusting the gauge accuracy to that standard. This activity would be documented in a calibration-type record."

15. In lines 291-295, the draft Guidance states: "The second calibration would ensure that vacuum gauges are calibrated based on standards established by the National Institute of Standards and Technology (NIST) on an annual basis at a minimum."

As noted in the preceding comment, only one annual calibration is needed (there is no "second" calibration). With respect to the annual calibration, the vacuum gauges are calibrated using equipment that has been certified to nationally-recognized standards such as NIST, ASTM, and ASME. Praxair is unclear of the rationale for limiting vacuum gauge calibration equipment to that calibrated exclusively to NIST standards, as there are no known problems with the more flexible current industry practice of using equipment calibrated to other nationally recognized standards. Accordingly, Praxair recommends that foregoing statements be replaced with the following: "The annual calibration would

ensure that vacuum gauges are calibrated based on a nationally-recognized standard (such as NIST, ASTM, and ASME) on an annual basis at a minimum."

16. In lines 300-306, the draft Guidance states: "We also recommend that medical gas companies ensure that check valves used in a supply system to prevent the back flow of a foreign product or contaminant into the lines create a proper seal and cannot be compromised. This recommendation applies to check valves placed at various points in a supply line to protect the pump, manifold, or other equipment from over-pressurization or an undesirable back flow. Check valves do not need to be qualified if they are intended to act only as an added safety feature and do not prevent the cross contamination of gases or do not affect product identity, strength, purity, or quality."

As noted above, check valves are devices used to protect equipment, such as pumps, from damage. More specifically, these check valves are intended to prevent back-pressure against the high-pressure pump, for the purpose of both performance and pump-life enhancement. While Praxair and other medical gas firms recognize that safeguards must be in place to ensure appropriate pressure differential to preclude system backflow, these safeguards currently are addressed through standard operating procedures. Consistent with these facts, Praxair recommends that the statements above be replaced with the following: "We also recommend that medical gas companies implement procedures to prevent the back flow of a medical gas process stream."

E. Comments Relating to Components, Containers, and Closures

17. In lines 385-386, the draft Guidance states: "Cylinders failing any of these procedures would be quarantined to prevent their use in any subsequent filling operation."

Consistent with current industry practice, Praxair recommends that the following text be added to the end of this sentence: "or until the cylinder has been reconditioned or otherwise made suitable for filling gases."

18. In lines 386-387, the draft Guidance states: "We recommend that medical gas manufacturers document all prefill inspections on a batch production record."

Consistent with current industry practice, Praxair recommends that the following sentence be inserted after the above: "A cylinder, previously failing a pre-fill step, may be subsequently reconditioned in accordance with established procedures. Only failures identified during the production process itself should be recorded on the batch production record."

19. In lines 397-399, the draft Guidance states: "Any cylinder found to have any of these conditions would be removed from service and placed in an appropriate quarantine area until their suitability has been determined by the QCU."

The phrase "by the QCU" in the above sentence should be deleted. Current industry practice is that cylinders are subject to an external examination prior to filling, but does not include QCU release of cylinders at this point in the pre-fill process. The QCU need not to be involved at this early stage in the filling process, provided that properly trained personnel have determined cylinder suitability, and adequate cylinder suitability documentation is available for QCU review.

20. In lines 408-409, the draft Guidance states: "Use only medical gases, as an industrial gas could contain industrial contaminants."

This statement should be made consistent with the CGA/GAWDA overarching theme #6. Supplementing CGA/GAWDA's comments, it is Praxair's view that the implied distinction between industrial and medical gases warrants further clarification. Praxair agrees that when not manufactured according to cGMPs, an industrial gas is meaningfully distinct from a medical gas. However, an industrial-grade gas produced under a cGMP-compliant quality management system, and also meeting the USP/NF standard, is indistinguishable from a medical-grade gas. The draft Guidance should acknowledge these facts and conditions of manufacture.

21. In lines 421-422, the draft Guidance states: "It is not necessary to [hammer] test cylinders with a 5-year test date."

