AMERICAN
ASSOCIATION
FOR
HOMECARE

Supporting Quality Health Care Services at Home

Via FedEx

October 31, 2003

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

Re: **Docket No. 03D–0165: Draft Guidance for Industry on the Current Good Manufacturing Practices for Medical Gases**

Dear Sir or Madam:

The American Association for Homecare (AAHomecare) provides the following comments as they relate to the "Draft Guidance for Industry on the Current Good Manufacturing Practices for Medical Gases," Docket 03D–0165. The Notice of Availability for comment appeared in the Federal Register on May 6, 2003 at pages 24005 and 24006.

AAHomecare represents approximately 3,000 health care providers, manufacturers and suppliers who furnish home health services, rehab and assistive technologies, and durable medical equipment, prosthetics, orthotics, and supplies (DMEPOS) to millions of Medicare and other government and private payors' beneficiaries. A significant percentage of our members provide medical gases, primarily oxygen, to respiratory care patients at their residences. AAHomecare, therefore, limits its comments to those issues within this draft guidance that impact the manufacture and/or distribution of medical gases provided to patients at their residences.

AAHomecare would like to thank the agency for allowing Messrs Duane Sylvia and Paul Haynie, and Ms. Pamela Schweikert, to meet with us on August 21, 2003. During that meeting we discussed our draft comments and our concerns with the Draft Guidance document, and the agency provided answers to many of our questions. The meeting assisted us in preparing this formal response, and providing the agency with, in our opinion, more meaningful comments and recommended changes. We believe incorporating our proposed changes will assure the document provides the industry with clear guidance, and

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assure our mutual goal, to assist the homecare industry with its CGMP compliance efforts is met.

The attached table (Attachment 1) itemizes our comments and proposed changes. The table provides for each item: (a) page and line numbers from the draft guidance, (b) the existing guidance verbiage, (c) our proposed change(s) or proposal(s), and (d) our rationale for the proposed change or comment. Attachment 2 provides a copy of the version of the draft Guidance document we used to generate our comments (the .pdf version), given that different versions of the guidance (with different line numbers) are available on the Internet.

Three of our General Concerns (issues that are prevalent throughout the draft document) are presented below, with references to Attachment 1, where applicable. We then identify several Specific Issues with references to specific item numbers detailed in Attachment 1. Most of these issues will have a significant impact on our industry if the draft Guidance is not modified. We have also included in this listing items that are editorial in nature for agency consideration.

GENERAL CONCERNS:

Concern 1 – 'Recommendation' Phraseology:

The use of the phrase "the agency recommends" throughout this document concerns the membership of AAHomecare. Although the agency indicates in the boxed introduction that alternative approaches may be used for compliance, the use of the phrase "the agency recommends" has a tendency of conferring greater authority to the agency-recommended practice. A firm's use of an alternative approach in a "state inspection", for example, may prove very onerous given the threshold afforded the "recommended" method versus totally acceptable alternatives. The agency confirmed its position at our August 21, 2003, meeting that all future guidance documents will use the terminology "the agency recommends" as their future standard. We continue to disagree with this position, as it is not reflected in agency guidance documents that have been published recently. Therefore we continue to exert our position that the phraseology be changed.

Our concern is that by using this phraseology, we will limit the use of safe and acceptable alternate approaches to comply with the regulation. We anticipate that if this phraseology remains, companies will include only the recommended practice in their SOP. The agency indicated that when an agency-recommended practice was included in a company SOP, it would consider the company in violation of CGMP if they did not follow their SOP (i.e. the recommended practice becomes a required practice for that company). We agree with this statement; however, this will cause

by default, the agency-recommended practice (without using the proper rulemaking processes) to become CGMP for the industry when alternate and perhaps better practices may be acceptable.

In addition, there were occasions (e.g., the recommended content of complaint records) when the agency indicated that if we did not follow a recommended practice, we would need to prove to the agency how our alternate practice met the intent of the guidance, not just the regulation.

The agency indicated that all guidance documents published by the agency will now use the words "the agency recommends" as opposed to "should," "could," etc., per the Office of Chief Councel. By copy of this letter to Mr. Daniel Troy, Chief Counsel, we respectfully request that the agency reconsider this policy. We propose the use of the words "one method of complying with this regulation is to..." or "a firm may comply by..." as a substitute for "the agency recommends", throughout the guidance.

We also propose that the agency incorporate an introduction, similar to that in the 1989 Compressed Medical Gases Guideline. That introduction stated: "This guideline describes practices and procedures for compressed medical gas (CMG) fillers ... that constitute acceptable means of complying with certain sections of the current good manufacturing practice (CGMP) regulations for drug products (21 CFR Parts 210 and 211)".

In the Federal Register Notice for the proposed rule, the "Supplementary Information" provided on page 24005 indicates, "This guidance is intended to provide recommendations on how to comply with CGMPs for manufacturing, filling, transfilling, cascading, and transferring compressed and cryogenic medical gases. The guidance should help manufacturers and distributors comply with the CGMP requirements to ensure the identity, strength, quality, and purity of medical gases." Our two remaining General Concerns revolve around statements in the guidance that, in our opinion, do not provide guidance to medical gas manufacturers on how to comply with CGMPs.

Concern 2 – Paraphrasing of Regulations (for examples/specific concerns see items 1, 4, 11, 13, 15, 21, 28, 30, 48, 52, 64, 69, 73, 79, 94, 98, 99, and 107 in Attachment I)

We are concerned about the significant amount of paraphrasing of the CGMP regulations throughout the draft guidance and the blurring between regulation and guidance. We strongly suggest that where regulations are presented in the guidance, they reflect the actual words used in the regulation. We also strongly suggest that regulation and guidance be organizationally separated and clearly identified.

Paraphrasing regulations, which contain carefully considered language, may inadvertently have the effect of eliminating or adding requirements without regulatory basis. Although the regulatory citations are not in quotation marks, they are named immediately following each paraphrased passage within parentheses, giving the impression that the citation is a direct quote. In addition, substituting the word "must" for the word "shall" when paraphrasing the regulation in the guidance document appears to confer greater regulatory authority to the guidance than stated in the regulations.

In most instances where regulation is included in this draft guidance, the words "medical gases" have been substituted for the words "drug product." With this type of substitution, regulations that may not be directly applicable to medical gases now appear to be explicitly applicable to medical gases. Although agency personnel at the August 21, 2003 meeting with AAHomecare, indicated if a regulation is not applicable to a particular operation, one would not need to comply with it. The "medical gas" for "drug product" word substitution makes it appear the operation cited in the guidance is in fact applicable to medical gases and perhaps only to medical gases. If the agency does not accept our suggestion to cite the regulation as published in the CFR, then we suggest that the paraphrasing reflect only operations applicable to medical gases and not those applicable to typical traditional pharmaceuticals.

Historically, medical gas guidance documents (and most guidance documents where regulation is cited) have cited the regulation specifically, through either exact quotation or direct citation to a specific paragraph or section number, and then detail how the industry can comply. In the draft guidance, no direct correlation is provided between the paraphrased regulation and the guidance provided. In addition, there is a blurring of the line between what is "required" by regulation and "recommended" in the guidance.

During our August 21, 2003 meeting with the agency, it was suggested that this guidance document would be used as a teaching tool. We believe the proposed guidance could be a more effective teaching tool if organized like the 1989 CMG guidance. In its current form, the proposed guidance more closely resembles a talk-paper rather than a stand-alone written teaching tool, in that the organizational units of "regulation" and "guidance" are blurred because there are no headings to announce which language is regulation and which is guidance.

Part of a talk-paper's organizational effectiveness lies in the elements of the presentation (i.e., projected slides, handouts, and the speaker's vocal cues, gestures and timing). These elements are not present in a written guidance, therefore using headings to differentiate guidance from regulations would be helpful. We

recommend that throughout the proposed guidance, the regulatory citations be better segregated from the guidance language by clearly and specifically citing regulations under a "requirement" heading, and guidance under the "guidance" heading.

Throughout the proposed guidance, there are numerous cases where regulations are paraphrased and regulatory citations are blurred together with guidance. Please see Attachment I, item 69, as one example. We propose to reverse or limit paraphrasing of regulations and to segregate the cited regulations from the guidance to enhance its clarity and organizational effectiveness as a teaching tool, as previously seen in the 1989 Compressed Medical Gases Guideline. We propose that this strategy be employed not only with respect to item 69, but also throughout the proposed guidance document.

Concern 3 – Citation of Historical Incidents: (specifically items 3, 62, 81, 108, and 110 in Attachment I)

We are concerned about the citation of historical incidents where medical gas mix-ups and other incidents have occurred causing death, with inference that these incidents were a result of a failure of the industry's manufacturers to follow or comply with CGMP. Although medical gas manufacturers or distributors may have caused some of the incidents, many of the incidents were not directly related to manufacturer CGMP non-compliance, but rather to users circumventing the existing safety systems or not reading the product label.

We understand that the agency is seeking to use this document as a training tool, however we believe this is not the appropriate venue for citation of historical incidents. We suggest that either the Federal Register notice introduction to this guidance or the FDA Medical Gases web-site may be more appropriate for the background justification. We propose that if the agency strongly believes some incidents should be included in the document, then they be provided in general terms as opposed to the specific cases currently included in the draft guidance. In our opinion, if they must be included, the most appropriate place in the document would be at lines 65 through 75 (see item 3 in Attachment I).

SPECIFIC ISSUES

The following issues in the draft guidance are of specific concern given their impact on our industry and their questionable value from a patient protection perspective. See the specific item numbers cited within Attachment 1 for our proposed changes and accompanying rationale. The referenced items also offer recommend changes to the proposed guidance document that we believe will enhance its overall effectiveness, both as a guidance document and as a teaching tool. In some instances an item may be listed under more than one issue, and/or also under a General Concern.

A.) **Issues related to the need to conduct Stability Studies, applying Expiration Dates, and Check Cylinder Pressure for Backup Cylinders in Patients' Homes**
Items 71 and 72 (and also reflected in items 93, 94, 96, and 103)

B.) **Issue related to Calculating Theoretical and Actual Yields**
Item 59

C.) **Issues associated with or potentially impacting Curbside Filling**
Items 2, 52, 60, 70, and 74

D.) **Issues associated with the Quality Control Unit (QCU) Organization and its Responsibilities; Personnel Qualifications and Responsibilities; and Consultants**
Items 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 34, 49, 52, 74, and 86

E.) **Issues related to Facility Organization, Warehousing and Distribution, and Security as related to 21 CFR Part 205 - State Licensing of Wholesale Prescription Drug Distributors**
Items 18, 19, 20, 73, 74, 75, 76, 77, and 78

F.) **Issues related to Equipment Cleaning and Maintenance**
Item 21, 22, 23, 24, 88, and 98

G.) **Issues related to Process Equipment Control, Calibration, and Validation, including Evacuation Issues, Computer Validation issues, and 21 CFR Part 11 compliance**
Items 25, 26, 27, 29, 42, 50, 51, 78, 83, 95 and 109

H.) **Issues related to Control of Components, Containers, and Closures**
30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 43, 44, 45, 46, 47, 48, 57, 58, and 113

I.) **Issues related to Production and Process Controls**
Items 53, 54, 55, 56, 57, 58, and 111

J.) **Issues related to Product Labels/Labeling and Other Product Identification**
Items 17, 40, 41, 46, 47, 53, 60, 61, 63, 64, 65, 66, 67, 68, 69, 70, 77, and 117

K.) **Issues related to Laboratory Controls including Test Method Validation**
Items 79, 80, 82, 83, 84, 85, 89, 91, 92, 104, 112, and 115

L.) Issues related to Records and Reports
Items 94, 97, 98, 99, 100, 101, 102, 104, 105, 107, and 112,

M.) Issues related to the Glossary, Other Terminology, and Minor Editorial Comments
Items 1, 44, 87, 106, 111, 112, 113, 114, 115, 116, and 117

AAHomecare firmly believes the information put forth in this letter in conjunction with the 117 items in the accompanying Attachment, provide the rationale for the agency to modify the proposed guidance document. If the agency does not concur with our proposed changes, we request the agency meet with the American Association for Homecare prior to the final issuance of the guidance, to further discuss these concerns, issues and recommendations, and to discuss the degree this guidance will impact this industry with, in our opinion, minimal positive, no, or in some cases, potential negative impact on the health benefit to the patient.

AAHomecare appreciates the opportunity to comment on this proposed draft guidance. If there are any questions regarding our concerns, issues, or proposals presented in this letter or the attachment, please do not hesitate to contact Kay Cox, President, AAHomecare, via e-mail at kayc@aahomecare.com, or via phone at (703) 836-6263. We will contact you on November 5, 2003 to verify your receipt of this letter and to discuss when a meeting, if necessary, could be scheduled. Thank you for your consideration.

Sincerely,

Kay Cox

Kay Cox
President & CEO
American Association for Homecare

ATTACHMENT 1

AAHomecare

Comments and Proposed Changes to

Guidance for Industry

Current Good Manufacturing Practice for Medical Gases

DRAFT GUIDANCE

Notice of Availability for Comment Published in the Federal Register

Item 1.	Page Number: 1	Line Start: n/a	Line Stop: n/a
Current Wording: Footnote 2 currently states, "For the purposes of this document, the term *manufacturer* includes fillers, transfillers, cascaders, distributers, and transferers of medical gases.			
Proposed Change: "For the purposes of this document, the term *manufacturer* includes any person or firm that manufactures, separates, or purifies a medical gas; fills gaseous drugs into dispensing containers or transfers a medical gas (in gaseous or liquid state) from one container to another; or modifies the labeling of a medical gas container prior to distribution."			
Rationale: More correctly states the actions taken that make a person or firm a manufacturer (without relying on industry terminology), is consistent with the definition of a manufacturer per 21 CFR § 201.1(b)(10), and does not include persons or firms that merely distribute medical gases received from a manufacturer without manipulating the container contents or labeling in any manner.			

Item 2.	Page Number: 2	Line Start: 61	Line Stop: 62
Current Wording: For example, each time a medical gas is filled into another container, finished product testing must be performed in accordance with § 211.165(a).			
Proposed Change: DELETE THIS SENTENCE			
Rationale: The preceding sentence stating that medical gas manufacturers must comply with CGMP regulations is sufficient. The example is inconsistent with the guidance provided elsewhere in the document, in the fact that finished product testing is not always required when a medical gas is moved from one container to another (e.g., liquid oxygen units filled at a patient's home from a previously qualified supply).			

Item 3.	Page Number: 2	Line Start: 65	Line Stop: 78

Current Wording: "A number of injuries and deaths have resulted from mix-ups of medical gases associated with CGMP violations including:

- Mislabeling (in some cases the container had two or more labels)
- Inadequate training, including training of medical gas filling personnel as well as delivery personnel
- Inadequate finished product testing
- Inadequate quality control unit
- Failure to qualify equipment prior to use (e.g., stainless steel hoses, large cryogenic containers)
- Inadequate written procedures for manufacturing, processing, testing

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."

