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MG Industries

October 31, 2003

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Re: Comment to Docket No. 03D-0165—Draft Guidance for Industry on Current Good Manufacturing Practice for Medical Gases, 68 Fed.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:

MG Industries ("MG") appreciates the opportunity to comment on the U.S. Food and Drug Administration's ("FDA's") Draft Guidance for Industry on the Current Good Manufacturing Practice for Medical Gases ("the draft Guidance"), issued in the Federal Register on May 6, 2003.

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MG is a leading supplier of medical gases, including oxygen, nitrogen, carbon dioxide, helium, nitrous oxide, and medical air. MG has a solid safety record with respect to medical gases, and is fully committed to maintaining this standard of excellence.

As an industry leader and Chair of the Medical Gases Regulatory Policy Task Force Subcommittee responsible for the Compressed Gas Association ("CGA")/Gases and Welding Distributors Association ("GAWDA") consensus comments filed on October 23, 2003, MG has been actively involved in working with other medical gas industry representatives to advance the responsible development of current good manufacturing practice ("cGMP") requirements for medical gases. MG believes that the application of cGMP requirements to medical gases should be based on good science and risk assessment principles.

As Chair of the Subcommittee, MG has had the opportunity to engage in extensive dialogue with others in the medical gas industry concerning the draft Guidance, and to review several of the independent comments submitted by industry members, which augment the industry's October 23 consensus comments. In particular, MG supports the separate comments submitted by Praxair, Inc., and shares the concerns addressed in the Praxair submission, many of which are echoed in our comments that follow. MG's 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 (which we incorporate herein by reference), in addition to providing specific recommendations, MG also has several general

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recommendations with respect to the draft Guidance. A number of these general comments were raised in CGA's July 21, 2003 letter to David Horowitz; discussed 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, MG respectfully requests that there be formal notice-and-comment responses to the issues we have raised.

I. General 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). MG's concern about this approach to guidance relates to its enforcement implications, once the Guidance is finalized.

   "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. MG 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.

   We believe that the Guidance 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.

2. **The Absence of Meaningful Risk-Based Analysis:** We have several concerns with the apparent absence of risk-based principles in the draft Guidance and subsequent FDA commentary on risk-based themes.

   a. 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 appears

to run counter to the 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. MG 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. MG respectfully suggests 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, for example, we are unaware of any patient death or injury as a result of the bulk manufacturing process. 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 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. MG continues to devote resources and personnel to educate its customers and distributors about the proper handling and use of medical gases. We believe that this type of

Agency-industry collaboration will continue to advance our mutual goal of avoiding misuse of medical gases.

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 irresponsible. MG, 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 MG believes that a number of the new substantive proposals in the draft Guidance could not be justified based on risk principles, MG 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 MG is gratified with FDA's statement's regarding the non-binding nature of the Guidance document, we are still concerned that the Guidance nevertheless will have practical binding effect, once introduced to the field. If FDA's Guidance leads MG 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, regardless of language to the contrary. MG continues to believe that formal rulemaking may be a more 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 development, MG believes that significant and costly changes in industry standards will be inevitable and, thus, must be scrutinized and justified through economic analysis protections.

Given the importance of this issue to MG and industry generally, we 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. Our understanding of current law is that the FDA should use standards developed by private consensus organizations. Accordingly, similar to references to the United States Pharmacopeia, MG 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 comments. MG 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.

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 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. MG 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, MG 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 as part of the official public record.

8. **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, MG requests that FDA separately enumerate its recommendations for these different medical gas activities.

9. **Editorial Comments Offered in the Draft Guidance:** As a general matter, MG believes that, consistent with good guidance principles, this Guidance document should be stated as concisely as possible, and avoid non-constructive dialogue. Therefore, the Agency should strike all references that offer no guidance, 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 isn't any 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. 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 MG believes should 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. 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." 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. To the extent the draft Guidance only recites the cGMP regulations, MG recommends that those references be removed, because no guidance is offered to industry.

d. Finally, the draft Guidance includes detailed restatements of external standards (e.g., USP standards). Standards are subject to change over time and 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 overarching concerns represent the bases for many of MG's specific comments on the draft Guidance recommendations. As with the CGA/GAWDA submission, MG'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."