While the hammer test is one of the DOT requirements for cylinders that have a ten-year retest interval, it is still performed on steel cylinders with less than a ten-year retest interval, as it is a valuable indication of internal corrosion or contamination. Praxair recommends that the Guidance not discourage this practice for safety reasons.

F. Comments Relating to Production and Process Controls

22. In lines 532-533, 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."

Consistent with CGA/GAWDA comments #2 and #3, this text should be deleted. As explained, the regulations allow a local QCU to establish and implement written procedures, and local QCUs therefore need not be limited in their functions as described.

23. In lines 546-549, the draft Guidance states: "We recommend that portable racks, such as those added to the main header or manifold via pigtails, be evaluated to ensure that the cylinders being filled on the portable rack are being properly vacuum evacuated and are being filled to the correct pressure, as indicated by the net content statement on the label."

Praxair recommends that this statement be clarified. It is unclear how FDA believes the recommendation concerning portable racks (to ensure cylinders are being properly vacuum evacuated and filled to the correct pressure), can be satisfied. For example, it is unclear whether the Agency accepts that portable racks can be sufficiently evaluated by the proper placement of calibrated and qualified instrumentation. If this practice is sufficient, as Praxair believes, clarification in the Guidance would be helpful. Also, consistent with CGA/GAWDA's comments concerning the net content labeling recommendations, the text "as indicated by the net content statement on the label" should be deleted from the above statement.

24. In lines 555-574, the draft Guidance states: "B. Charge-in of Components ... Written production and control procedures must include the following, which are designed to ensure that the medical gases produced have the identity, strength, quality, and purity they purport or are represented to possess (§ 211.101). ..."

FDA defines written production and control procedures related to the charge-in of components. Other than for gas mixtures, "component" testing is unnecessary, because subsequent finished product testing of medical gases verifies compliance with USP/NF. Consequently, there is no rationale for applying the recommendations concerning charge-in of components to all medical gas products. Praxair recommends that the Guidance reflect that written production and control procedures for charge-in of components be limited to medical gas mixtures, and that the following sentence therefore be inserted as the first statement in the section: "These recommendations for written production and control procedures of charge-in of components concern the production of gas mixtures."

25. In lines 564-565, the draft Guidance states: "Components for medical gas manufacturing must be weighed, measured, or subdivided as appropriate (§ 211.101(b))."

This statement should be clarified and tailored to the unique characteristics of medical gas production. Liquid medical gases can be filled by weight, but medical gases properly are not considered components—they are finished drugs.

26. In lines 570-574, the draft Guidance states: "The Agency recommends that all high-pressure cylinders and cryogenic containers be filled according to the net content statement indicated on the label in accordance with section 502(b)(2) of the act. This includes blends or mixtures of medical gases (i.e., multiple gases). The net content statement can be the same as the fill pressure or the service pressure. Refer to § 201.51, Declaration of net quantity of contents, for further information."

Consistent with CGA/GAWDA comments #29, #38, and #39, this text should be deleted. It is the medical gas industry's position that a net contents statement is unnecessary for medical gases, as this would confuse the public and would require labeling changes.

G. Comments Relating to Packaging and Labeling Controls

27. In lines 654-655, the draft Guidance states: "Labels for each different medical gas must be stored separately with suitable identification. Access to the storage area must be limited to authorized personnel (§ 211.122(d))."

Consistent with industry practice, this statement should be clarified to indicate that different labels can be in the same storage cabinet, provided they have adequate separation and segregation.

28. In lines 662-663, the draft Guidance states: "Dedication of labeling lines to each different strength of each different medical gas (§ 211.122(g)(1))."

Praxair recommends that the phrase "different strength of each" be deleted from this sentence. It is unclear what the term "strength" means in this context; there are not different strengths of medical gases.

29. In line 681, the draft Guidance states: "It is industry practice to apply labels by hand, therefore, we recommend a second person verify the correctness of the label and document the verification."

Praxair recommends that this statement be modified to reflect current industry practice and the unique characteristics of medical gas production. While there is often no second person at a medical gas manufacturing facility to verify label correctness, this practice is considered acceptable, because standard medical gas operating and quality functions include 100% label inspection and there is subsequent review of labeling documentation by QCU personnel. Also, there is considerable oversight by the several trained personnel that subsequently handle a cylinder before it is delivered to a customer (e.g., cylinder handlers, drivers, other depot personnel, etc.).