Proposed Change: "CGMP violations, including the following, can and in some instances have, resulted in medical gas mix-ups that in turn resulted in injuries or death:

- Mislabeling (in some cases the container had two or more labels)
- Inadequate training, including training of medical gas filling personnel as well as delivery personnel (inadequate training of healthcare facility personnel has also contributed to medical gas mix-ups)
- Inadequate finished product testing
- Inadequate quality control unit
- Failure to qualify equipment prior to use (e.g., stainless steel hoses, large cryogenic containers)
- Inadequate written procedures for manufacturing, processing, testing

DELETE THE SENTENCE: "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"

Rationale: The citation of specific historical adverse events provides no guidance. See our rationale and discussion presented in "Concern 3" in our cover letter.

Item 4.	Page Number: 3	Line Start: 100	Line Stop: 111

Current Wording: The paraphrase, of § 211.22(a) changes the regulatory "shall" to a "must", and the paraphrased citation excludes the words "components" and "packaging material".

Proposed Change: Quote regulation as published in the CFR, OR paraphrase by including "components" and "packaging material"

Rationale: The proposed change is in keeping with our overall paraphrasing concern, Concern 2.

Item 5.	Page Number: 3	Line Start: 113	Line Stop: 114
Current Wording: We recommend that the QCU perform more than a testing function, be independent of the production process, and have both quality assurance and quality control responsibilities.			
Proposed Wording: A firm may comply by having the QCU's function be independent of the production process being reviewed.			
Rationale: 1. Historically, industry has utilized manufacturing personnel to perform testing of the product in compliance with the regulation, and utilized the "QCU" for record review and approval, including test results. 2. Historically, independence of the QCU has meant that the individual performing the QCU function at the time of its performance is independent of the process it is reviewing. Multitasking is imperative to optimize efficiency. 3. Unless defined, the terms "quality assurance" and "quality control" (inferring different responsibilities) should be dropped from these lines in the guidance. The responsibilities of the QCU are already detailed in the regulations (as presented in lines 100-105 of the attached guidance document).			

Item 6.	Page Number: 3	Line Start: 114	Line Stop: 116
Current Wording: Ideally, the QCU would participate in and have final responsibility for all functions that could affect product quality.			
Proposal: DELETE THIS SENTENCE.			
Rationale: The use of the words "participate in," "final" and "all" go beyond what is required by the regulation, and the word "ideally" indicates more than minimum current good manufacturing practice.			

Item 7.	Page Number: 3	Line Start: 116	Line Stop: 117
Current Wording: The corporate QCU would be responsible for reviewing and approving all written procedures, even those written by each individual location's organizational units.			
Proposed Change: Delete the word "corporate" and add the words "that impact medical gas quality" so the sentence will read: "The QCU would be responsible for reviewing and approving all written procedures impacting medical gas quality in accordance with the responsibilities assigned within a firm's SOP.			
Rationale: 1. Regulations do not specify a "corporate" QCU function. If a "local" QCU has the qualifications to review and approve procedures impacting medical gas quality, there should be no recommendation that this cannot occur. 2. The QCU, per regulation § 211.22(c) is only required to approve or reject procedures "...impacting on the identity, strength, quality, and purity of the drug product." not "all written procedures."			

Item 8.	Page Number: 3	Line Start: 119	Line Stop: 120
Current Wording: We recommend that all individuals who are part of the QCU be identified in the manufacturer's operating procedures.			
Proposed Change: All individuals who are part of the QCU may be identified in writing in a manufacturer's operating procedures or other document.			
Rationale: Although we agree that QCU members should be identified, it may be inappropriate or logistically impractical to include this information in some manufacturers' SOPs.			

Item 9.	Page Number: 3	Line Start: 121	Line Stop: 122
Current Wording: In a well-structured and well-defined corporate structure, the QCU would be included as a separate unit. A small medical gas manufacturer can designate a single individual as the QCU.			
Proposed Change: The size and complexity of a Quality Control Unit varies greatly with the size of the operation and tasks assigned. Medical gas manufacturers may operate one or more locations where a single qualified individual may be appropriately designated as the QCU at each location. Other locations may require more than one qualified QCU individual.			
Rationale: Size of the manufacturer should not dictate the setup of the QCU, just that the QCU must be qualified to perform its operations, and that when performing the operations, independence is maintained.			

Item 10.	Page Number: 3	Line Start: 124	Line Stop: 125
Current Wording: We recommend that QCU individuals receive adequate CGMP training on a continuing basis including quality assurance training			
Proposed Change: DELETE THIS SENTENCE IN ITS ENTIRETY, or delete just the words "including quality assurance training"			
Rationale: The phrase "quality assurance training" is not commonly known by the industry and the other requisite training (per job function) is already covered in § 211.25 (section III B).			

Item 11.	Page Number: 4	Line Start: 131	Line Stop: 137
Current Wording: Each person engaged in the manufacturing, filling, processing, packing, or holding of a medical gas must have…			
Proposed Change: **A)** Quote regulation as published in the CFR OR if the agency is not in agreement with our proposal stated in Concern 2 of our cover letter, paraphrase the regulation in keeping with current medical gas practice: **B)** 1.) Remove the word "filling" from line 131 between the words "manufacturing" and "processing," and 2.) Delete the word "regulations" on line 134 and replace it with the parenthetical statement, "(including the current good manufacturing regulations found in 21 CFR Parts 210 and 211 and written procedures required by these regulations)".			
Rationale: The recommendation is in keeping with our overall paraphrasing concern stated in Concern 2 of our cover letter. Also, the word manufacturing already by previous definition, includes any filling operation (therefore the word "filling" is redundant), and the actual regulation as published in the CFR indicates that training in the current good manufacturing practice not only requires training in the CGMP regulations, but also in a firm's SOPs that are in turn required by the regulations. Without this change, the draft guidance is relatively silent on SOP training.			

Item 12.	Page Number: 4	Line Start: 139	Line Stop: 141
Current Wording: 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.			
Proposed Change: To comply with the training frequency requirements, CGMP training may be presented in manageable sessions at a minimum of once per year or more frequently if determined by the QCU to assure employees remain familiar with the requirements applicable to them.			
Rationale: Once a year may or may not be sufficient based on the subject matter being presented. Each firm should be free to determine the frequency and method of training for compliance with the regulation.			

Item 13.	Page Number: 4	Line Start: 145	Line Stop: 146
Current Wording: Regulations at § 211.25(c) require an adequate number of qualified personnel be available to perform and supervise the manufacturing, processing, or holding of medical gases.			
Proposed Change: Quote the regulation as published in the CFR, reverting to "drug product" instead of "medical gases."			
Rationale: The recommendation is in keeping with our overall paraphrasing concern stated in Concern 2 of our cover letter.			

Item 14.	Page Number: 4 -5	Line Start: 170	Line Stop: 173
Current Wording: We recommend that an individual responsible for performing an odor test not have an ailment (e.g., a cold or allergies) that would adversely affect his or her sense of smell. Likewise, employees responsible for performing the inspection for the standardized colors should be able to distinguish colors.			
Proposed Change: Individuals who may have ailments or conditions that could adversely affect their ability to perform a requisite test or inspection effectively should exclude themselves from that activity.			
Rationale: Although we agree in principal with this statement, it may prove onerous for manufacturers to implement, and difficult to verify.			

Item 15.	Page Number: 5	Line Start: 179	Line Stop: 182
Current Wording: Consultants advising on the manufacturing, processing, packing, or holding of medical gases must have sufficient education, training, and experience, or any combination thereof, to advise…			
Proposed Change: Quote the regulation as published in the CFR, reverting to "drug products" instead of "medical gases."			
Rationale: The recommendation is in keeping with our overall paraphrasing concern stated in Concern 2 of our cover letter.			

Item 16.	Page Number: 5	Line Start: 184	Line Stop: 185
Current Wording: We recommend that consultants hired to provide assistance in achieving CGMP compliance have sufficient medical gas education, training, and/or experience.			
Proposed Change: DELETE THIS SENTENCE			
Rationale: § 211.34 already requires that consultants have education, training, and/or experience to advise on the subject for which they are retained. The statement does not offer additional guidance for the requirement, and there may be areas where "medical gas" experience is not required, e.g. electronic records, computer validation.			

Item 17.	Page Number: 5	Line Start: 216	Line Stop: 217
Current Wording: The Agency recommends the use of 360-degree wrap-around label to identify medical gases in large cryogenic containers.			
Proposed Change: A 360-degree wrap-around label may be used to identify medical gases in large cryogenic containers (excludes vessels permanently or semi-permanently mounted in vehicles).			
Rationale: Although this guidance occurs under Design and Construction of Buildings and Facilities (IV.A.), the paragraph in which the 360-degree wrap-around label is introduced begins with recommendations about delivery vehicles. Vessels mounted in delivery vehicles are not delivered to facilities or patients where medical gas mix-ups may occur, but remain affixed to their vehicles. Therefore, we recommend the exclusion statement above.			

Item 18.	Page Number: 6	Line Start: 224	Line Stop: 226
Current Wording: Medical gas manufacturers are wholesale distributors who are subject to the requirements of § 205.50 - Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.			
Proposed Change: 1. Insert the words "who are also" for the word "are" so the sentence begins: "Medical gas manufacturers who are also wholesale distributors..." 2. Add the following sentence at the end of current line 226, "Medical gas manufacturers may wish to contact their appropriate state agency for further guidance."			
Rationale: Some manufacturers are only retail operations and do not wholesale. §205.50 refers to wholesalers (distribution to non end user) and no one else - law speaks to wholesalers only. The agency agreed with our proposed change during AAHomecare's meeting on 8/21/03.			

Item 19.	Page Number: 6	Line Start: 232	Line Stop: 232
Current Wording: We recommend areas where nitrous oxide is held be especially secure			
Proposed Change: Firms who supply nitrous oxide may wish to assure the nitrous oxide is maintained in a secure area, given the additional potential for theft or diversion of this product. These firms may wish to consult CGA publication SB-6 for appropriate measures that may be taken to prevent theft or improper use.			
Rationale: As stated above, 21 CFR part 205 (and hence § 205.50) refers only to wholesale distribution, as opposed to retail operations, and state laws mandate the extent of the security required for distributors. We are aware, however, of the need for additional security for Nitrous Oxide and strongly suggest that firms that supply nitrous oxide follow the recommendations found in CGA Safety Bulletin SB-6.			

Item 20.	Page Number: 6	Line Start: 234	Line Stop: 237
Current Wording: The security requirements of § 205.50(b) apply to all facilities used for medical gas distribution. FDA interprets this regulation to include all facilities where loaded medical gas delivery trucks are parked prior to making deliveries, including at an employee's home when a loaded medical gas delivery truck is driven there and parked overnight for early morning runs.			
Proposed Change: Add the word "wholesale" between "for" and "medical" in the first sentence and delete all remaining sentences in this paragraph, to read: "The security requirements of § 205.50(b) applies to all facilities used for wholesale medical gas distribution."			
Rationale: • Some manufacturers are retail operations and do not wholesale. • The requirements of 21 CFR 205 are enforced by each individual state and their interpretation of what is included or excluded. • The agency agreed with our proposed change during AAHomecare's meeting on 8/21/03.			

Item 21.	Page Number: 6	Line Start: 250	Line Stop: 252
Current Wording: Equipment must be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the medical gas beyond the official or other established requirements (§ 211.67(a)).			
Proposed Change: **A)** Quote regulation as published in the CFR OR if the agency is not in agreement with our proposal stated in Concern 2 of our cover letter, paraphrase the regulation in keeping with current medical gas practice: **B)** Equipment must be cleaned and maintained at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the medical gas beyond the official or other established requirements (§ 211.67(a)).			
Rationale: Paraphrasing § 211.67(a) insinuates that the regulation specifically states that *only* medical gas equipment must be "sanitized at appropriate intervals", rather than all drug product manufacturing equipment. In addition, sanitization is not a typical activity performed by medical gas manufacturers. The proposed change is in keeping with our overall paraphrasing concern, Concern 2.			

Item 22.	Page Number: 6	Line Start: 259	Line Stop: 260
Current Wording: We recommend that equipment used in the manufacture of medical gas (e.g., manifolds, pigtails, valve assemblies, hoses, and gauges) be cleaned at initial use and if exposed to a contaminant.			
Proposed Change: Equipment used in the manufacturing of medical gas (e.g., manifolds, pigtails, valve assemblies, hoses, and gauges) should be appropriately cleaned by a qualified individual prior to initial use and if contaminated internally.			
Rationale: • It should be sufficient to have this work contracted and certified by an equipment supplier prior to first use. Most medical oxygen fillers do not have the capability of cleaning manifolds, pigtails, valve assemblies, hoses, etc. In addition, it may be hazardous for an unqualified individual to perform "cleaning" and in some instances this "recommendation" has the potential to create problems that may not currently exist. • Only equipment that has become internally contaminated would require cleaning.			

Item 23.	Page Number: 6	Line Start: 261	Line Stop: 262
Current Wording: We recommend that hoses used to fill cryogenic containers have protective end caps to prevent contamination from insects, dirt, debris, and other materials.			
Proposed Change: Change to read, "Firms may comply with applicable portions of §211.67 by having hoses used to fill cryogenic containers protected to prevent contamination from insects, dirt, debris, and other materials."			
Rationale: The recommendation to use "end caps" is overly prescriptive and other means of protection may be acceptable. Some hose configurations do not allow for the use of end caps.			

Item 24.	Page Number: 7	Line Start: 267	Line Stop: 271
Current Wording: We recommend that storage tanks (especially those installed at a health care facility, nursing home, or hospital), tractor trailers, rail cars, high-pressure cylinders, and cryogenic containers prior to the introduction of a medical gas be cleaned in the following circumstances: when they previously contained industrial gases; when they are first received, whether new or used; and when they are or could be, contaminated.			
Proposed Change: Move to container section of guidance (around line number 350) and change to read: "Storage tanks..., high-pressure cylinders, and cryogenic containers may be appropriately cleaned by a qualified individual prior to the introduction of a medical gas if any of the following conditions exist 1) prior to initial use, 2) if they previously contained industrial gas, or 3) if internally contaminated."			
Rationale: • The guidance refers to containers not equipment. • It should be sufficient to have this work contracted and certified by an equipment supplier prior to first use. Most medical gas fillers do not have the capability of cleaning tanks, high-pressure cylinders or cryogenic containers, etc. In addition, it may be hazardous for an unqualified individual to perform "cleaning" and in some instances this "recommendation" has the potential to create problems that may not currently exist. • The "used" in "whether new or used" could be inferred to mean whenever the container is returned to the filler, if the container was out of the filler's control, i.e. provided to a customer. • Odor test is used to ascertain if the high-pressure cylinder has become contaminated. (Cryogenic home containers are not typically odor tested). If the container has pressure, contaminants would not enter the container. • Only equipment that has become internally contaminated would require cleaning.			

Item 25.	Page Number: 7	Line Start: 289	Line Stop: 291
Current Wording: 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.			
Proposed Change: Vacuum gauges may undergo a daily check and a periodic calibration (minimum once per year) in order to comply with the equipment calibration requirements for vacuum gauges. The daily check would ensure that the needle on the gauge returns to zero with no vacuum or pressure (above atmospheric pressure) present. This check could be recorded on either a batch production record or a separate log.			
Rationale: The "first calibration" is a check, not a calibration (adjustment to a standard), and no positive pressure should be present when the check is made.			

