COMPRESSED GAS ASSOCIATION
4221 Walney Road, 5th Floor, Chantilly, VA 20151-2923
(703) 788-2700 ■ Fax: (703) 961-1831 ■ E-mail: cga@cganet.com ■ Web Site: www.cganet.com

October 9, 2003

2087 '03 OCT -9 P12 :22

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

Re: Docket No. 00N-1484, Comments to Proposed Rule – Safety Reporting Requirements for Human Drug and Biological Products

Dear Sir or Madam,

The Compressed Gas Association (CGA) and the Gases and Welding Distributors Association (GAWDA), on behalf of our member companies, request an exemption for medical gas products from the proposed rule regarding safety reporting requirements for human drugs as published in the Federal Register on March 14, 2003[1]. We fully support the intent of the proposed rule with respect to drug products for which pharmacological effects are important, but for the reasons explained below, the requirements specified in the draft regulation would not advance the stated goals of the proposal for medical gas products.

As you may be aware, CGA and GAWDA consist of approximately 1,000 member companies distributed throughout the United States. Together, we represent almost half of all registered drug sites and a high percentage of FDA regulated small businesses. As we have conveyed in the context of other rulemaking and guidance development processes, our products and their clinical applications present unique characteristics for the medical gas industry. FDA recognized this uniqueness, in the 1978 preamble regarding CFR 21, Parts 210 and 211 where they differentiated this sector from other aspects of the pharmaceutical industry. These important distinctions warrant special consideration for exemption from the proposed rule.

The comments provided below: (1) offer an historical and clinical perspective of medical gases, to help explain and support the need for postmarket rulemaking distinctions between medical gases and conventional pharmaceutical products; (2) discuss how a number of proposals in the Federal Register notice raise special questions and concerns for the medical gas sector; and (3) request that certain procedural protections be applied to this industry segment, as part of this rulemaking process in the event that the agency does not concur with our requested exemption.

I. The Historical Risk Profile and Clinical Uses of Medical Gas Products

There are clearly some incidents involving medical gas products for which reporting is warranted. Specifically, any incident involving the use, or potential use, of a wrong medical gas product by end users, should always be considered a serious unexpected event that must be reported. Industry strongly supports the Agency's access to prompt, complete, and accurate data related to all such incidents. Similarly, industry recognizes and supports reporting of any incident where, in the medical judgment of end users or healthcare personnel, there is a reasonable question of medical gas being a contributing factor to a patient safety concern.

[1] "Safety Reporting Requirements for Human Drugs and Biological Products," 68 Fed. Reg. 12406 (proposed March 14, 2003).

00N-1484

C 11

The proposed rule as drafted, however, goes well beyond these legitimate Industry and Agency interests. In order to tailor medical gas reporting so that it extends only to postmarket information of true public health value, the Agency must first consider the historical profile and clinical context of medical gas products.

A. Historical Experience
Medical oxygen represents approximately 90% of all medical gas applications. Reports of adverse incidents for this product over the years have been extremely rare as compared to other conventional drug products. As noted in the Agency's proposal, 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 based on hundreds of thousands of uses annually and millions of uses over time, industry is aware of only eight incidents involving medical gas associated fatalities and industry has effectively worked with FDA to reduce the risk of similar future problems. This historical safety profile, with events so rare as to preclude any meaningful statistical trend analysis, has not been considered in the proposed rule.

Likewise, historical root causes for medical gas incidents have not been considered. In the Agency's recent accounting of past medical gas fatalities and other injuries,[2] we can conclude that all such incidents are related to either product mix ups at point of use (all incidents since March of 1996), contamination of supply lines (1 incident) or labeling/identification errors (two incidents, both prior to 7/86). No reports reflect on the pharmacology of the drug products themselves when administered as intended.