30. In lines 696-699, the draft Guidance states: "Procedures must be used to reconcile the quantities of labeling issued, used, and returned, and must require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued if the discrepancies are outside narrow preset limits based on historical operating data (§ 211.125(c))."

Praxair recommends that this statement be clarified. As noted above and in the CGA/GAWDA comments, standard medical gas operating and quality functions include 100% label inspection of batches consisting of relatively small quantities of finished drugs. Medical gases are unlike conventional drugs, where there are generally multiple dosages and forms of a given drug. Reconciliation of conventional drug labels may provide additional protection given these facts, but there should be further discussion of risk-based need for its application in the medical gas context. For example, it should be

an acceptable practice to receive a certified or otherwise verified label count from the label printer.

31. In lines 723-724, the draft Guidance states: "Assigning a single lot number to an entire day's production is not appropriate."

This statement needs to be clarified with respect to its specific context. There historically has been significant confusion about what a batch means, particularly with respect to bulk product. For continuous bulk operations, this is an arbitrary matter, and requires further clarification—current industry practice, which Praxair believes should be the recommendation in this context, is that an ASU bulk batch consists of product produced over 24 hours of continuous ASU operations. For cylinder filling operations, the meaning of a batch is better understood. As noted in CGA/GAWDA's overarching comments, there needs to be differentiation of the requirements and definitions for these two contexts. For clarification, Praxair proposes that the foregoing statement be replaced with the following: "Assigning a single lot number to an entire day's cylinder filling production is not appropriate."

32. In lines 724-726, the draft Guidance states: "Each manifold filling sequence; each uninterrupted filling sequence; and each filled cryogenic container, storage tank, and trailer would be considered a new lot and be assigned a unique lot number."

This statement needs to be clarified with respect to its specific context; packaging and labeling operation requirements properly should not apply to ASU bulk storage tanks. For clarification, Praxair proposes that the foregoing sentence be replaced with the following: "With the exception of ASU bulk storage tanks, each manifold filling sequence; each uninterrupted filling sequence; and each filled cryogenic container, storage tank, and trailer would be considered a new lot and be assigned a unique lot number."

33. In lines 730-732, the draft Guidance states: "Cryogenic home containers filled at a patient's home do not need a lot number. However, we recommend that cryogenic home containers filled on site or by a third party in advance for future delivery be given a lot number."

For purposes of clarification, Praxair recommends that the reference to "on site" should be changed to "manufacturing site," and the term "home" properly should extend beyond a patient's primary residence (e.g., nursing home). Accordingly, the above statement should be changed to the following: "Cryogenic home containers filled at a patient's residence (including a private residence, nursing home, assisted care facility, etc.) do not need a lot number. However, we recommend that cryogenic home containers filled at a manufacturing site or by a third party in advance for future delivery be given a lot number."

34. In lines 748-749, 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."

Praxair recommends that the Guidance be clarified as to whether FDA intends to limit the emergency use of medical oxygen to emergency medical services (as defined in the draft Guidance).

H. Comments Relating to Holding and Distribution

35. In line 810, the draft Guidance states: "Storage of medical gases under appropriate conditions (§ 211.142(b))."

Praxair recommends that this statement be modified to reflect that storage conditions should be consistent with CGA standards and/or risk-based need.

36. In lines 812-816, 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."

Praxair agrees with CGA/GAWDA's comments concerning this statement, but notes supplementally that adequate signage, training and other precautions are the key mechanisms to prevent medical gas mix-ups. Praxair therefore requests that a parenthetical ("e.g., through adequate signage, training, and other precautions") be added at the end of the last statement.

Additionally, it is unclear whether the Agency's warehousing procedure recommendations apply to all aspects of medical gas production and distribution, e.g., bulk production, cylinder filling, cargo trailers. Recommendations in the bulk and cargo trailer contexts would appear to be inappropriate in this context.

37. In lines 818-819, the draft Guidance states: "We recommend medical gas containers be stored under protective covering and not be subject to temperature extremes."