Item 26.	Page Number: 7	Line Start: 297	Line Stop: 298
Current Wording: We recomment that thermometers be calibrated in accordance with manufacturer recommendations, and that the calibrations be documented in a separate log.			
Proposed Change: Thermometers may be replaced or calibrated a minimum of once per year. Calibration may be performed in accordance with manufacturer recommendations, or compared to a like thermometer (that is used only for calibration purposes) in the same environment. Document these calibrations.			
Rationale: Some thermometers cannot be calibrated. Many thermometer manufacturers do not provide calibration recommendations. The practice proposed using a "like thermometer in the same environment" has been previously cited by FDA as an acceptable practice, and acknowledged as an acceptable practice at the AAHomecare Continuum of Care presentation by FDA on 10/8/03.			

Item 27.	Page Number: 7	Line Start: 300	Line Stop: 304
Current Wording: 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.			
Proposed Change: Medical gas manufacturers using check valves in their medical gas systems may comply with the equipment design requirements of § 211.63 by ensuring the valves have been properly designed by the check valve manufacturer to assure they prevent backflow of a foreign material/contaminant or over-pressurization of the system, and that they have been installed properly (i.e., correct direction) in the medical gas system.			
Rationale: More correctly reflects an acceptable method to comply with the regulation and within the means of most medical gas manufacturers to comply.			

Item 28.	Page Number: 8	Line Start: 313	Line Stop: 318
Current Wording: Paraphrase of § 211.68(b).			
Proposed Change: Quote regulation as published in the CFR, reverting to "shall" instead of "must," and reinserting the words "formulas or" in line 315 before the word "records." Place the regulation citation, § 211.68(b), in a heading above the paragraph, rather than repeat it after each sentence.			
Rationale: The recommendation is in keeping with our overall paraphrasing concern stated in Concern 2 of our cover letter			

Item 29.	Page Number: 8	Line Start: 320	Line Stop: 329
Current Wording: The Agency recommends that computerized systems, including hardware and software, used in the manufacturing, processing, and holding of medical gases be validated. The depth and scope of the validation depends on the diversity, complexity, and significance of the computerized application. Commercially available software that has been qualified does not need the same level of testing as software that has been specifically developed for a company. The Agency recommends that computerized systems have sufficient controls to prevent unauthorized access or changes to data and to preclude omissions in data. The Agency also recommends that records be kept of any changes made to data, including who made the change, when the change was made, and the previous entry.			
Proposed Change: Computerized systems, including hardware and software used in the manufacturing, processing, and holding of medical gases may require different levels of validation. See the agency's current guidance on software validation and 21 CFR Part 11 and its associated guidance documents when electronic records and/or signatures are used.			
Rationale: Firms using computerized systems require more information on how to comply than this guidance can provide. Where electronic records and/or signatures are used, firms need to review Part 11 and its associated guidance.			

Item 30.	Page Number: 8, 9	Line Start: 345 350 355	Line Stop: 347 352 357

Current Wording: Manufacturers must have written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and medical gas containers and closures (§ 211.80(a)). Containers and closures must at all times be handled and stored in a manner to prevent contamination (§ 211.80(b)).

Each medical gas container and closure, upon receipt and before acceptance, must be examined visually for appropriate labeling as to contents, container damage, and contamination (§ 211.82(a)). Containers and closures must be stored under quarantine until they have been tested or examined, as appropriate (§ 211.82(b)).

Medical gas containers and closures must be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit (QCU) (§ 211.84(a)).

Proposed Change:

A) Quote regulations as published in the CFR,

OR if the agency is not in agreement with our proposal stated in Concern 2 of our cover letter, paraphrase the regulation in keeping with current medical gas practice:

B) 1) (For Lines 345 – 347) DELETE the word "sampled," so the sentence will read, "Manufacturers must have written procedures describing in sufficient detail the receipt, identification, storage, handling, testing, and approval or rejection of components and medical gas containers and closures (§ 211.80(a))."

2) (For Lines 350 – 352) DELETE the words "upon receipt," so the sentence will read, "Each medical gas container and closure, before acceptance, must be examined visually for appropriate labeling as to contents, container damage, and contamination (§ 211.82(a)).

3) (For Lines 355 – 357) REPLACE the phrase "the lot has been sampled" with the words "they are," and DELETE the words "and released for use by the Quality Control Unit (QCU)" so the sentence will read, "Medical gas containers and closures must be withheld from use until they are tested or examined, as appropriate. (§ 211.84(a)).

(See next page for Rationale)

Rationale: Our proposed change is in keeping with our overall paraphrasing concern, Concern 2. of our cover letter, and specifically:

- (For lines 345 – 347) Medical gas containers and closures (high pressure and liquid) are not "sampled," they are 100% inspected prior to use
- (For lines 350 – 352) Medical gas containers and closures (high pressure and liquid) generally are inspected immediately prior to fill as opposed to "upon receipt"
- (For lines 355 – 357) Medical gas containers and closures (high pressure and liquid) are not received as a "lot," and the container filler, as opposed to the QCU, releases containers and closures (high pressure and liquid) prior to their use at time of fill. The QCU will review the records associated with the container and closure inspection as a part of record review prior to distribution for all product, except product filled curbside. The record review for liquid oxygen filled at curbside will occur after product distribution.

Item 31.	**Page Number: 9**	**Line Start: 375**	**Line Stop: 377**
Current Wording: In addition, we advise medical gas manfacturers to determine valve assembly compatibility prior to installation on a high-pressure cylinder and during the lifetime of the valve.			
Proposed Change: Qualified persons or firms initially installing or replacing valves may comply with § 211.94 by obtaining valves from valve manufacturers that can assure the compatibility of their valve assembly with the high-pressure cylinder and the gas it shall contain.			
Rationale: • Typically the valve manufacturer, not the medical gas manufacturer, determines compatibility. • Many cylinder fillers do not install or replace valves on high-pressure cylinders. • Compatibility does not change during the lifetime of the valve if it remains in the cylinder. The only additional compatibility issue may occur at time of valve replacement.			

Item 32.	Page Number: 9	Line Start: 384	Line Stop: 387
Current Wording: We recommend that the following prefill inspections be performed on each medical gas cylinder prior to the start of the filling operation. Cylinders failing any of these procedures would be quarantined to prevent their use in any subsequent filling operation. We recommend that medical gas manufacturers document all prefill inspections on a batch production record.			
Proposed Change: To comply with § 211.80 – § 211.94 a medical gas manufacturer may perform the following pre-fill inspections on each medical gas cylinder prior to the start of the filling operation. Quarantine cylinders failing any of these inspections or tests to prevent their use in any subsequent filling operation before the failure condition is corrected, or the cylinder is condemned. Medical gas manufacturers must document all pre-fill inspections on a batch production record. Manufacturers may wish to consult Compressed Gas Association (CGA) publication P-15 and other CGA documents as additional resources regarding pre-fill inspections. During the discussion, the agency expressed concern that the cost of CGA documents may be cost-prohibitive to some firms. We believe, however, that the information provided in CGA publications is helpful and should be included in the guidance document.			
Rationale: Provides additional guidance, and source of information that this guidance cannot fully provide.			

Item 33.	Page Number: 9	Line Start: 390	Line Stop: 391
Current Wording: Ultrasonic inspection of steel high-pressure cylinders can be performed instead of internal visual and hydrostatic testing.			
Proposed Change: Ultrasonic inspection of steel and aluminum high-pressure cylinders may be performed instead of internal visual and hydrostatic testing.			
Rationale: Adds ultrasonic inspection of aluminum high-pressure cylinders, as is current permissible practice.			

Item 34.	Page Number: 9	Line Start: 397	Line Stop: 399
Current Wording: 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.			
Proposed Change: Any cylinder found to have any of these conditions would be removed from service and placed in an appropriate quarantine area until its suitability has been determined.			
Rationale: The person correcting the condition, not the QCU, has historically determined the suitability of the container.			

Item 35.	Page Number: 10	Line Start: 401	Line Stop: 403
Current Wording: If any gas is present in a cylinder, venting or blowing down a cylinder can be performed until atmospheric pressure occurs. We recommend that cylinders containing liquid be inverted and drained.			
Proposed Change: If any gas is present in a cylinder, it can be vented from the cylinder (or blown down) by opening the valve slowly and allowing the pressure in the container to equalize with atmospheric pressure. Small post-valved cylinders may be inverted to assure no liquid is contained in the cylinder. Large cylinders would only be inverted if another pre-fill inspection indicates the possible presence of a liquid (e.g. odor test, dead-ring). High-pressure cylinders containing liquefied compressed medical gas (e.g., nitrous oxide, carbon dioxide) may be inverted and drained to expedite venting, but may also be vented in the upright position.			
Rationale: • Only small post-valved cylinders containing non-liquefied gas (i.e. those that may be used in a horizontal position) are typically inverted. Large cylinders (e.g. M, H, and T size) are used in an upright position, and unless liquid is suspected (e.g. via an odor test or other pre-fill inspection) the cylinder would not be inverted. • Differentiates issue with liquid in non-liquefied gas cylinders vs. liquefied gas product. • High-pressure cylinder containing liquefied compressed medical gas may also be "blown down" in the upright position.			

Item 36.	Page Number: 10	Line Start: 405	Line Stop: 412
Current Wording: Odor test: The odor test is a very important prefill test for detecting the presence of any foreign gas or odor. Do not perform this test on carbon dioxide, nitrous oxide, toxic, or corrosive gases. If a cylinder is empty (contains no pressure), a medical gas can be introduced into the cylinder at a predetermined pressure, and an odor test can be performed on the resulting gas. Use only medical gases, as an industrial gas could contain industrial contaminants. ***Do not confuse this odor test with the finished product odor test conducted under § 211.165(a) and required by the USP.***			
Proposed Change: • Starting at the 3rd sentence of the current wording, modify the sentence to read, "If a cylinder is empty (contains no pressure), a medical gas can be introduced into the cylinder at a low pressure, and an odor test performed on the resulting gas in the cylinder. Only medical gases should be introduced for odor testing, as an industrial gas could contain industrial contaminants. Preferably, introduce Nitrogen, NF, due to the possibility that a non-inert medical gas may react with a contaminant in the cylinder, if one were present." • Move all Odor test text to line 400 (prior to "venting or blowing down")			
Rationale: • Provides additional guidance. • Reflects the order that test are performed in. Odor test must be performed prior to venting or blowing down.			

Item 37	Page Number: 10	Line Start: 418	Line Stop: 422
Current Wording: This procedure cannot be performed on aluminum or fiber wrapped cylinders because the test would not indicate internal corrosion. A hammer test works best on empty unpressurized cylinders with a 10-year test date (stamped into the cylinder shoulder area). It is not necessary to test cylinders with a 5-year test date.			
Proposed Change: This procedure cannot be performed on aluminum or composite cylinders because the test would not indicate internal corrosion (as no sustained ring could be obtained) and may damage the cylinder wall.			
Rationale: • The term "composite cylinders" is proper. "Fiber wrapped cylinders" is a subset of composite cylinders. • Delete reference to "unpressurized cylinders," as the hammer test will work on cylinders that contain gas under pressure. It may be necessary to hammer test pressurized cylinders prior to placement on a fill rack where they will be vented, in order to obtain an acceptable "ring." • Delete reference to DOT requirement that only cylinders with a star after the manufacture date (10 year retest) must be "hammer tested" prior to fill. Although steel cylinders that have a 5-year retest are not "required" to be "hammer tested" they may be "hammer tested" without causing harm.			

Item 38.	Page Number: 10	Line Start: 424	Line Stop: 428
Current Wording: The inspection would examine whether any of the threads on the valve or on top of the valve stem are damaged; whether the handwheel or valve stem is bent; and whether there are indications of damage, corrosion inside the valve, or excessive heat or fire damage.			
Proposed Change: The inspection would examine the valve to assure (a) the valve is properly inserted in the cylinder, (b) that the valve stem or any of the threads on the valve (gas connection and cylinder to valve connection) are not damaged; (c) that the hand wheel or valve stem is not bent; and (d) whether there are indications of damage, corrosion inside the valve, or excessive heat or fire damage. The pressure relief device (PRD) should be properly rated for the cylinder and not damaged.			
Rationale: Provides additional guidance consistent with current practice.			

Item 39.	Page Number: 10	Line Start: 442	Line Stop: 443
Current Wording: Color coding alone cannot be relied on for identification of the medical gas; use color coding in addition to examining the product label on the cylinder.			
Proposed Change: DELETE ";use color coding in addition to examining the product label on the cylinder" so sentence reads "Color coding alone cannot be relied on for identification of the medical gas."			
Rationale: Both are currently required, statement does not provide guidance.			

Item 40.	Page Number: 11	Line Start: 448	Line Stop: 449
Current Wording: We suggest that you ensure that cylinders bear only one manufacturer or filler's label and that you not apply new labels on top of an old label.			
Proposed Change: To comply with CGMP labeling regulations, cylinders may bear only one manufacturer's (filler's) or distributor's label that meet the applicable requirements of 21 CFR Part 201. A new drug label should not be applied on top of an old drug label.			
Rationale: Clarifies issue of label over label and more correctly identifies whose label may appear on the container.			

Item 41.	Page Number: 11	Line Start: 450	Line Stop: 450
Current Wording: NONE			
Proposed Change: **A)** Insert the following quotes of the regulation and/or provide additional guidance regarding 21 CFR Part 201 here or as an attachment to the guidance that will indicate: • Name requirements as found in 21 CFR § 201.1 (f), (g), and (h) • Address requirements as found in 21 CFR § 201.1 (i) and (j) • Legend requirements (Prescription) as found in 21 CFR § 201.100 • Other Exemptions as found in 21 CFR § 201.161 **B)** Discuss that medical gas labels must also comply with DOT requirements, and **C)** Discuss that CGA publication C-7 offers guidance regarding DOT and FDA compliance and also provides appropriate language to include on labels for safety and handling, such as warnings, cautions, and precautions.			
Rationale: We propose adding this language for educational purposes to assist medical gas manufacturers who may not have sufficient knowledge as to what information must appear on a label and in what format. During our discussion on 8/21/2003, the agency agreed that references to the FDA regulations would be beneficial. Also during the discussion, the agency expressed concern that the cost of CGA documents may be cost-prohibitive to some firms. We believe, however, that the information provided in CGA publications is helpful and should be included in the guidance document. In addition, the brief reference to "applicable DOT requirements" would assist firms in suggesting to them that they obtain this appropriate information.			

Item 42.	Page Number: 11	Line Start: 451	Line Stop: 452
Current Wording: We recommend that residual gases be removed from medical gas cylinders by means of a vacuum pump prior to filling a medical gas.			
Proposed Change: MODIFY this sentence to read, "To remove the prior contents that in turn could negatively impact the strength (assay) of the final product, medical gas cylinders in single component service should be evacuated to at least 25 inches of mercury at sea level by means of a vacuum pump prior to filling a medical gas. (NOTE: If not performed the filler would need to conduct full appropriate testing, usually full USP/NF testing on each cylinder not evacuated).			
Rationale: Provides additional guidance (also see item 50) and in some cases an acceptable alternative to not removing residual gas.			