MG requests that this and all related commentary on adverse events from mix-ups be deleted for the reasons set forth in our General Recommendations above.

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."

MG recommends that this paragraph be deleted for the reasons stated in our General Recommendations above.

B. <u>Comments Relating to Organization and Personnel</u>

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 in our General Recommendations above.

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."

MG 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."

MG 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 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."

MG 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

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

MG 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."

8. 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."

MG 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, MG notes FDA's July 31 meeting discussion concerning this issue, during which the Agency stated that it has rejected a formal rulemaking approach rulemaking to require that medical and industrial gases be separated during the

distribution process, because industry could comply voluntarily without the need for new rulemaking.

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

Given the complexity of medical gas labeling issues, MG recommends that any significant decisions on these matters be deferred pending additional FDA/industry discussions.

MG is prepared to work with FDA and other industry representatives on this important issue. 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, MG 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")."

D. Comments Relating to Equipment

9. 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, MG 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."

10. 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 MG recognizes that safeguards must be in place to ensure appropriate pressure differential to preclude system backflow, these safeguards currently are addressed through standard operating procedures and proper training. Consistent with these facts, MG 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

11. 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, MG 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."

12. 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, MG recommends that the following sentence be inserted after the above: "A cylinder, previously failing a pre-fill step, should be appropriately identified, removed from the filling process, and subsequently reconditioned in accordance with established procedures. Only failures identified during the production process itself should be recorded on the batch production record."

13. 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.

14. 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. MG's view is that the implied distinction between industrial and medical gases warrants further discussion. MG agrees that an industrial gas is meaningfully distinct from a medical gas only when not manufactured according to cGMPs. 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.

F. Comments Relating to Production and Process Controls

15. 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. MG's view is that a fully implemented quality management system can be effective without continuous oversight by corporate staff.

16. 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, we do not understand the rationale for applying the recommendations concerning charge-in of components to all medical gas products. MG 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 apply to the production of gas mixtures."

17. 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. MG agrees with the consensus industry view 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

18. 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."

MG 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, and other depot personnel).

19. 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))."

MG 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. MG's view is that, in a medical gas production setting, counting labels used does not influence the quality control release decision-making process, because the number of labels used should not affect product quality or patient safety.

20. 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 MG 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, MG 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."

21. 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, MG 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."

H. Comments Relating to Holding and Distribution

22. 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."

MG 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. MG 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.

23. 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 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. MG concurs with the proposed revision suggested by Praxair in its comments.

24. 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."

MG recommends that this statement be clarified. It is unclear as to what FDA means by "well-ventilated" and "combustible materials." 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.

I. Comments Relating to Laboratory Controls

25. 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."

These statements should be deleted for the reasons set forth above in our General Recommendations.

26. 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. MG agrees with the proposed recommendation made by Praxair on this issue.

27. 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 accurately stated in terms of the "first manifold filling sequence." The FDA's 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.

28. 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."

MG concurs with the Praxair recommendation for amending this Agency proposal.

29. 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."

MG does not believe that supplier auditing of liquid nitrogen manufacturing processes are necessary when the manufacturer receives USP/NF grade product 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, MG 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).

J. Comments Relating to Records and Reports

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

MG 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, to the best of our knowledge, has not resulted in historical safety or other quality problems, and, thus, should be permitted to continue.

31. 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 for 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.

32. 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."

MG 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.

33. 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, MG recommends that the Guidance be clarified with respect to the production/distribution context for the recommendation of a witness and a related signature.

34. 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)."

MG 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.

35. 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 Storage Tank Installations at Health Care Facilities

36. 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. MG 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, we request that the FDA reconsider this proposal.

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

As outlined in prior comment, current industry practice is to provide COA documentation as part of contractual requirements. MG 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.

38. 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, MG recommends that the following text be added to the end of the above statement: " ... with respect to regulatory compliance obligations."

* * *

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

Yours truly,

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