As discussed in CGA/GAWDA's comments, FDA properly should acknowledge and adopt CGA/industry standards that address this particular recommendation. FDA recommendations should also acknowledge that medical gas cylinders are designed to be stored outside, and are installed outside at customer locations. Accordingly, the statement should be changed to delete references to any Agency-specified conditions.

Proposed revised language could read as follows: "We recommend medical gas containers be stored consistent with CGA storage condition standards (see, P-2 Characteristics and Safe Handling of Medical Gases, see generally, Handbook of Compressed Gases, Fourth edition)."

38. In lines 819-820, the draft Guidance states: "Based on this recommendation, storage areas would be clean, dry, well ventilated, and free of combustible materials."

Praxair recommends that this statement be clarified. It is unclear as to what FDA means by "well-ventilated" and "combustible materials." It is also unclear whether FDA is referring to OSHA, NFPA, or some other set of standards. Such standards should be specifically referenced if applicable to cGMPs, but otherwise deleted if beyond the purview of FDA. We also note that the scientific rationale for the recommendation is unclear, as medical gas production operations are closed systems protected by positive pressure differential, such that potential contamination from storage areas does not represent a known risk to product quality.

39. In lines 845-846, the draft Guidance states: "We recommend that handheld computer devices or computers used during distribution operations be validated to ensure proper performance."

Praxair recommends that this statement be modified to reflect that validation requirements only apply to computers that record mandated records under FDA rules, and that the draft Guidance reference FDA's new Part 11 guidance and policies. If these items are subject to validation, the scope of validation properly should be based on the specific intended use(s) of the handheld devices and related risk analyses of such use(s).

I. Comments Relating to Laboratory Controls

40. In lines 879-888, the draft Guidance states: "In the past, deaths and injuries have resulted from adulterated products that contained contaminants or impurities that were not detected. In one example, a carbon dioxide (CO_2) manufacturer in Tennessee failed to include an analysis for hydrogen cyanide in its finished product testing. As a result, the manufacturer released several large liquid batches of medical CO_2 that were contaminated with this deadly toxin. The source of this problem was the lack of an agreement between the supplier and the CO_2 manufacturer requiring notification of any change in the manufacturing process. Fortunately, the problem was discovered before any injury occurred. Our investigation found the supplier of the raw material had changed the manufacturing process, which resulted in elevated hydrogen cyanide levels. Because testing for hydrogen cyanide was not performed, an adulterated drug product was released."

It is our understanding that there were no patient death/injuries associated with this incident and it did not concern medical product. These statements should be deleted for the reasons set forth above in Sections I.A.2.b. and I.B.2.a.

41. In lines 901-934, the draft Guidance describes the USP Oxygen monograph.

Praxair recommends that this section be abbreviated, with only general references to relevant current USP and NF monographs, for the reasons set forth in the CGA/GAWDA comments and above at Section I.A.4.

42. In lines 943-944, the draft Guidance states: "The FDA recommends that gas manufacturers not use other medical or industrial gases as the basis for calibrating their instruments."

This standard should be based on the relevant analyzer manufacturer's recommendations and instructions. Praxair therefore recommends that the above statement be changed to the following: "The FDA recommends that gas manufacturers use a standard of sufficient accuracy (per the analyzer manufacturer's recommendation) that is suitable for the analytical equipment used to measure medical gases."

43. In lines 1024-1025, the draft Guidance states: "The container has not been completely emptied (i.e., gaseous pressure below 15 pounds per square inch in gauge) and has not been out of service."

Praxair is unaware of the specific standard of 15 pounds per square inch, and recommends that the referenced language be changed to reflect industry practice. Specifically, the parenthetical should be replaced with the following: "i.e., that the vessel has positive pressure relative to the external environment to prevent contamination."

44. In lines 1035-1044, the draft Guidance states: "Testing of a cryogenic home container is less of a concern if:

- Liquid oxygen is the only liquid being filled on the premises,
- The incoming liquid oxygen is tested according to one of the methods outlined above under Testing of Incoming Liquid Oxygen or Testing of an Oxygen Storage Tank, [or]
- The container is filled by the company that owns it."