Item 43.	Page Number: 9 - 11	Line Start: 382	Line Stop: 454
Current Order: 1. Hydrostatic testing date inspection 2. External examination 3. Venting or blowing down 4. Odor test 5. Hammer or dead-ring test 6. Valve assembly examination 7. Color code examination 8. Label Inspection 9. Residual gas removal			
Proposed Order: 1. Hydrostatic testing date inspection 2. External examination 3. Color code examination 4. Label Inspection 5. Valve assembly examination 6. Hammer or dead-ring test 7. Odor test 8. Venting or blowing down 9. Residual gas removal			
Rationale: Although not required, we suggest that the pre-fill inspections/tests be conducted in the order specified under "Proposed Order." The odor test must be conducted prior to the venting or blowing-down step.			

Item 44.	Page Number: 11	Line Start: 475	Line Stop: 477
Current Wording: Large Cryogenic Containers			
Proposed Change: Re-title the section name to: Large Cryogenic Containers not Permanently or Semi-Permanently Mounted in a Vehicle			
Rationale: The glossary only defines the term "Cryogenic containers." Based on the draft guidance lines 1828 thorough 1830, the term Large Cryogenic Containers appears to include Vehicle Mounted Vessels, however, section 4 on page 11 of the draft guidance, appears to apply to "large" cryogenic vessels that are not permanently or semi-permanently mounted in a vehicle. We believe our proposed change clarifies this section's applicability (also see item 113, where we recommend additional definitions).			

Item 45.	Page Number: 11	Line Start: 483	Line Stop: 483
Current Wording: Permanently attach all connections or fittings to the container.			
Proposed Change: All connections or fittings shall be attached to the container by either brazing or using a device that prohibits the user from tampering with the connection.			
Rationale: Gives some indication as to what "permanently attached" means and is consistent with current industry practice as recommended in CGA SB-26.			

Item 46.	Page Number: 11	Line Start: 487	Line Stop: 488
Current Wording: These labels are designed to repeat the drug product name (e.g., Medical Oxygen) in the appropriate color around the entire container.			
Proposed Change: These labels are designed to repeat the identity of the drug (e.g., **Oxygen USP** or Medical Oxygen) in the appropriate color around the entire container.			
Rationale: Recommending the 360-degree wrap-around label to say only "Medical Oxygen" instead of "Oxygen USP" could cause re-labeling of containers that are already properly labeled with Oxygen USP 360-degree wrap-around labels. The proper name of the drug product is Oxygen USP. The proposed change allows an option to use the wording preferred by the manufacturer, whether "Oxygen USP" or "Medical Oxygen," either of which would aid workers in product recognition. The agency in our 8/21/03 meeting, indicated the goal of the 360-degree wrap is to provide distinction between medical and industrial grade products. The agency also indicated that hospital employees sometimes confused "USP" with "UPS" – the rationale for changing the name from "Oxygen USP" to "Medical Oxygen." The agency also indicated there was a potential that all official names for medical gases with a USP/NF monograph may be changed to "Medical (name of gas)" (See USP/NF Pharmacopeial Forum 28(4) [July-Aug, 2002] pages 1312-1314 "Stimuli to the Revision Process"). We believe the issue is training, not re-labeling. The notion that hospital personnel confuse the term "USP" with the United Parcel Service or the United States Postal Service, is very disconcerting and should be the subject of face-to-face discussion between the USP, FDA, JCAHO, and the appropriate medical gases and healthcare industry associations, prior to implementing such a change.			

Item 47.	Page Number: 12	Line Start: 502	Line Stop: 502
Current Wording: An inspection of the product label			
Proposed Change: An inspection of the product identification – For example, inspecting the permanently mounted cryogenic container for the presence of a sign or marking indicating "Oxygen, Refrigerated Liquid." A product label is not required for permanently mounted cryogenic containers, as these containers are not for patient-use.			
Rationale: Permanently mounted cryogenic containers are not patient-use vessels, and therefore are not required to bear an actual Product Label. This point was reviewed at length with the agency during the 8/21/2003 AAHomecare meeting. It was determined that displaying the name of the product on the permanently mounted vessel is sufficient in lieu of an actual product label for these containers. This proposed language is consistent with current industry practice and previous guidance. See item 67 also.			

Item 48.	Page Number: 12	Line Start: 506	Line Stop: 509
Current Wording: Containers and closures must be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the QCU in accordance with § 211.84 as necessary (e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the medical gas container or closure) (§ 211.87).			
Proposed Change: DELETE			
Rationale: Containers maintained under normal storage conditions will not be adversely affected. Any empty container is inspected immediately prior to use in filling operations as part of the pre-fill inspections. Length of time in storage has no impact on empty medical gas containers (the focus of this section of the guidance). The result of containers exposed to adverse conditions, such as to fire or water (causing rust) would be identified in the pre-fill inspection process.			

Item 49.	Page Number: 13	Line Start: 533	Line Stop: 534
Current Wording: 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.			
Proposed Change: DELETE or restate as indicated in item 7 and as follows: The QCU would be responsible for reviewing and approving all written procedures impacting medical gas quality in accordance with the responsibilities assigned within a firm's SOP.			
Rationale: See rational provided for item 7 related to lines 116-117.			

Item 50.	Page Number: 13	Line Start: 541	Line Stop: 545
Current Wording: We recommend that a manufacturer or individual, especially a manufacturer filling multiple gases, have data on file demonstrating the amount of vacuum evacuation required to remove all contaminants from high-pressure cylinders. We also recommend that the manufacturer have data demonstrating that each different gas it fills would be removed by the established vacuum evacuation limit.			
Proposed Change: Manufacturers filling single component medical gases (i.e., Oxygen, USP, Nitrogen, NF, etc.) may evacuate all cylinders prior to filling to a minimum of 25 inches of mercury at sea level, in order to remove the cylinders' prior contents that could negatively impact the strength (assay) of the final product, if they were not evacuated. Manufacturers filling multiple component gases may be required to evacuate their cylinders to a higher level, or employ other procedures to assure those cylinders have had their prior contents removed to a sufficient level so as to not negatively impact the strength (assay) of the components in the final product. These manufacturers should maintain data demonstrating the sufficiency of their evacuation level or alternate procedure to assure no negative impact on the assay of the components in the final product.			
(See following two pages for Rationale)			

Rationale: At our meeting with the agency on 8/21/03, we discussed that the 25-inch Hg vacuum has been a long-held and FDA-accepted industry standard. The purpose of the 25-inch Hg vacuum is not to "pull out all contaminants," but rather to remove a significant portion of the one atmosphere of residual gas. This "one atmosphere" is typically the residual of the same gas to be filled, room air (if the cylinder had been opened to the air for any length of time), or Nitrogen NF that had been introduced for odor testing. This vacuum is performed to remove the majority of the residual gas, so as to not negatively impact the strength percentage of the gas being filled into the cylinder. The odor test is used to determine the presence of contaminants, and if the odor test indicated the presence of contaminants, the cylinder would be removed from service until properly inspected and cleaned. The vacuum is not used, nor was it ever intended to be used to "remove" the suspected contaminant.

We also verified that the agency's concern was the validity of the 25 inch Hg vacuum standard and not whether the indication on a vacuum gauge on a manifold control panel equated to a 25 inch Hg vacuum at the far end of a manifold after a certain period of time. This would be a different potential validation issue if a vacuum gauge were not placed at the end of the manifold furthest away from the vacuum pump. Clarification of this point was necessary to determine if an industry study, versus a site-by-site study was required. The agency agreed an industry study would suffice. During this same meeting, a committee member suggested that proof of the adequacy of a 25-inch Hg level of evacuation could be provided mathematically. Although some of the agency personnel present were skeptical of a mathematical proof, the following data is provided for agency consideration:

- One atmosphere (atm) is equal to 14.696 pounds per square inch (psi) pressure.
- One atmosphere (atm) is equal to 29.921 inches of mercury (Hg).
- An absolute vacuum (or the removal of all pressure at sea level) is equal to an evacuation of one atm, or an evacuation of 29.921 inches Hg.
- An evacuation of 25 inches Hg therefore equates to an evacuation of 0.836 atm [25.000" Hg / 29.921" Hg/atm] with the amount of gas remaining in the cylinder after an evacuation of 25 inches equal to 0.164 atm [1.000 atm – 0.836 atm].
- 2200 psi positive pressure is equal to 149.701 atm [2200 psi / 14.696 psi/atm] of positive pressure.
- When a cylinder is filled to 2200 psi, one can calculate the number of atmospheres that will be new product (149.701 atm + 0.836 atm = 150.537 atm), the atmospheres of residual product (0.164 atm), and the total contained in the cylinder (150.537 atm + 0.164 atm = 150.701 atm).
- These values can then be converted into percentages giving 99.891% new product (150.537 atm/150.701 atm x 100%) and 0.109% residual product (0.164 atm/ 150.701 atm x 100%).
- Values for other fill pressures can be similarly calculated as presented in the table on the following page:

Fill pressure	Positive pressure in atm	25" Hg vacuum in atm	Residual amount in atm	Total atm	Percent new	Percent residual
1800	122.482	0.836	0.164	123.482	99.867	0.133
1900	129.287	0.836	0.164	130.287	99.874	0.126
2000	136.091	0.836	0.164	137.091	99.880	0.120
2100	142.896	0.836	0.164	143.896	99.886	0.114
2200	149.701	0.836	0.164	150.701	99.891	0.109

- Assuming the worst-case scenario for oxygen filling (that the remaining residual after evacuation is pure nitrogen because nitrogen had to be added to perform an odor test), the residual would have 0.0% Oxygen. [Note: In actuality even if nitrogen were used on a cylinder that contained only one atmosphere of air because a valve was left open, the residual would still have some oxygen.]
- If a 99.8% supply was used to fill a cylinder to 2200 psi, the resultant percentage of the final product in the cylinder would be at worst 99.7% (99.891% of 99.8%).
- Based on the assay of the supply used, the resultant assay percentages for the product in the cylinder as provided in the following table would be obtained. (Based on a 25 inch evacuation level and the total top pressures listed):

	Resultant % of oxygen based on **% of oxygen supply** and 25" level of evacuation where residual content is 100% nitrogen					
Fill pressure	**100.0**	**99.9**	**99.8**	**99.7**	**99.6**	**99.5**
1800	99.9	99.8	99.7	99.6	99.5	99.4
1900	99.9	99.8	99.7	99.6	99.5	99.4
2000	99.9	99.8	99.7	99.6	99.5	99.4
2100	99.9	99.8	99.7	99.6	99.5	99.4
2200	99.9	99.8	99.7	99.6	99.5	99.4

The data presented above demonstrates that a 25-inch Hg evacuation level (at sea level) is sufficient when filling single component medical gases. In addition, the long-standing acceptable practice of using a 25-inch Hg evacuation level prior to filling single component medical gases into high-pressure cylinders has consistently resulted in purities above minimum standards, empirically demonstrating that this evacuation level is sufficient. We believe the mathematically calculated data combined with the historical evidence, supports our proposed change.

Item 51.	Page Number: 13	Line Start: 547	Line Stop: 550

Current Wording: 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.

Proposed Change: To assure the cylinders being filled on portable racks (such as those added to the main header or manifold via pigtails) or on extended manifolds are being properly vacuum evacuated, a vacuum gauge should be installed at the end of the portable rack(s) or manifold, or the system should be evaluated via proper studies, to assure the requisite vacuum level has been attained.

Rationale:

- The industry practice of placing a vacuum gauge at the end of each portable rack (at the furthest point on the manifold from the vacuum pump) to verify proper evacuation prior to each fill is an acceptable alternative to "evaluating" the system via studies to assurance the proper level is attained. [NOTE: The following information supports the need to install vacuum gauges at the end of a manifold or to conduct proper validation studies. This information also provides assistance in explaining why pressure gauge installed at the end of a manifold should not be required, or why validation studies assuring proper pressurization (and hence net contents) should not be required.] Atmospheric pressure at sea level is equal to 0 inches of Hg, 0 psi gauge (psig) on a positive pressure gauge, or 14.696 psi absolute (psia) on an absolute pressure gauge. A 25-inch evacuation level equates to 2.4 psia. The time required to evacuate/reduce the pressure from 14.696 psia to 2.4 psia (a total of 12.3 psia) and to assure this level is consistent across the manifold, may be significant. Depending on the size of the manifold and the number of add on racks, the variance between the control manifold vacuum gauge when it reaches 25 inches of Hg and the gauge at the end of the manifold may be 3 inches of Hg less (1.5 psia) or 12% of the total amount to be evacuated. To assure the proper vacuum level has been attained across the entire manifold, one needs to wait until the vacuum gauge attached to the end of the add-on rack has attained the requisite vacuum level. Several member companies have conducted studies verifying this condition and supporting the need for a vacuum gauge at the end of the manifold (or the need to conduct proper validation studies).
- Contrary to vacuum, where the differential between a vacuum reading on the control manifold and the reading on a vacuum gauge attached to the end of the manifold may be significant, a differential between the control manifold pressure gauge and a pressure gauge attached to the end of a manifold, when the cylinders are "full" (i.e., the control manifold reads approximately 2000 psig) will be undetectable. The time required to evacuate 12.3 psia with a vacuum pump is significantly greater then the time required to raise the pressure a similar 12 psia with a high-pressure pump (almost instantaneous). Even if there was a 12 psia variance between the pressure reading on the control manifold and the end of the manifold, the impact on the net quantity of contents would be less than 1% (12 psi/2000 psi), supporting the position that a pressure gauge need not be installed at the end of a manifold, and why validation studies assuring proper pressurization (and hence net contents) should not be required). Some member companies have also verified this condition.

Item 52.	Page Number: 13	Line Start: 558, 568	Line Stop: 560, 569
Current Wording: Paraphrase of §211.101 and § 211.101(d)			
Proposed Change: **A)** Quote regulations as published in the CFR, OR if the agency is not in agreement with our proposal stated in Concern 2 of our cover letter, paraphrase the regulation in keeping with current medical gas practice: **B)** Change Line 568 – 569 to read: "Each component must be added to the batch by one person and verified by a second person either" (a) at the time of addition, (b) after manufacturing operations have been completed but prior to distribution, or (c) after distribution if product is filled at the customer site.			
Rationale: The proposed change is in keeping with our overall paraphrasing concern, Concern 2. AAHomecare's members do not have, and it would not be fiscally sound to have, a second person verify that liquid oxygen (each component) filled into a patient's vessel curbside (has been added to the batch) by a driver technician (one person). This has been regarded as acceptable because oxygen is the only component involved and because of the unique circumstances of meeting the needs of home oxygen patients (lines 568-569). Similarly, the filling of high pressure cylinders is not observed by a "second" person, rather the documentation is reviewed by a second person (QCU) after all manufacturing operations are completed.			

Item 53.	Page Number: 13	Line Start: 571	Line Stop: 575
Current Wording: 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.			
Proposed Change: REPLACE WITH: To assure compliance with §§ 211.101(a) and 211.101(b), single component and multi-component medical gases in high-pressure cylinders may be filled by weight or by using appropriate temperature-pressure charts to assure labeled net contents are achieved. Cryogenic containers may either be filled by weight or in accordance with their manufacturer's recommendations to assure labeled net contents are achieved when the vessel is full. The net content statement for high pressure gaseous product is typically expressed in terms of gaseous liters or cubic feet based on a standard temperature and pressure. For liquefied compressed gases in high pressure cylinders, the net content statement is typically expressed in terms of gaseous liters or cubic feet based on a net weight. For liquid in cryogenic containers, the net content statement is typically expressed in terms of gaseous liters, cubic feet, liquid liters, or pounds.			
Rationale: We believe this text reflects the requirements of §§ 211.101(a) and 211.101(b), and also reflects current industry practice.			