In each of the cases reported in more recent years, information about the events has been disseminated quickly throughout the industry and to regulatory authorities where they were fully and openly discussed and evaluated for root cause. To further address root cause concerns from these few events, there has been intensive FDA and industry collaboration over the past two years to mitigate end-use mix- ups and related risks through training and related "awareness" initiatives. Since that time, there has been no reported fatalities involving medical gas products, suggesting that these collaborative interactions have begun to be successful. These well- understood, and now collaboratively managed, root cause assessments, do not seem to have been recognized in FDA's postmarket reporting proposal.

B. Clinical Applications
As with the historical postmarket experience for medical gases, the unique clinical context, particularly for medical oxygen, has not been recognized in the proposal. Oxygen is an element that is used extensively for life support, rather than for a specific pharmacological effect, as is provided by most conventional drug products. Given the supporting (rather than altering) role of oxygen in sustaining human life, it is not surprising that industry knows of no incident where patients have had a negative pharmacological reaction to this product when administered as prescribed. Similarly, industry knows of no reactions of medical oxygen with other drug products. Consequently, unlike conventional pharmaceutical products, where postmarket analyses often shed important insights into short and long-term adverse effects, and now concomitant medication concerns and risks, these concerns and risks are irrelevant for medical oxygen.

We request that these important and unique historical and clinical distinctions be factored into the request that medical gases be exempt from the proposed rule requirements.

---

[2] FDA, Current Good Manufacturing Practice for Medical Gases (Draft Guidance, May 2003)

II. Aspects of the Proposed Rule of Particular Concern

Because the reporting rule, as drafted, has not considered the historical profile and clinical context of medical gas products, there are a number of proposals that raise important questions and concerns for this industry sector, that would not serve any public health benefit and would possibly confound FDA's true post-market reporting interests.

Industry's principal concerns, as described below, relate to: (1) data collection and data review requirements; (2) new causation standards for Suspected Adverse Drug Reactions; (3) new standards for "acute respiratory failure" which appear to trigger "always expedited reports"; and (4) the use of standardized medical terminology as applied to the medical gas industry.

A. Data Collection and Review Requirements

The medical gas industry fully supports that any investigation of significant adverse events requires thorough efforts to determine root causes of problems. Industry also believes, however, that there are fundamental distinctions between root cause investigations for medical gases and more conventional pharmaceutical products. With traditional pharmacological agents, investigations necessarily involve the full array of clinical issues present with a given patient and therapeutic regimen (e.g., the expected or unexpected adverse effect profile of a given pharmacologic agent; the underlying disease condition(s) of a patient; concomitant medications; medical care and error; and related factors). By contrast, for medical gases, root cause investigations are more straightforward and focus primarily on the actions of involved parties (those who distribute or administer the drug) to determine the cause of the mix- up or related use concerns. Thus, the extensive need for medical evaluation, including active querying of adjunctive medical issues, and a review of the data by a licensed physician, brings no apparent value when considering our industry's historical product safety issues. As described below, the proposed rule appears to require significant new reporting for medical gas companies. Active querying and physician review obligations in this context run the risk of masking, or even potentially delaying the review of, legitimate incidents and analysis to identify root cause concerns. We support general concepts and intent of active querying to ensure that appropriate information is aggressively procured and that investigations are undertaken by qualified individuals. For medical gas products, we believe that these goals would be best served through a focus on manufacture, distribution and administration factors as opposed to extensive gathering of medical information.

B. Causation of Suspected Adverse Drug Reactions ("SADRs")

Approximately 120,000 patients die each year as a result of Chronic Obstructive Pulmonary Disease (COPD), either in the homecare or hospital environments. These patients, as well as hundreds of thousands of other patients, are routinely on supplemental oxygen for life support, some almost continuously, and most with an anticipated terminal outcome. Hospitals are, of course, aware when expired patients have been administered oxygen and homecare companies are routinely notified to retrieve their equipment when a patient expires. Currently, such cases are not reported as serious adverse events necessitating a 15-day alert report, unless there is medical cause to suspect that the wrong product was administered or that the product was in some other way compromised, extremely rare events, as noted above. Thus, until recently, virtually all events involving terminal patients on oxygen, have been presumed not to be reportable upon notice of death, absent information suggesting a contributing medical gas problem.