It is unclear what guidance is be being provided by this recommendation, and the specific implications of the circumstances presenting "less of a concern." Reliance on CGA standards properly should be considered acceptable, because the unique connections specified in those standards have been highly effective at preventing possible

mix-ups. Presumably because of CGA specifications, there have been no mix-up incidents relating to home care operations.

45. In lines 1042-1044, the draft Guidance states: "If any other medical gas is filled on-site or if the incoming liquid oxygen is not tested by one of the testing methods discussed above, we recommend all filled cryogenic home containers be tested for conformance with USP or established specifications."

Praxair recommends that this statement be clarified. It is unclear if FDA is recommending that there be testing of all cryogenic home containers to the USP standard beyond an identity test. Current industry practice is limited to identity testing, which is considered acceptable and historically has assured adequate safety.

46. In lines 1055-1057, the draft Guidance states: "This can be done either by taking a sample directly from the storage tank or by testing one cylinder from the first medical filling sequence."

In response to draft Guidance recommendations concerning the need to test product in a storage tank or single cylinder " before use," industry has explained that the time for such testing is more accurate stated in terms of the "first manifold filling sequence." Of note, the above proposal appears to confirm the appropriateness of the industry practice that "before use" is interpreted to extend to the point of first fill. See CGA/GAWDA comments #1, #43 and #58.

47. In lines 1081-1082, the draft Guidance states: "If a product is a mixture of two gases, the Agency recommends that each cylinder of the blended product be tested for the identity and strength of one of the gases, usually the active ingredient."

Praxair recommends that this statement be replaced with the following: "If a product is a mixture of two gases, the Agency recommends that each cylinder of the blended product be tested for the identity and purity of one of the gases." This suggested revision seeks to avoid the conventional pharmaceutical concepts of "active ingredients" and "strength."

48. In lines 1090-1092, the draft Guidance states: "An assay of the finished product using the official gas chromatographic method would not be necessary for a manufacturer who receives shipments of medical nitrogen. However, we recommend a manufacturer meet all of the following conditions."

Praxair does not believe that supplier auditing of liquid nitrogen manufacturing processes are necessary when the manufacturer receives USP/NF grade product from a registered site and does testing using the official monograph standards. To clarify that the listed recommendations (that follow the above statements) properly only apply to those situations where routine USP testing is not performed, Praxair recommends that the

above statements be changed to the following: "An assay of the finished product using the official *USP monograph* would not be necessary for a manufacturer who receives shipments of medical nitrogen. However, we recommend that a manufacturer *that does not test in accordance with the USP monograph* meet all of the following conditions" (emphasis added).

49. In lines 1102-1107, the draft Guidance states: "Initially and at appropriate intervals, testing for complete specifications is recommended. Once the reliability of the supplier is established, a manufacturer can rely upon the supplier's certificate of analysis. Auditing the supplier's testing and manufacturing is an additional measure that would be used to determine that the product complies with the USP. This testing can be performed by the manufacturer, by a third party, or by a contract-testing laboratory."

Praxair recommends that these statements be clarified to reflect that appropriate control measures can be used to assure Nitrogen NF conformance to specifications. Specifically, it is unclear why supplier audits of liquid nitrogen manufacturing processes are necessary when the manufacturer receives USP/NF grade product and does testing using the official monograph standards. The Agency's draft recommendation should only apply to those situations where routine USP/NF testing is not performed.

50. In lines 1112-1115, the draft Guidance states: "In light of several reported injuries due to patient exposure to toxic compounds contained in a supply of contaminated *industrial* nitrogen used to power surgical or dental equipment, the FDA strongly recommends the use of *medical* nitrogen by hospitals and dentist offices, even when the nitrogen is used for industrial purposes in those settings."

Praxair recommends that this statement be replaced with the following: "FDA recommends that Nitrogen NF be used in medical applications." The known drug uses for nitrogen are somewhat rare. The Guidance proposal properly should be limited to drug uses, with device issues addressed separately through Quality System Regulation principles.

J. Comments Relating to Records and Reports

51. In line 1228, the draft Guidance states: "Statement: The disposition of rejected medical gas containers, closures, and labeling."