Item 54.	Page Number: 14	Line Start: 580	Line Stop: 581
Current Wording: Overfilled cylinders could reach dangerously high pressures if exposed to elevated temperatures, even if the pressure at room temperature is safe.			
Proposed Change: DELETE			
Rationale: Although there may be a concern with liquefied compressed gases (e.g. nitrous oxide, carbon dioxide), the pressure relief device is designed to relieve "dangerously high pressure" regardless of ambient temperature (elevated or otherwise).			

Item 55.	Page Number: 14	Line Start: 587	Line Stop: 588
Current Wording: Before the filling is complete, the temperature and pressure reading would be recorded on the batch production record.			
Proposed Change: Upon completion of the fill, the actual temperature and pressure readings on the thermometer and pressure gauge should be recorded on the batch production record.			
Rationale: Procedure must be complete prior to documenting.			

Item 56.	Page Number: 14	Line Start: 590	Line Stop: 594
Current Wording: We recommend that, when filling cylinders one at a time (also known as the cascade method), each cylinder have a thermometer attached to it.			
Proposed Change: When filling cylinders one at a time, place a thermometer on the cylinder to monitor temperature during fill.			
Rationale: Cascade method includes multiple cylinders to multiple cylinders (gas-to-gas filling), not only one to one filling or several to one filling.			

Item 57.	Page Number: 14	Line Start: 597	Line Stop: 598
Current Wording: It is critical not to overfill aluminum cylinders.			
Proposed Change: No overfill allowance is made for aluminum or composite cylinders which should not be stamped with a "+" symbol.			
Rationale: The current wording infers that only aluminum cylinders cannot be overfilled, which is not true. Any cylinder that does not bear a plus sign cannot, by DOT regulation, be overfilled.			

Item 58.	Page Number: 14	Line Start: 611	Line Stop: 613
Current Wording: After the filling of high-pressure cylinders, and after all valves have been closed, we recommend a second valve assembly leak test be performed to detect any valve outlet leaks. If any leaks were detected, the cylinder would be removed from service and quarantined until repaired.			
Proposed Change: After the filling of high-pressure cylinders, and after all valves have been closed and the cylinders disconnected from the manifold, conduct a second valve assembly leak test to determine if there are any valve outlet leaks. If any leaks are detected, the cylinder would be removed from service and quarantined until repaired or the cylinder is blown down and the valve replaced.			
Rationale: • The proposed change is more descriptive of the 2nd leak check process. • If a valve is found to be leaking, the valve may need to be replaced. Repair may not be possible.			

Item 59	Page Number: 15	Line Start: 626	Line Stop: 639
Current Wording: Actual yields and percentages of theoretical yield must be determined at the conclusion of each appropriate phase of manufacturing, processing, packing, or holding of medical gases. Such calculations must be performed by one person and independently verified by a second person (§ 211.103). FDA recognizes that accurate inventory records and reconciliation of use are difficult to maintain for liquefied gases. Normal losses of gas occur through vaporization, the filling process, and venting and could reach 10 percent or more. The FDA does not expect the reconciliation to be 100 percent accurate. A manufacturer's procedures for reconciling the use of medical gases can include allowances for normal storage and operating losses. The procedures would include provisions for further investigation when unexplained discrepancies occur, such as losses beyond established normal levels.			
Proposed Change: Delete the current wording and substitute the words, "Actual yields and percentages of theoretical yield do not need to be calculated for medical gases, as they provide no means of additional process control."			
Rationale: The use of a theoretical yield and its comparison to a calculated actual yield does not provide any additional process control, the purpose for the yield requirement as specified in the preamble to the cGMP regulations, given: • the significant "losses" that occur through vaporization, due to the "heat" of the container being filled and the saturation of the liquid supply, and • the variation in the product mix (quantity of high pressure cylinders filled versus cryogenic containers filled on a given day), • the variation in the types of cryogenic vessels filled – given that each type of vessel has a normal evaporation rate - expected loss of product, and • the normal liquid to gas expansion ratio In addition, the agency has previously acknowledged, via "Gas What" and internal agency correspondence, the validity of the industry's argument to exempt medical gases from the requirement for calculation of yields and reconciliation.			

Item 60.	Page Number: 16	Line Start: 670, 682	Line Stop: 673, 683
Current Wording: Use of visual inspection to conduct a 100 percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination must be performed by one person and independently verified by a second person (§ 211.122(g)(3)). 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.			
Proposed Change: Add a sentence stating that, "Visual verification of labeling by a second individual does not apply to filling cryogenic home vessels at a patient's residence (curbside fills)."			
Rationale: Although it is industry practice to apply labels by hand, it is not industry practice, in all instances, to have labeling performed by one person and independently verified by a second person. Although we understand the regulatory requirement, this cannot be reasonably accomplished, nor is it industry standard for labeling of cryogenic home vessels filled at the patient's residence.			

Item 61.	Page Number: 16	Line Start: 675	Line Stop: 676
Current Wording: Upon receipt from the printer, labels would be counted to verify the quantity received and would be examined to ensure correctness when compared against the master label.			
Proposed Change: "To ensure correctness, examine and compare received labels against the master label. Quantities of labels received from the printer shall be verified (physical count, versus printer count or certification) as necessary to assure no diversion of labels has occurred. The verification activity need not be completed immediately upon receipt, but must occur prior to issuance of labels from the new roll or package.			
Rationale: Current regulation does not require verification of printer count upon receipt.			

Item 62.	Page Number: 16	Line Start: 683	Line Stop: 685
Current Wording: In light of recent deaths and injuries, this examination is critical to ensure that the correct label has been applied to a container of medical gas.			
Proposed Change: DELETE			
Rationale: Per Concern 3 of our cover letter, this statement offers no guidance.			

Item 63.	Page Number: 16	Line Start: 703	Line Stop: 705
Current Wording: Before release of issued labels to an employee, we recommend a representative label be checked against the master label to ensure correctness.			
Proposed Change: DELETE			
Rationale: The current statement is the same as the information provided in lines 694 – 695 of the draft guidance (paraphrase of § 211.125(b)). The current wording offers no additional guidance.			

Item 64.	Page Number: 16	Line Start: 711	Line Stop: 713
Current Wording: There must be written procedures designed to ensure that correct labels and labeling are used for medical gases; such written procedures must be followed. These procedures must incorporate the following features (§ 211.130):			
Proposed Change: Quote the regulation as published in the CFR, thrice reverting to "shall" instead of "must," and once reverting to "drug products" instead of "medical gases."			
Rationale: The recommendation is in keeping with our overall paraphrasing concern stated in Concern 2 of our cover letter.			

Item 65.	Page Number: 17	Line Start: 732	Line Stop: 733
Current Wording: 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.			
Proposed Change: Cryogenic home containers filled on site and stored for future delivery (i.e., where there is no knowledge to whom the vessel will be delivered when it is filled), or filled by a third party should be given a lot number. Where a specific cryogenic home container is filled on site and it is destined for a specific patient (i.e., not to stock), a lot number need not be placed on the container. Whenever cryogenic home containers are filled, there must be traceability to the lot or batch contained in the vessel used to fill the cryogenic home container.			
Rationale: Reflects current industry practice, and if filled for a specific patient on site, is similar to filling at the patient's home.			

Item 66.	Page Number: 17	Line Start: 739	Line Stop: 741
Current Wording: We recommend that the net contents appear on the body label or shoulder label and not on (1) a removable tag, (2) a certificate of analysis, or (3) a small separate sticker.			
Proposed Change: DELETE.			
Rationale: Lines 738 – 739 already states the requirement. We do not question the requirement in section 502(B)(2) of the Act but we do not believe the Act or any regulation prohibits the use of a tag or separate sticker on the container to provide the net quantity of contents information. If a labeling regulation exists that is contrary to our understanding and requires the net contents to appear on the body label or shoulder label, we request that it be specified.			

Item 67.	Page Number: 17	Line Start: 753	Line Stop: 755
Current Wording: We recommend the labeling for large permanently mounted containers, trailers, and rail cars bear a statement consisting of "Name of the Medical Gas, Refrigerated Liquid USP or NF," such as "Oxygen Refrigerated Liquid USP."			
Proposed Change: NO CHANGES REQUIRED PROVIDED THAT: • The definition of "labeling" includes documents that "accompany an article," **and** • The guidance does not require a product label to be placed directly on the container, **and** • A sign or marking on the permanently mounted container that indicates the name of the product will suffice in lieu of an actual product label.			
Rationale: Permanently mounted vessels are labeled and placarded in accordance with DOT requirements as applicable. In addition, permanently mounted containers are not patient-use vessels. The above information was reviewed at length with the agency during our 8/21/2003 meeting. We believe that displaying the name of the product (i.e., "Oxygen, Refrigerated Liquid") on the permanently mounted vessel is sufficient in lieu of an actual product label for these containers, as other accompanying documentation should be considered part of the "labeling" for the container. See items 41 and 47.			

Item 68.	Page Number: 18	Line Start: 757	Line Stop: 758
Current Wording: The Agency recommends the use of a 360-degree wrap-around label to identify medical gases in large cryogenic containers.			
Proposed Change: A 360-degree wrap-around label may be used as an additional means to identify medical gases in large cryogenic containers that are not permanently or semi-permanently mounted in vehicles.			
Rationale: Reflects current guidance that does not specifically require 360-degree wrap-around labeling. For example, the FDA Public Health Advisory flier, "Medical Gas Mix-ups Can Cause Death and Serious Injury," states to, "Educate and train personnel who are directly responsible for handling medical gas to: recognize medical gas labels [and to] examine all labels carefully before hooking containers to the system," but does not mention 360-degree wrap-around labels. The "FDA Public Health Advisory: Potential for Injury from Medical Gas Misconnections of Cryogenic Vessels," dated 7/20/01, does not mention 360-degree wrap-around labeling. The FDA Public Health Advisory, "Guidance for Hospitals, Nursing Homes, and Other Health Care Facilities," makes the following recommendation: "**If** your supplier uses 360-degree wrap-around labels..., personnel should be trained to make sure each vessel they connect to the oxygen system bears such a label." The proposed change, which is consistent with current guidance, still makes the public aware of the use of 360-degree wrap-around labels, but does not exceed the language in other guidance papers. The proposed change excludes large cryogenic containers that are not permanently or semi-permanently mounted in vehicles, because they are not exchanged at medical facilities. Therefore, they are not subject to medical gas mix-ups of the nature the guidance is intended to prevent.			

Item 69.	Page Number: 18	Line Start: 760	Line Stop: 772
Current Wording: Paraphrase of § 211.134(a), § 211.134(b) and § 211.134(c)			
Proposed Change: Quote regulations as published in the CFR. Delete line 762 and place the regulatory citation § 211.134, in the header next to "Drug Product Inspection," then place an "a)" in front of lines 764-765, a "b)" in front of lines 767-768, and a "c)" in front of lines 770-771. Delete the parenthetical regulation citations at the end of lines 765, 768 and 771. Insert a "Guidance" header at line 772 in order to differentiate lines 773-774, which are guidance from the regulation citations.			
Rationale: The recommendation is in keeping with our overall paraphrasing concern stated in Concern 2 of our cover letter. Our proposed change to this item also exemplifies our proposed strategy of segregating regulations from guidance for the document's clarity and organizational effectiveness as a teaching tool, as previously seen in the 1989 Compressed Medical Gases Guideline.			

Item 70.	Page Number: 18	Line Start: 773	Line Stop: 774
Current Wording: Only one medical gas label would appear on a cylinder or container, and the manufacturer of the medical gas would apply the label in accordance with section 502(b) of the act.			
Proposed Change: To comply with CGMP labeling regulations and section 502(B) of the Act, cylinders or containers may bear only one manufacturer's (filler's) or distributor's drug label. A new drug label should not be applied on top of an old drug label. The filler may not need to replace the label, if the label is current and compliant with labeling regulations. A cryogenic home vessel manufacturer's device label should not be removed from the container.			
Rationale: Similar to Item 40, clarifies issue of label over label and identifies whose label (manufacturer and/or distributor if properly qualified) may appear on the container. Clarifies that existing labeling may not need to be removed if compliant. Clarifies that the guidance applies to the drug product label and not the device labe, if present. This wording has been added, as the device manufacturer's label is part of the device approval process.			

Item 71	Page Number: 18, 26-27	Line Start: 776, 1136	Line Stop: 788, 1156

Current Wording: Requirements regarding Expiration Dating and Stability Testing

Proposal:

A) AAHomecare members recommend that all medical gases, especially oxygen, be exempt from the expiration dating requirements.

B) If the agency does not concur with A), AAHomecare recommends that all medical liquid oxygen be exempt from expiration dating requirements.

C) If the agency does not concur with A) and/or B), AAHomecare also recommends that the wording in the guidance reflect words similar to "Fresh Air 2000" and allow the industry a sufficient amount of time to bring this segment of the industry "into compliance" over the course of time (a minimum of 5 years from date of publication of the final guidance).

Rationale: It is our understanding, based on discussion with agency personnel, that there is no concern that common medical gases such as oxygen have "stability" problems (i.e. no degradation or combination products over time). It is also our understanding that the agency's primary concern is maintaining pressure in unopened, high-pressure cylinders (also see item 72 following).

Agency personnel have made comments regarding aluminum cylinders because the studies conducted by the Compressed Gas Association in support of their Citizens Petition to exempt medical gases from the expiration dating requirement (started in the late 1970's, concluded in the mid-1980's, presented to the agency in the early 1990's, and evaluated by the agency in the late 1990's) did not include this type of container. Aluminum cylinders are the prevalent high-pressure container used in the homecare setting. We believe the issue is more of a need to document "compatibility" (the potential interaction between the gas and the material) as opposed to "stability." This issue may be best resolved by presenting the agency with existing compatibility data from cylinder manufacturers.

Agency personnel also made comments regarding cryogenic containers, again because the studies did not include this type of container. The agency, during a seminar on 10/8/03, indicated that due to normal evaporation rates, there was an expectation that cryogenic liquids would not be required to bear an expiration date.

Prior to issuing this draft guidance, the agency indicated that expiration dating was not required. If the agency feels compelled to require further testing, AAHomecare is prepared to complete joint testing with other industry groups with agency interaction. These trials will be representative of and serve all member companies. We believe it would be better for the agency to continue to use its enforcement discretion as stated in "Fresh Air 2000" as opposed to enforcing a potential confusing graduated expiration dating requirement (i.e., a one year expiration date until one year's worth of data is collected, a two year expiration date until two year's worth of date is collected, etc.). We believe that such a phased in approach may be difficult to communicate to both the manufacturers of medical gases, as well as the users of medical gases.