Based on the newly proposed definition of SADR, however, every patient death, including those that historically have been classified as "expected," would need to be reported. The proposed regulation

states that, those deaths "probably" caused by the underlying disease and not the result of the product, would need to be reported.[3] Even if a medical gas manufacturer determines that the likelihood of a causal relationship between its product and an adverse event is "unlikely" or "remote", the event must still be reported to FDA.[4]

Since reports of death virtually never provide statements of causation with clinical certainty, the causation standards, as now drafted, would seem to require that every death of every terminal patient on supplemental medical gas, be reported. If left unrevised, the reporting burdens would be of monumental proportion, not only for the medical gas industry, but for the hospitals and other aspects of the health care system as well.

For COPD patients alone, the proposal would theoretically increase reports by approximately 120,000 submissions per year. This consequence is fundamentally inconsistent with the premise of minimal additional reporting of a "spontaneous" nature that is assumed under the proposal's cost projections.

A further question arises as to whether deaths of COPD patients would be reportable on an expedited basis. To the extent FDA considers these events "unexpected" – i.e., not anticipated in the U.S. labeling of the medical gas product – they could be considered reportable within the expedited 15-day window provided for "serious and unexpected" SADRs.

Without an express presumption of non-reportability, absent awareness of information that would suggest a medical gas problem, the new SADR definition of causation would not advance the goal of improving drug postmarket safety reporting. Moreover, without such a non-reporting presumption, FDA's postmarket system would be flooded with needless over-reporting, that would simply burden and confound FDA's oversight of this industry sector, possibly masking a rare legitimate incident that might occur.

C. Always Expedited Reports

Under the proposed rule, it appears that all situations involving patients who expire while on oxygen support would be deemed "always expedited reports" under the category of "acute respiratory failure". There are several concerns with this apparent standard. First, the term itself requires better definition; our clinical consultants and colleagues indicate that this terminology may apply to almost all cases of patient death. Second, and of greater importance to the medical gas industry, the potential impact would be the same as that described under the new causation standard for SADRs, discussed above. This overreporting of uninformative events would increase significantly the burden on industry, regulatory agencies, and eventually, the health care system, all without advancing the safety and postmarket surveillance of medical gas products.

If reports were required for all expired COPD patients, due to spontaneous reports or due to classification as "always expedited reports," there is also a significant multiplying effect that could result from this interpretation. Specifically, any reports initially generated for medical oxygen would provide FDA with information regarding numerous other drugs taken by the expired patients, and, presumably, a report should then be issued for each such drug. The reportable events under the "spontaneous" or "always expedited" categories, therefore, would not only increase by as much as 120,000 annually, but potentially many times more, due to the prevalent use of multiple concomitant

[3] 68 Fed. Reg. at 12417.
[4] Id.

medications by most terminally ill patients. The Agency's reporting objectives cannot and will not be served by this unintended cascade of potentially hundreds of thousands of additional reports annually.

Applying this same logic to all patients that expire and receive oxygen, the reporting requirements could run into the millions per year.

D. Standardized Terminology
Although there are certain applications within the pharmaceutical industry that would benefit from standardized medical terminology, given the rare reportable incidents for the medical gas industry sector, and the fact that the root cause of fatalities and injuries are not the result of pharmacological action, there is no clear benefit from such terminology in the medical gas context. Safety issues in this sector, as described above, relate to training and other downstream handling and use issues. Consequently, the application of a highly specialized, sophisticated medical terminology system such as MedDRA, which is oriented to pharmacology and related patient clinical conditions, is unwarranted, and indeed irrelevant to this segment of industry.