Praxair recommends that this statement be clarified to reflect the unique aspects of medical gas containers. Medical gas containers are not formally rejected. Rather, these containers go through an inspection for suitability and, if necessary, are refurbished. This current industry practice has not resulted in historical safety or other quality problems, and, thus, should be permitted to continue.

52. In lines 1269-1270, the draft Guidance states: "--Inspection of the packaging and labeling area before and after use (§ 211.188(b)(6)) ... --Complete labeling control records (§ 211.188(b)(8)) ... --Identification of the persons performing and directly supervising or checking each significant step in the operations (§ 211.188(b)(11))."

To avoid confusion and inadvertent noncompliance, these statements need to be reconciled and consolidated with other Guidance recommendations concerning labeling documentation. There also needs to be clarification about how certain aspects of the recommendations apply to different aspects of medical gas operations. For example, in the transfilling context, it is current industry practice not to inspect "the packaging and labeling area before and after use" because such operations (other than mixtures) utilize dedicated lines and the same label for all cylinder sizes. Also, it is unclear what risk FDA is seeking to address by its recommended "identification of the persons performing and directly supervising or checking each significant step in the operations." Compliance should be satisfied by a general recommendation that the Quality Control function review, and approve or reject the lot of finished product as part of the overall release function.

53. In lines 1332-1334, the draft Guidance states: "A description of the sample received for testing with identification of source (that is, location from where the sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing (§ 211.194(a)(1))."

In medical gas production, the dates that samples are taken and received are nearly always the same. In recognition of this fact, and to reduce unnecessary recordkeeping, Praxair recommends that the following text follow the above statement: "(but the "date sample was taken" and "date sample was received" should be recorded only if occurring on separate dates)."

54. In lines 1369-1371, the draft Guidance states: "The Agency recommends that when using a handheld oxygen analyzer to perform an identity test, the actual value obtained be recorded, and the manufacturer establish written procedures describing an acceptable range that meets the accuracy of the analyzer."

Praxair questions the purpose and use of recording the "actual value" obtained with a handheld analyzer used to perform an identity test. Because a pass/fail criterion is sufficient to satisfy the USP/NF standard (given that the recording of such a number is not indicative of purity), Praxair recommends reference to this criterion in lieu of the phrase "actual value."

55. In lines 1391-1394, the draft Guidance states: "Certain changes made to instrumentation may be substantive enough that they would be considered a change in the

method itself; these changes would require additional documentation of accuracy and reliability (see § 211.194(b), above) or a new validation study."

Praxair recommends that this statement be moved to another section of the draft Guidance; it might be more appropriately included in the discussion of laboratory controls as opposed to laboratory records.

56. In lines 1398-1399, the draft Guidance states: "The medical gas industry routinely relies on COAs to reduce the amount of finished product testing performed."

Praxair recommends that the statement be changed to the following: "The medical gas industry routinely relies on COAs to properly qualify incoming material." COAs do not reduce the level of finished product testing; they eliminate the need for redundant testing. Also, it is unclear whether FDA is recommending COAs for all deliveries of medical gases. COA's are used to properly qualify incoming material and are usually provided to customers only at their request. The flexible, non-mandatory use of COAs for medical gas customers should continue to be permitted.

57. In line 1423, the draft Guidance states: "Signature of the employee witnessing any testing at a supplier, if applicable."

FDA recommends that COAs for incoming deliveries of liquid medical gas contain the "[s]ignature of the employee witnessing any testing at a supplier, if applicable," but there are very few contexts in which a COA that would accompany an incoming delivery of liquid medical gas, would include the signature of the employee witnessing testing at a supplier. To avoid confusion by FDA and industry as to the applicability of this recommendation, Praxair recommends that the Guidance be clarified with respect to the production/distribution context for the recommendation of a witness and a related signature (e.g., source medical product for homecare, typically medical fill vans).

58. In lines 1434-1435, 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)."

Praxair recommends that the statement be changed to the following: "Distribution records must contain the name of the product, name and address of the consignee, and date and quantity shipped (§ 211.196)." As rewritten, "strength" and "dose" are no longer retained as medical gas concepts.