Item 72.	Page Number: 18	Line Start: 794	Line Stop: 799

Current Wording: The Agency recommends that high-pressure cylinders stored for long periods of time, such as those provided to patients as a backup to their oxygen concentrator, be monitored to ensure they contain the correct net contents (i.e., pressure). We recommend that companies, especially home care companies and durable medical equipment suppliers, establish and follow a written plan to periodically verify the pressure (i.e., net content) of each high-pressure cylinder stored at a patient's home and that the results be documented.

Proposed Change: DELETE

Rationale: This recommendation is impractical, very burdensome, offers no additional safety to the patient (and may, in fact, create an unsafe condition), and in our opinion, has no basis in CGMP regulation.

We provide the following, in support of our rationale why the proposed inspection and testing regimen is impractical, burdensome, and potentially unsafe:

- Many homecare patients will have cylinders in various locations (i.e., other family relatives or caregivers homes), making it impossible for a firm to check all cylinders that might be delivered and left over a period of time. Even if possible, the data obtained provides only a snapshot at the time the cylinder is checked.
- The recommended practice would require HRC firms to remove the seals on post-valve cylinders that many patients traditionally rely on to ascertain if the container has been used (has a seal = full, does not have a seal = empty). Requiring a firms employee to break (remove) the seals to check cylinder pressure, may lead to confusion on behalf of the patient and thereby in itself create an unsafe condition.
- There is a possibility that a firm's employee would not properly close a cylinder valve on a cylinder that had the proper contents at the time it was checked, causing it to "leak" out. In many instances where cylinders are unexpectedly "empty," the patients themselves have failed to correctly close the valve after use, allowing the contents to "leak" out. Valves must be closed properly on all cylinders when they are not in use.
- Patients utilizing an oxygen concentrator as their stationary system and high-pressure cylinders as backup, will have one or two backup systems in case of equipment failure or electrical power outage. The backup systems will include a portable oxygen system (usually several small high-pressure cylinders such as the M6 style, E style, etc.) to allow for mobility, and may also include where needed, a large high-pressure cylinder such as an M style or H style cylinder. In addition, Homecare Companies typically have 24-hour, 365-day on-call emergency services available, in the unlikely event that a backup cylinder was found to be empty and required replacement for whatever reason.

(Rationale continues on the following two pages)

Based on discussions with the agency on 8/21/03, we understand the basis of this proposed recommendation relates to:

1.) Concerns with the Compressed Gas Association stability study (i.e., some cylinders "leaked" their contents over a period of time),
2.) Recalls related to cylinders without proper pressure, and
3.) Concern that when a backup cylinder is needed, the cylinder will be empty and the patient will die.

Responding to each of these items:

1.) Regarding the CGA stability studies - Additional plausible explanations for why some of the stability study cylinders did not have the "expected" amount of product contained within them based on the pressure reading and test result data presented to the agency (in support of CGA's citizen petition) were discussed at the 8/21/03 meeting. The agency indicated they could not take these reasons under consideration (e.g., additional testing (non-USP/NF tests) performed on stability cylinders but only USP/NF specification results reported, the person analyzing the test cylinder failing to properly close a valve after test), and could only proceed based on the information that was presented with the study and assume there were leaks. An AAHomecare member indicated that the study, at the time that it was initiated in the late 1970's, was never designed to check the container closure system but to show that the gases were themselves stable (i.e., there were no combination or degradation products). We agree that current pharmaceutical stability study protocols also require an evaluation of the container/closure system in which the drug will be marketed.

2.) Regarding recent recalls – The agency indicated there recently were "massive" recalls of cylinders that were delivered or received "empty." Although the members present at the meeting were not aware of these recalls, we did not disagree that one possible reason that a cylinder could have been empty on receipt is due to a leak. There are also several other reasons that cylinders could have been received or delivered empty, aside from "leaks," all potential CGMP violations, including a) driver obtained cylinders from "empty" stock as opposed to from "full released" stock (inferring improper segregation/identification and training), b) cylinders were not properly filled (inferring that a proper heat check was not performed), and c) cylinder valves were not properly closed after completion of fill (inferring that a proper 2nd leak check was not performed). If a customer determined the "empty condition" a significant period of time after delivery, there is also the potential that the customer improperly segregated, designated, or identified his or her empty and full cylinders. We would recommend that the agency suggest to the firms implicated in these recent recalls, that the firms undertake an investigation into the root cause for a cylinder being empty on delivery, and that they institute any required corrective action to prevent recurrence. If it is determined that a valve did in fact leak over time as a result of a design flaw, stability issue, or compatibility issue (as opposed to a customer's improper use of a cylinder), this should be reported to the industry as a whole to assure proper corrective action is

taken.

3) Regarding backup cylinder being empty when needed – The agency drew an analogy between a.) the ability to rely on a working fire extinguisher being available if a home fire were to break out – enabling the fire to be extinguished, and b.) the need to assure a respiratory care patient has a full oxygen cylinder available if the power went out – preventing the patient from dying. We believe the analogy is inaccurate. The inference that oxygen supplied to patients at their residence is "life supporting" (i.e., that without oxygen, the patient will die within a short period of time) is also inaccurate. Most oxygen supplied to patients at their residence is provided as a supplement to enhance a patients "quality of life" as opposed to "supporting life". In those instances where oxygen is supplied to a patient on a ventilator, there will be multiple backups (not reliance on "one" cylinder), given that the patient or their family member, may improperly close a cylinder valve and cause a cylinder to go empty. At the 8/21/03 meeting the AAHomecare members discussed anecdotally, that with the massive power outage that took place in the Northeast, not one complaint was received (by these AAHomecare members) relating to empty cylinders, and certainly no deaths were reported. Similarly, no complaints have been received related to this issue with the recent power outages associated with the hurricane impacting the east coast.

We question FDA's regulatory basis, especially absent evidence of a significant problem or a potential problem to require product that has already been distributed and in most cases already purchased by a consumer or other payer, to be 100% rechecked periodically to verify net contents. If there is a regulatory basis, we question how the agency can limit its recommendation to "especially home care companies and durable medical equipment suppliers..." and to limit its recommendation to ...high-pressure cylinder[s] stored at a patient's home." In our opinion, it would be equally impractical, burdensome, and potentially unsafe to require non-HRC medical gas firms to periodically verify net contents at their customers (e.g., within a hospital, at EMT facilities, etc.).

In conclusion, we believe the information provided above provides sufficient basis for the agency to remove this recommendation from the proposed guidance, and if the agency does not concur, that the agency cite within the guidance the regulation that supports this impractical, burdensome, and potentially unsafe recommendation.

Item 73.	**Page Number: 19**	**Line Start: 804**	**Line Stop: 813**
Current Wording: Paraphrase of § 211.142			
Proposed Change: Quote the regulation as published in the CFR. Delete line 806 and place the regulatory citation § 211.142, in the heading in line 804.			
Rationale: The recommendation is in keeping with our overall paraphrasing concern and our proposed organization strategy stated in Concern 2 of our cover letter.			

Item 74.	Page Number: 19	Line Start: 811	Line Stop: 811
Current Wording: Quarantine of medical gases before release by the QCU (§ 211.142(a))			
Proposed Wording: ADD TWO SENTENCES: Home care companies filling cryogenic vessels at the customer site are exempt from the requirement for QCU release prior to distribution. Documentation associated with this activity must be reviewed by the QCU within a reasonable period of time after distribution.			
Rationale: Exemption is required for the home care industry when conducting filling at the patient's residence. Current industry practice is to have the QCU review the documentation associated with the filling of vessels at the patient's home within a reasonable period of time.			

Item 75.	Page Number: 19	Line Start: 814	Line Stop: 817
Current Wording: The Agency recommends that separate areas be designated 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.			
Proposed Change: Modify the beginning of the current wording, inserting the words "defined or identified" between the words "separate" and "areas," and adding the words "or such other control systems" in the first sentence. The revised sentence would then read, "Compliance with § 211.42(c) may be achieved by having separate defined or identified areas or other control systems for the following:"			
Rationale: We believe this recommendation relates to §§ 211.42(c) and 211.42(b) as opposed to § 211.142. This regulation (§ 211.42(c)) states, "There shall be separate or defined areas or such other control systems..." Many, if not most medical gas facilities typically are not large enough to have separate and "permanently" designated areas indicated in the current wording. We believe appropriate signage in areas that may have multiple uses (current industry practice), is adequate to prevent mix-ups, the goal of § 211.42(b). The manufacturer should therefore be able to define in it's SOP's, how signage or other barriers would or could separate product to prevent mix ups.			

Item 76.	Page Number: 19	Line Start: 820	Line Stop: 823
Current Wording: We recommend medical gas containers be stored under protective covering and not be subject to temperature extremes. Based on this recommendation, storage areas would be clean, dry, well ventilated, and free of combustible materials. Also all valve assemblies, hoses, and other relevant equipment would be protected from contamination such as insect infestation.			
Proposed Change: Medical gases shall be stored under appropriate conditions so that their identity, strength, quality, and purity are not affected.			
Rationale: Proposed guidance is overly prescriptive. The proposed change reflects § 211.142(b).			

Item 77.	Page Number: 19	Line Start: 840	Line Stop: 845
Current Wording: As mentioned above, the Agency recommends the use of a 360-degree wrap-around label to identify medical gases in large cryogenic containers. If a manufacturer applies a 360-degree wrap-around label to its large cryogenic containers, and the manufacturer has established adequate driver training, written procedures, and proper stock inventory systems, physical separation on a delivery vehicle is not critical.			
Proposed Change: A 360-degree label that encircles and is applied near the top of large portable cryogenic containers may be used to identify medical gases in large portable cryogenic containers. (A 360-degree label is not applied to cryogenic containers that are mounted semi-permanently or permanently in vehicles). If a manufacturer applies a 360-degree wrap-around label to its large portable cryogenic containers, and the manufacturer has established adequate driver training, written procedures, and proper stock inventory systems, physical separation on a delivery vehicle is not critical.			
Rationale: As stated in item 68, large cryogenic containers that are permanently, or semi-permanently mounted in a vehicle, should not be required to have 360-degree wrap around labels.			

Item 78.	Page Number: 20	Line Start: 847	Line Stop: 848
Current Wording: We recommend that handheld computer devices or computers used during distribution operations be validated to ensure proper performance.			
Proposed Change: We recommend that handheld computer devices or computers used during distribution operations be validated to ensure proper performance, and comply with the requirements of 21 CFR Part 11.			
Rationale: Provides additional guidance and reference to 21 CFR Part 11.			

Item 79.	Page Number: 20	Line Start: 858	Line Stop: 863
Current Wording: The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by Subpart I of 21 CFR Part 211, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, must be drafted by the appropriate organizational unit and reviewed and approved by the QCU. The requirements in Subpart I of 21 CFR Part 211 must be followed and must be documented at the time of performance (§ 211.160(a)).			
Proposed Change: **A.)** Quote regulation as published in the CFR, OR if the agency is not in agreement with our proposal stated in Concern 2 of our cover letter, paraphrase the regulation in keeping with current medical gas practice: **B.)** After the word "performance" at the end of line 863, insert the last sentence of § 211.160(a), that states, "Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified."			
Rationale: The recommendation is in keeping with our overall paraphrasing concern stated in Concern 2 of our cover letter. Also, the actual regulations require that any deviations be recorded and justified; an important issue for compliance, yet the draft guidance is relatively silent on this point.			

Item 80.	Page Number: 20	Line Start: 875	Line Stop: 875
Current Wording: ...adulterant that might be present, including microbial contamination.			
Proposed Change: DELETE "including microbial contamination" so sentence ends as "adulterant that might be present."			
Rationale: Current wording suggests that microbial contamination may be present. Sentence as proposed would still require additional testing if microbial contamination were present, however, does not infer that it would be present.			

Item 81.	Page Number: 20	Line Start: 881	Line Stop: 890
Current Wording: 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.			
Proposed Change: DELETE			
Rationale: These statements provide no guidance. See the rationale and discussion presented in "Concern 3" in the body of the cover letter.			

Item 82.	Page Number: 21	Line Start: 935	Line Stop: 935
Current Wording: The accuracy of the USP procedure is ± 0.1 percent.			
Proposed Change: ADD the following sentence at end of the current sentence: "Alternate test methodologies may be acceptable, see guidance on alternate testing methods (Section X.C.) in this section."			
Rationale: Most Oxygen USP manufacturers/fillers utilize the paramagnetic method of analysis for assay as opposed to the official USP orsat method. The proposed change provides the link to alternate testing methods in the document.			

Item 83.	Page Number: 22	Line Start: 939	Line Stop: 942
Current Wording: Laboratory controls must include the calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met (§ 211.160(b)(4)).			
Proposed Change: ADD the following words at end of sentence: Calibration of gauges and other mechanical or electronic equipment used for process control (e.g. manifold gauges, low pressure gauges) is discussed in section V.B. of this document.			
Rationale: Cross-references the equipment section for calibration of mechanical and electronic process control equipment for clarity.			

Item 84.	Page Number: 22	Line Start: 957	Line Stop: 957
Current Wording: Analytical methodology used to assay the calibration standard			
Proposed Change: DELETE			
Rationale: Many COAs for calibration standards do not indicate the method of analysis. There appears to be no regulatory basis for requiring this information in either 21 CFR Part 58 or Part 211. Given that homecare companies do not manufacture calibration standards, we are concerned with a recommendation that our suppliers may not follow, yet for which we may be found "out of compliance."			

Item 85.	Page Number: 22-23	Line Start: 977	Line Stop: 980
Current Wording: For high-pressure cylinders filled on a multiple outlet manifold, the Agency recommends that one or more cylinders from each manifold filling sequence be assayed for identity, strength, and odor.			
Proposed Change: For high-pressure cylinders filled on a multiple outlet manifold, at least one cylinder from each manifold filling sequence should be tested for identity, strength (assay) and odor. Multiple manifolds connected together during the filling sequence (i.e. are evacuated and pressurized together) would be considered one manifold filling sequence.			
Rationale: Clarifies standard industry practice of testing at least one cylinder per manifold sequence (instead of "one or more") and also provides guidance consistent with industry practice when multiple manifolds are connected together during the filling sequence.			

Item 86.	Page Number: 23	Line Start: 995	Line Stop: 996
Current Wording: Training would be documented by the employee's company.			
Proposed Change: The employee's company should retain the documentation of the training.			
Rationale: Training may be conducted either by the supplier, a third party, or the homecare company itself. A supplier or third party may provide the documentation of training. It is the homecare company's responsibility to retain documentation of the training, regardless of how it is obtained.			

Item 87.	Page Number: 23	Line Start: 1004	Line Stop: 1004
Current Wording: ... analysis, the HCC can submit to a third party a sample...			
Proposed Change: Replace the word "can" with "may" so the phrase reads: "...analysis, the HCC may submit to a third party a sample..."			
Rationale: Editorial – reflects that this is one optional method as opposed to physical capability.			

Item 88.	Page Number: 24	Line Start: 1032	Line Stop: 1035
Current Wording: We recommend that appropriate methods be developed to control situations where external contamination may occur, such as failing to cap or cover the ends of a filling hose to prevent dirt, debris, or insect infestation.			
Proposed Change: DELETE			
Rationale: Already included (with proposed revision) under Equipment section – see Item 23.			