III. Rulemaking Protections for Medical Gas Companies
In the event that the Agency does not concur with our request for exemption of medical gas products, the following concerns properly should be addressed prior to publication of any final rule.

A. Economic Impact Considerations
CGA and GAWDA member companies are strongly of the view that potential financial burdens from the proposed rule could be enormous, not simply for the medical gas industry, but potentially for the entire health care system, depending upon how interpretations are applied. In spite of this concern, the government's cost projections, perhaps inadvertently, have given no focus to the medical gas industry, which comprises roughly 50% of registered pharmaceutical entities.

Since the government's economic impact discussion in the proposed rule does not account for the medical gas industry, equity requires that this analysis be provided in writing prior to issuance of any final rule. As with other companies affected, medical gas companies must be given a meaningful opportunity to evaluate the government's assertions and conclusions, before the regulations are issued in final form. Any cost analysis developed by the government for this industry, must acknowledge that a significant percentage of registered medical gas entities have small business status.

B. Risk-Based Regulation
While industry fully supports the concept of expeditious and thorough reporting for serious events, the proposal as applied to medical gas products would add enormous burdens to the gathering and analysis of product safety data and offer little if any benefit.

History supports that the current system is capable of identifying all meaningful postmarket reports and we feel that the imposition of an expensive, vastly expanded reporting regime, would provide little tangible benefit, and could potentially create confounding harm. Safety concerns for this mature product line do not center around issues of pharmacologic effect, which is the focus of the proposed regulation.

Thus far, Agency officials have failed to address the risk-based need for new requirements in the medical gas industry. If a formal risk based analysis were performed for safety reporting of medical gases, it would be clear that this proposal would require significant restructuring to avoid needlessly overwhelming both industry and the FDA.

CGA and GAWDA request that this risk-based need analysis be undertaken if FDA plans to apply the proposed rule requirements to medical gas products. As with the request for economic impact analysis, this analysis should be disclosed to industry before publication of any final rule, to permit meaningful evaluation of the Agency's risk-based conclusions.

As part of this risk-based assessment, we note that international harmonization, a stated key objective of the proposed rule, is important for a number of segments of the drug and biologic industries. This is appropriate in situations involving significant numbers of patients who are taking new and widely distributed drug products for which understanding of pharmacologic interactions and effects are not fully appreciated. We see no such benefit of harmonization when dealing with a mature product, that has been used clinically for nearly 100 years, and for which there are no known pharmacological reactions or concomitant medication concerns. As noted above, the few events reported worldwide are disseminated quickly throughout industry and to regulatory authorities, where there is open discussion and focus on problem elimination. Since medical gas product safety concerns are very well understood, both by industry and regulators, it is unclear how international harmonization needs would be further served by significant new reporting obligations for medical gas companies. We believe that this conclusion would be reached through a comprehensive risk analysis.

IV. Conclusion

Based on careful review of the proposal and its stated intentions, we have concluded that an exemption from the proposed rule is appropriate for Medical Gas products. We would welcome an opportunity to review the issue of safety reporting with the Agency to identify ways that might improve safety reporting with consideration for the unique nature of our industry.

If the Agency does not agree with our request that medical gas products be exempt from the proposed rule, we request a meeting between Agency officials and CGA/GAWDA prior to any rule implementation. The purpose of the requested meeting would be twofold: (1) to discuss the degree to which this regulation would impact the medical gas industry; and (2) to assess how risk modeling should be applied so that the rule extends only to legitimate medical gas product safety concerns.

We appreciate the opportunity to comment on this proposed rule. If there are any questions regarding the proposed recommendations for exemption and clarification, please do not hesitate to contact me via e- mail at cjohnson@cganet.com or via phone at 703-788-2712. We will contact the FDA shortly to discuss if and when a meeting might be required. Thank you for your consideration.

Sincerely,

Carl T. Johnson
President
Compressed Gas Association

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

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