59. In lines 1442-1447, the draft Guidance sets forth recommendations for complaint files.

There needs to be clarification of the relationship between the recommendations for complaints and the recent proposed rule on significant adverse drug reaction reporting. The medical gas industry, through CGA, previously provided comments on the new proposed rule, and has requested that the Agency exempt medical gases from new adverse drug reaction reporting requirements.

K. Comments Relating to Air Separation Plants or Units (ASU)

60. In lines 1533-1534, the draft Guidance states: "ASUs separate atmospheric air into the constituent gases of oxygen, nitrogen, and argon by using a purification process of cleaning, compressing, and cooling."

Praxair believes that setting forth specific recommendations for ASUs in this section is confusing because there are references throughout the Guidance that arguably apply to ASU operations. The format suggests that this is a free-standing section that addresses all ASU requirements. Praxair requests that the Guidance be clarified by reorganizing sections to address bulk manufacturing, transfilling, and home use contexts.

L. Comments Relating to Storage Tank Installations at Health Care Facilities

61. In line 1572, the draft Guidance states: "Log equipment cleaning and use, especially for storage tanks."

Consistent with CGA/GAWDA's comments and questions regarding cleaning and use logs, there needs to be clarification as to the information that the Agency recommends in this area. The referenced recommendation concerns cGMPs for storage tank filling at health care facilities. Equipment (e.g., storage tank) cleaning and use information can be retrieved by medical gas manufacturers, but this information generally is not maintained in a log. Praxair believes that it would be impractical to maintain a use log at each health care facility, that would be accessible by many truck drivers, and, therefore, requests deletion of this concept.

62. In line 1574, the draft Guidance states: "Provide COAs to the receiving facility with each delivery."

As explained by the comment at Section II.J.56., current industry practice is to provide COA documentation as part of contractual requirements. Praxair believes that the flexible, non-mandatory use of COA documentation should continue to be permitted for medical gas deliveries, and recommends that the Guidance be clarified accordingly.

63. In lines 1580-1581, the draft Guidance states: "The supply firm would consider itself responsible for the actions of the third party installer."

So that this reference is not inadvertently used in broader commercial or product liability disputes, Praxair recommends that the following text be added to the end of the above statement: " ... with respect to regulatory compliance obligations."

M. Comments Relating to Carbon Dioxide and Helium Manufacturers and Wholesale Distributors

64. In lines 1645-1647, the draft Guidance states: "Carbon dioxide and helium manufacturers, as well as shippers, wholesale distributors, jobbers, and transporters that fill these medical gases into or out of rail cars, storage tanks, trailers, and containers are required to comply with CGMP, including the following."

Praxair recommends that this statement be clarified to reflect only those entities that are subject to cGMPs and the Guidance recommendations.

65. In line 1664, the draft Guidance states: "Conduct training, including for CGMP ... Test residual gas in tankers, trailers, and rail cars prior to filling."

Praxair recommends that this statement be clarified. Consistent with the comment at Section II.M.64. above, Praxair also notes that industry practice is to perform testing after delivery unless delivery is to an end-use customer (e.g., hospital installation).

N. Comments Relating to Terminology or Glossary

66. In lines 1873-1877, the draft Guidance states: "Uninterrupted filling sequence: A single, continuous filling sequence with no breaks or shutdowns occurring during the filling operation. This procedure uses the same personnel, equipment, and lot of component. It does not apply to the filling of high-pressure cylinders on a multiple outlet manifold or rack. The filling of nitrous oxide and carbon dioxide is covered by this definition."

Praxair recommends that this statement be clarified. It is unclear why breaks are a criterion for defining uninterrupted filling, and, therefore, defining a single lot. For instance, if another qualified individual covers an operation while an individual goes on a break, Praxair believes that this should not necessitate a new lot number. Exceptions that are not truly interruptions of operation should be permitted. Also, the foregoing recommendation should be defined exclusively in terms of nitrous oxide and carbon dioxide.

* * *

Praxair looks forward to FDA's written responses to these and CGA/GAWDA's comments on the draft Guidance, and stands prepared to engage in further dialogue with the Agency to resolve all remaining issues.

Sincerely,

Joel Zemke
Director, FDA Compliance