Item 89.	Page Number: 24	Line Start: 1044	Line Stop: 1044
Current Wording: If any other medical gas is filled on site or if the incoming liquid oxygen is not tested by one of the			
Proposed Change: DELETE the word "medical" so sentence reads: If any other gas is filled on site, or if the incoming liquid oxygen is not tested by one of the…			
Rationale: There should be no differentiation if the "other gas" filled on site is medical or industrial.			

Item 90.	Page Number: 24	Line Start: 1048	Line Stop: 1050
Current Wording: If cryogenic home containers are filled by another individual or another company prior to release to the patient, we recommend that the manufacturer distributing the containers inspect each container to ensure that a correct label including a lot number has been applied.			
Proposed Change: Change the word "manufacturer" to "firm" so the sentence reads, "If cryogenic home containers are filled by another individual or another company prior to release to the patient, we recommend that the firm distributing the containers inspect each container to ensure that a correct label and lot number has been applied. ALSO ADD a new sentence at the end of this sentence: "The company filling the container is responsible for assuring the container is acceptable for filling and that it is properly labeled."			
Rationale: We agree that distributors should assure containers or cylinders are properly labeled. The proposed change clearly identifies that the manufacturer (the one filling the vessel) has the responsibility for the activities stated (assuring proper labeling and acceptability of the container prior to fill). Also, the firm distributing a vessel filled by a third party may or may not be a manufacturer of medical gases. In this case they are acting only as a distributor.			

Item 91.	Page Number: 26	Line Start: 1125	Line Stop: 1126
Current Wording: We recommend that any alternative testing method (e.g., spectrophotometer, handheld analyzers) used to analyze a medical gas be compared against the official testing methodology.			
Proposed Change: ADD "paramagnetic analyzer" and SUBSTITUTE "electrochemical cell" for "handheld" within the parenthetical: "Any alternative testing method (e.g., paramagnetic analyzer, spectrophotometer, electrochemical cell analyzer) used to analyze a medical gas should be compared against the official testing methodology."			
Rationale: To reflect the most commonly used alternate method used by the industry.			

Item 92.	Page Number: 26	Line Start: after 1132	Line Stop: before 1134
Current Wording: N/A			
Proposed Change: Analytical equipment manufacturers may perform validation studies showing their instruments are equal or superior to the official method. If a medical gas firm relies on the equipment manufacturer's study: • a copy of the actual study (including protocol and data) should be maintained by the medical gas manufacturer (may be maintained at a corporate office for branch locations), • a copy of the manufacturer's instruction manual should be on file, and • the analytical equipment should be calibrated and operated in accordance with the manufacturer's instructions and in accordance with the study protocol (i.e. temperature ranges, altitude compensation if required, etc.).			
Rationale: We propose to add the above language to reflect current industry practice. Homecare companies typically rely upon manufacturers' instructions and validation study data. We received clarification from the agency during the 8/21/2003 AAHomecare meeting, that a copy of the actual validation data by the equipment manufacturer would suffice, as long as the medical gas manufacturer (or their corporate office) maintained a copy of the data itself, and not simply a letter from the equipment manufacturer (see also item 97 and 104)			

Item 93.	Page Number: 26 - 27	Line Start: 1134	Line Stop: 1156
Current Wording: Stability Testing			
Proposed Change: DELETE			
Rationale: See comments for item 71			

Item 94.	Page Number: 27	Line Start: 1169	Line Stop: 1171
Current Wording: Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of medical gas must be retained for at least 1 year after the expiration date of the batch (§ 211.180(a)).			
Proposed Change: **A.)** Quote regulation as published in the CFR, AND **B.)** ADD a recommendation that: "Records and reports related to medical gases that are not expiration dated, should be retained for 3 years after distribution of the batch." OR if the agency is not in agreement with our proposal stated in Concern 2 of our cover letter, paraphrase the regulation in keeping with current medical gas practice: **C.)** ADD the words "or retained for 3 years after distribution of the batch, if the medical gases are not expiration dated." at the end of the paraphrased sentence.			
Rationale: The recommendation is in keeping with our overall paraphrasing concern stated in Concern 2 of our cover letter. Assuming the agency agrees with the industry that medical gases do not require expiration dating/stability studies, guidance should be provided as to how long records must be retained. Current industry practice, previously agreed to by the agency, indicates that a three-year record retention requirement is reasonable.			

Item 95.	Page Number: 27	Line Start: 1183	Line Stop: 1184
Current Wording: Electronic records must comply with the requirements of 21 CFR part 11			
Proposed Change: Electronic records, other than faxed records, must comply with the requirements of 21 CFR Part 11.			
Rationale: Provides clarity, as faxed records could be considered electronic records, yet they are not under Part 11 per current guidance.			

Item 96.	Page Number: 27	Line Start: 1197	Line Stop: 1197
Current Wording: Stability studies (§ 211.194(e))			
Proposed Change: DELETE			
Rationale: See item 71			

Item 97.	Page Number: 28	Line Start: after 1201	Line Stop: before 1203
Current Wording: N/A			
Proposed Change: Records maintained at other company locations, (e.g., test method validation studies) in compliance with § 211.180(c) are "readily available," as long as they are capable of being provided for authorized inspection within 1 business day of the request, typically via overnight courier.			
Rationale: Describes current practice that is acceptable to both FDA and industry.			

Item 98.	Page Number: 28	Line Start: 1207	Line Stop: 1213

Current Wording: A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments) and use must be included in individual equipment logs that show the date, time, product and lot number of each batch processed (§ 211.182). In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use must be part of the batch record (§ 211.182). The persons performing and double-checking the cleaning and maintenance must date and sign or initial the log indicating that the work was performed (§ 211.182).

Proposed Change:

A.) Quote regulation as published in the CFR,

OR if the agency is not in agreement with our proposal stated in Concern 2 of our cover letter, paraphrase the regulation in keeping with current medical gas practice:

B.) 1.) Reinsert the following sentence from § 211.182 that was left out in the proposed guidance: "If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence."

2.) Delete the word "must" and replace it with the word "may" in line 1210, and add the phrase "may be maintained on a separate maintenance log, or other appropriate document," so the sentence will read, "...may be part of the batch record, be maintained on a separate maintenance log, or be maintained on another appropriate document."

3.) In line 1211, delete the words "double-checking" and replace them with the words "reviewing the documentation for," so the sentence reads, "The persons performing and reviewing the documentation for the cleaning and..."

Rationale:

- The recommendation is in keeping with our overall paraphrasing concern stated in Concern 2 of our cover letter.
- If the agency does not agree to quote the regulation as published, the following rationale relates to B 1 through 3 of the proposed changes above:
  1. Allow for conditions when individual equipment logs are not required.
  2. Allow for separate cleaning/maintenance files as opposed to requiring this information to be "a part of the batch record." Separate cleaning/maintenance files are often maintained for dedicated medical gas equipment (e.g. vessel maintenance, manifold repair, etc.) Work may or may not be performed by in-house personnel, but rather by qualified outside vendors, who in turn may provide their own documentation for the maintenance work performed and therefore could not be part of the batch record. Records would be maintained in a separate file, even though the equipment is dedicated.
  3. Even though cleaning and maintenance records are reviewed by the QCU, the QCU typically does not physically "double-check" the work to verify performance.

Item 99.	Page Number: 28	Line Start: 1223	Line Stop: 1230

Current Wording : These records must include the following (§ 211.184):

- The identity and quantity of each shipment of each lot of medical labeling
- The results of any test or examination performed (including those performed as required by § 211.82(a), § 211.84(d), or § 211.122(a)) and the conclusions derived therefrom
- Documentation of the examination and review of labels and labeling for conformity with established specifications in accordance with § 211.122(c) and § 211.130(c)
- The disposition of rejected medical gas containers, closures, and labeling

Proposed Change:

A.) Quote regulation as published in the CFR,

OR if the agency is not in agreement with our proposal stated in Concern 2 of our cover letter, paraphrase the regulation in keeping with current medical gas practice:

B.) **1.)** Modify line 1233 to read, "These records, which may be part of the batch record, must include the following (§ 211.184):

2.) Insert the words "where appropriate," after the word "and" and prior to the word "the" in line 1227, so the sentence reads, "The results of any test or examination performed (including those performed as required by § 211.82(a), § 211.84(d), or § 211.122(a)), and where appropriate, the conclusions derived therefrom

3.) Insert the words, "initial, and/or where appropriate, the final" after the word "The" and prior to the word "disposition" in line 1230, so the sentence reads, "The initial, and/or where appropriate, the final disposition of rejected medical gas containers, closures, and labeling."

OR

C.) DELETE these lines in their entirety

(See next page for Rationale)

Rationale:

A) The recommendation is in keeping with our overall paraphrasing concern stated in Concern 2 of our cover letter.

B) Results of pre-fill inspection of containers, other than the fact that the operations were performed, are typically not included on the batch records. For example, if a cylinder were culled during the pre-fill inspection, the "rejected" cylinder would not become part of the batch nor the batch record. Similarly, the final disposition of rejected containers, either during the pre-fill inspection or during in-process inspections, would not be part of the record. For example, if a leaking cylinder were found during in-process inspections, the record would document that the cylinder had leaked and was removed from the lot, but the repair activity would not be part of the record.

C) No guidance is offered; current wording just paraphrases the regulation. Aside from a reference to § 211.84(d), very little is provided related to component (incoming supply) records. A potential improper inference could be made that such records need not be maintained. (Section H on page 32 and 33 concentrates only on COAs for liquid supplies.). In addition, there also appears to be a major focus on labeling records (all bullet points discuss labeling records) and only a minor focus on component, container, and closure records.

Item 100.	**Page Number: 29**	**Line Start: 1264**	**Line Stop: 1265**
Current Wording: An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed (§ 211.188(a)).			
Proposed Change: DELETE entirely OR eliminate the words "checked for accuracy, dated, and signed."			
Rationale: Unlike traditional pharmaceutical batch records that may vary (by quantity produced) from batch to batch, blank medical gas batch records (forms) are not "checked for accuracy, dated, and signed." Normally, medical gas companies maintain policies & procedures approved by the QCU, that contain the authorized "master" forms. These forms are typically either photocopied well in advance of the manufacture of a batch, or they are printed and padded.			

Item 101.	**Page Number: 29**	**Line Start: 1271**	**Line Stop: 1271**
Current Wording: --Inspection of the packaging and labeling area before and after use (§ 211.188(b)(6))			
Proposed Change: DELETE			
Rationale: Where medical gas manifolds are dedicated to a single product (e.g., oxygen) with label reconciliation (issued, applied, used) and 100% label verification, the inspection and documentation specified in § 211.188(b)(6) seems to be excessive.			

Item 102.	**Page Number: 30**	**Line Start: 1280**	**Line Stop: 1280**
Current Wording: Signature of the individual who checked the entries for accuracy and completeness			
Proposed Change: Identity of the individual who checked the entries for accuracy and completeness			
Rationale: 21 CFR § 211.188(b)(11) does not require full signature.			

Item 103.	Page Number: 31	Line Start: 1368	Line Stop: 1369
Current Wording: Complete records must be maintained of all stability testing performed in accordance with § 211.166 (§ 211.194(e)).			
Proposed Change: DELETE			
Rationale: See item 71.			

Item 104.	Page Number: 32	Line Start: 1387	Line Stop: 1387
Current Wording: N/A			
Proposed Change: Insert the following after the word "study" at the end of the sentence and before the beginning of the next sentence: "Analytical equipment manufacturers may perform validation studies showing their instruments are equal or superior to the official method. If a medical gas firm relies on the equipment manufacturer-performed study: • a copy of the actual study (including protocol and data) should be maintained by the medical gas manufacturer (may be maintained at a corporate office for branch locations), • a copy of the manufacturer's instruction manual should be on file, and the analytical equipment must be calibrated and operated in accordance with the manufacturer's instructions, and in accordance with the study protocol (i.e. temperature ranges, altitude compensation if required, etc.).			
Rationale: We propose to add the above language to reflect current industry practice. Homecare companies typically rely upon manufacturers' instructions and manufacturer-performed validation study data. We received clarification from the agency during the 8/21/2003 AAHomecare meeting, that a copy of the actual validation data by the equipment manufacturer would suffice, as long as the medical gas manufacturer (or their corporate office) maintained a copy of the data itself, and not simply a letter from the equipment manufacturer (also see item 92).			

Item 105.	Page Number: 33	Line Start: 1422	Line Stop: 1423
Current Wording: • Test method used to perform the analysis. If an analyzer is used, the specific model number is indicated.			
Proposed Change: DELETE the words, "If an analyzer is used, the specific model number is indicated." so the resultant bullet point just reads, "Test method used to perform the analysis."			
Rationale: We believe indicating the "specific model number" of the analyzer used is not required by regulation to be recorded. If the agency is concerned with the model of analyzer being used by the supplier, the supplier would maintain this information within their record.			

Item 106.	Page Number: 33	Line Start: 1455	Line Stop: 1455
Current Wording: ... in accordance with § 301.305 (§ 211.198(a)).			
Proposed Change: Replace "301" with "310" so the revised phrase reads "... in accordance with § 310.305 (§ 211.198(a))."			
Rationale: Editorial. Citation to Part 310 not 301			

Item 107.	Page Number: 33 – 34	Line Start: 1463	Line Stop: 1474
Current Wording: Paraphrase of §§ 211.198(b)(1), 211.198(b)(2)			
Proposed Change: Quote Regulation as published in the CFR. • Line 1466 – Delete "address" because it is not in the CFR • Line 1467 – Delete "(and, where appropriate, title) and telephone number" because it is not in the CFR • Line 1470 – Delete all (not in the CFR) • Line 1471 – Delete all (not in the CFR) • Line 1472 – Delete and replace with the sentence beginning in 1476 and ending in 1477, after changing "must" to "shall" • Line 1473 & 1474 – Delete all ("date the response was sent" is not in the CFR and neither is the phrase "final outcome regarding the issues raised by the complaint") and replace with the sentence beginning in 1477 and ending in 1479, after changing "must" to "shall"			
Rationale: • This section exemplifies our overall paraphrasing concern, Concern 2, in which we suggest using headings to segregate cited regulations from guidance, such as was done in the 1989 guidance . • Proposed guidance requires more information than required by regulation. • The proposed guidance and the regulations are intermingled in a way that lends greater authority to the guidance than given by the CFR . • Through much of the document, the "recommendations" follow the paraphrased regulations; but here the structure is inconsistent because the guidance wording in the bulleted list is intermingled with language from the CFR, then is followed by further paraphrases of the CFR.			

Item 108.	Page Number: 36 – 37	Line Start: 1587	Line Stop: 1634
Current Wording: Section X.V. In its entirety regarding Medical Gas Mix-ups.			
Proposed Change: DELETE THESE SENTENCES			
Rationale: These statements provide no guidance. See rationale and discussion presented in "Concern 3" in the body of the cover letter.			

Item 109.	Page Number: 39	Line Start: 1689	Line Stop: 1691
Current Wording: The Agency recommends that companies only use adapters that reduce or expand the connection size for a specific medical gas while still maintaining the proper connection system.			
Proposed Change: ADD the words, "or provide a means to connect to proprietary fittings," after the word "gas" and before the word "while" so the sentence reads: "The Agency recommends that companies only use adapters that reduce or expand the connection size for a specific medical gas, or provide a means to connect to proprietary fittings, while still maintaining the proper connection system."			
Rationale: Reflects current and acceptable industry practice.			

Item 110.	Page Number: 40 – 42	Line Start: 1708	Line Stop: 1800
Current Wording: ATTACHMENT: MEDICAL GAS MIX-UPS (entire contents of attachment)			
Proposed Change: DELETE THIS ATTACHMENT			
Rationale: The statements within the attachment provide no guidance. See rationale and discussion presented in "Concern 3" in the body of the cover letter.			

Item 111.	Page Number: 43	Line Start: 1806	Line Stop: 1808
Current Wording: Cascading: This operation pertains to gas-to-gas filling of high-pressure cylinders only, and consists of a supply cylinder unit (usually called a *bank*) containing a group of *H* or *K*-sized cylinders, a receiving cylinder unit, a filling manifold, and a vacuum evacuation pump.			
Proposed Change: ADD the words "for example," after the word "containing" and before the word "group." The sentence would then read, "**Cascading:** This operation pertains to gas-to-gas filling of high-pressure cylinders only, and consists of a supply cylinder unit (usually called a *bank*) containing, for example, a group of *H, K, or T*-sized cylinders, a receiving cylinder unit, a filling manifold, and a vacuum evacuation pump."			
Rationale: Other size cylinders with higher pressure/capacity are often used.			

Item 112.	Page Number: 43	Line Start: 1817	Line Stop: 1818
Current Wording: Certificate of analysis (COA): A single document provided with each shipment of incoming liquid medical gas that undergoes further processing (filling, transfilling)….			
Proposed Change: DELETE the word "single" and ADD "one or more documents" so sentence reads: **Certificate of analysis (COA):** One or more documents containing the necessary information provided with each shipment of incoming liquid medical gas that undergoes further processing (transfilling)….			
Rationale: Regulation does not require that information be provided on a single document. Previously, it was acceptable, based on Fresh Air 2000, to permit a variety of documents, such as a letter of conformance, a bill of lading, an invoice, etc. as long as the document(s) contained all of the required information. A manufacturer could maintain on file the one or more documents that meet the definition of a COA.			

Item 113.	Page Number: 43	Line Start: 1826	Line Stop: 1830
Current Wording: Cryogenic containers: Containers used to hold a low-temperature, low-pressure liquid product that are similar in design to an insulated thermos bottle with a vacuum between the inner and outer container. They may be portable or permanently mounted in a vehicle, and are commonly known as VGLs (vertical gas liquids), GPs (gas packs), or PLCs (portable liquid containers), or HL119s, MDX 60s, 80s, and 190s. This does not include tankers, trailers, or rail cars			
Proposed Change: Cryogenic containers: Containers used to hold a low-temperature, low-pressure liquid product that are similar in design to an insulated thermos bottle with a vacuum between the inner and outer container. They may be further subdivided into: • Portable cryogenic home vessels – vessels typically filled by the patient or healthcare provider for patient mobility • Cryogenic home vessels/containers – see definition below • Large Cryogenic Vessels – commonly known as VGLs (vertical gas liquids), GPs (gas packs), or PLCs (portable liquid containers), that are portable and provided to a customer • Vehicle Mounted Vessels – GPs, VGLs or PLCs semi-permanently, or permanently mounted in a vehicle, and HL119s, MDX 60s, 80s, and 190s that are permanently mounted in a vehicle. This does not include • Bulk Transports – cryogenic tankers, trailers, or rail cars			
Rationale: There is conflict throughout the document regarding the common use of the term cryogenic container. We recommend that the agency consult with the CGA with regard to definition of Bulk Transports as these are cryogenic containers and are coupled with large cryogenic containers elsewhere in the document.			

Item 114.	Page Number: 43	Line Start: 1835	Line Stop: 1837
Current Wording: Distributor: An individual or a manufacturer that receives liquid and/or compressed gas in labeled high-pressure cylinders or cryogenic containers and does not manipulate or apply a label to the product.			
Proposed Change: DELETE the words "a manufacturer" and substitute the word "firm" so the sentence reads: **"Distributor:** An individual or firm that receives liquid and/or compressed gas in labeled high-pressure cylinders or cryogenic containers and does not manipulate (i.e. move product from one container to another) or apply a label to the product."			
Rationale: Consistent with the definition of distributor found in regulation.			

Item 115.	Page Number: 43	Line Start: 1844	Line Stop: 1845
Current Wording: Handheld oxygen analyzers: Oxygen analyzers that operate on the fuel cell, electrochemical cell, galvanic cell, or polarographic principle.			
Proposed Change: Handheld oxygen analyzers: Oxygen analyzers that operate on non-paramagnetic principles and are typically used for ID testing Oxygen USP and/or for testing the output of oxygen concentrators. These analyzers are not acceptable for conducting Oxygen USP assay testing.			
Rationale: Current wording does not account for the addition of new technologies. For example, it is our understanding that there are ultrasonic analyzers (another non-paramagnetic method) that may be used for identity testing.			

Item 116.	Page Number: 44	Line Start: 1849	Line Stop: 1852
Current Wording: Home care company/home respiratory care company (HCC): Manufacturers that sell durable medical equipment and usually supply liquid oxygen to patients at their home. They may also fill high-pressure cylinders by means of cascading as a back up for their oxygen concentrators.			
Proposed Change: Home care company/home respiratory care company (HCC): Firms that provide durable medical equipment and may manufacture or distribute liquid and/or high-pressure medical oxygen to patients at their residence or to other customers. Some HCCs may handle other medical gases.			
Rationale: Accurately defines scope of business for purposes of this document.			

Item 117.	Page Number: 44 – 45	Line Start: 1890	Line Stop: 1896
Current Wording: Wrap-around label: A 360-degree label that encircles and is applied to the top of large cryogenic containers			
Proposed Change: Wrap-around label: A 360-degree label that encircles and is applied near the top of large portable cryogenic containers that are not mounted semi-permanently or permanently in vehicles.			
Rationale: A 360-degree wrap-around label is typically applied *near the top* of large cryogenic containers, rather than *to the top,* which would be difficult to accomplish because valves and fill connections are located on the top. Differentiates the application of 360-degree wrap-around labels to large cryogenic containers that are not mounted in vehicles from vessels that are affixed to their vehicles, as explained in Items 17, 46, 68 and 77.			

ATTACHMENT 2

AAHomecare

Comments and Proposed Changes to

Guidance for Industry

Current Good Manufacturing Practice for Medical Gases

DRAFT GUIDANCE

Notice of Availability for Comment Published in the Federal Register

Guidance for Industry

Current Good Manufacturing Practice for Medical Gases

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document must be submitted within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Docket Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm.1061, Rockville, MD 20852. All comments must be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Duane Sylvia (301) 594-0095, sylviad@cder.fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 2003

Compliance

Contains Nonbinding Recommendations

Draft — Not for Implementation

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Draft — Not for Implementation

Guidance for Industry[1]

Current Good Manufacturing Practice for Medical Gases

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide recommendations on how to comply with the current good manufacturing practice (CGMP) regulations as they apply to manufacturing, filling, transfilling, cascading, transferring, and distributing compressed and cryogenic medical gases. The recommendations should help manufacturers, fillers, and distributors[2] comply with CGMP requirements to ensure the identity, strength, quality, and purity of medical gases. This guidance also provides recommendations to medical gas manufacturers on how to comply with certain aspects of the PDMA final rule (i.e., 21 CFR part 205). This guidance is not intended to be an all-inclusive listing of all relevant CGMP; instead, it covers certain sections of the CGMP regulations followed by a discussion of recommendations that the Agency considers acceptable means of meeting the requirements.

Three previous documents were published on current good manufacturing practice for medical gases. FDA's first guideline on compressed medical gases was issued in June of 1981 and revised in 1983. In February of 1989, FDA issued another revision of the guideline to address the evolving home care area, including the delivery of oxygen to patients at home. This guidance builds on the previous guidelines. It provides details on the filling of high-pressure cylinders and cryogenic containers and includes new information on CGMP policy for large cryogenic containers, as well as discussion of CGMP relating to storage tank installation, carbon dioxide and helium manufacturing, and emergency medical services. Once finalized, this version of the guidance will supersede those earlier guidelines.

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[1] This guidance has been prepared by the Division of Manufacturing and Product Quality in the Office of Compliance of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this document, the term *manufacturer* includes fillers, transfillers, cascaders, distributers, and transferers of medical gases.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. STATUTORY AND REGULATORY REQUIREMENTS

Medical gases (e.g., oxygen, carbon dioxide, helium, nitrogen, nitrous oxide, medical air, and combinations of these) are drugs within the meaning of section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 321(g)(1)) and pursuant to section 503(b)(1)(A) of the Act (21 U.S.C. 353(b)(1)(A) are required to be dispensed by prescription.

Medical gases are considered adulterated under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)) if the methods used in, or the facilities or controls used during their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with CGMP. The CGMP regulations are intended to ensure that a drug meets the safety requirements of the Act and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. Medical gases are finished drug products and are subject to the CGMP regulations at 21 CFR parts 210 and 211. Manufacturers of medical gases must follow the requirements in the CGMP regulations to comply with section 501(a)(2)(B). For example, each time a medical gas is filled into another container, finished product testing must be performed in accordance with § 211.165(a).

Medical gases that are not produced and handled in accordance with CGMP regulations can cause serious injury or death to the patients who use them. A number of injuries and deaths have resulted from mix-ups of medical gases associated with CGMP violations including:

- Mislabeling (in some cases the container had two or more labels)
- Inadequate training, including training of medical gas filling personnel as well as delivery personnel
- Inadequate finished product testing
- Inadequate quality control unit
- Failure to qualify equipment prior to use (e.g., stainless steel hoses, large cryogenic containers)
- Inadequate written procedures for manufacturing, processing, testing

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.

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.

III. ORGANIZATION AND PERSONNEL

A. Responsibilities of the Quality Control Unit

Medical gases are subject to the requirements in 21 CFR § 211.22 - Responsibilities of quality control unit (QCU).

Manufacturers must have a QCU with the responsibility and authority to approve or reject all product containers, closures, in-process materials, labeling, and drug products, the authority to review production records to ensure that no errors have occurred, or if errors have occurred, that they have been fully investigated. The QCU is responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company (§ 211.22(a)).

The QCU must have the responsibility for approving or rejecting all procedures or specifications affecting the identity, strength, quality, and purity of the drug product (§ 211.22(c)).

The responsibilities and procedures applicable to the QCU must be in writing and must be followed (§ 211.22(d)).

We recommend that the QCU perform more than a testing function, be independent of the production process, and have both quality assurance and quality control responsibilities. Ideally, the QCU would participate in and have final responsibility for all functions that could affect product quality. The corporate QCU would be responsible for reviewing and approving all written procedures, even those written by each individual location's organizational units.

We recommend that all individuals who are part of the QCU be identified in the manufacturer's operating procedures. In a well-structured and well-defined corporate structure, the QCU would be included as a separate unit. A small medical gas manufacturer can designate a single individual as the QCU.

We recommend that QCU individuals receive adequate CGMP training on a continuing basis, including quality assurance training.

B. Personnel Qualifications

Medical gases are subject to the requirements in § 211.25 - Personnel qualifications.

Each person engaged in the manufacturing, filling, processing, packing, or holding of a medical gas must have the education, training, and experience, or a combination thereof, to enable that person to perform the assigned functions. Training must be in the particular operations that the employee performs and in current good manufacturing practice regulations as they relate to the employee's functions. Training in the CGMP regulations must be conducted by qualified individuals on a continuing basis and with sufficient frequency to ensure that employees remain familiar with CGMP requirements applicable to them (§ 211.25(a)).

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. We recommend that the specific type of training received or covered, the time, and the attendance at each session be documented, and records of the training be maintained.

Regulations at § 211.25(c) require an adequate number of qualified personnel be available to perform and supervise the manufacturing, processing, or holding of medical gases.

Useful training information and training materials are available as shown below.

- The following FDA Internet sites:

  http://www.fda.gov/cder/dmpq/gases.htm

  www.fda.gov/cder/dmpq/cgmpregs.htm

  www.fda.gov/oc/industry
- Title 21 of the Code of Federal Regulations, Parts 210 and 211, available at: www.access.gpo.gov/nara
- Qualified suppliers who offer CGMP training
- A qualified medical gas consultant or consulting firm
- Industry or professional associations

The Agency recommends that each manufacturer establish and follow written training procedures for all truck drivers specific to their function, including CGMP training. Truck drivers responsible for delivery of medical gases should be trained to examine the drug label and distinguish between medical gases and industrial gases, prior to unloading a container.

We recommend that all manufacturers who allow their drivers to connect large cryogenic containers to customer gas supply systems train their drivers in the specifics of those supply systems. We recommend cargo tanker drivers who fill medical gases into storage tanks also be trained.

We recommend that an individual responsible for performing an odor test not have an ailment (e.g., a cold or allergies) that would adversely affect his or her sense of smell. Likewise,

employees responsible for performing the inspection for the standardized colors should be able to distinguish colors.

C. Consultants

Medical gases are subject to the requirements in § 211.34 - Consultants.

Consultants advising on the manufacturing, processing, packing, or holding of medical gases must have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. A company must maintain records stating the name, address, and qualifications of any consultants and the type of services they provide (§ 211.34).

We recommend that consultants hired to provide assistance in achieving CGMP compliance have sufficient medical gas education, training, and/or experience.

IV. BUILDINGS AND FACILITIES

A. Design and Construction

Medical gases are subject to the requirements in § 211.42 - Design and construction features.

Any building or buildings used in the manufacture, processing, packing, or holding of a medical gas must be of a suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations (§ 211.42(a)).

Buildings must have adequate space for the orderly placement of equipment and materials to prevent mix-ups and to prevent contamination (§ 211.42(b)).

Operations must be performed within specifically defined areas of adequate size. There must be separate or defined areas or other such control systems for the manufacturer's operations as are necessary to prevent contamination or mix-ups (§ 211.42(c)).

The Agency recommends that buildings be maintained in good physical condition, kept clean, and have a sufficient number of areas for organized sequential operations, such as a well-defined filling area and a well-defined quarantine area. The Agency also recommends the creation of quarantine areas to separate incoming medical gases, high-pressure cylinders, cryogenic containers, manufacturing equipment, rejected containers and closures, and the finished product. No matter how large your operation, we recommend you avoid storing industrial gases and medical gases in close proximity to each other.

We also recommend that delivery vehicles have well-defined, separate areas for medical gases and industrial gases to prevent mix-ups from occurring. For example, medical and industrial gases could be separated physically in the delivery truck, or a manufacturer could use a unique identifier to distinguish medical gases from industrial gases. The Agency recommends the use of 360-degree wrap-around label to identify medical gases in large cryogenic containers. If a

manufacturer applies a 360-degree wrap-around label to its large cryogenic containers, this could serve as the control system for preventing mix-ups, as long as a manufacturer has established adequate driver training, adequate written procedures, and proper stock inventory systems.

B. Security

Medical gas manufacturers are wholesale distributors who are subject to the requirements of § 205.50 - Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.

All facilities used for medical gas distribution must be secure from unauthorized entry (§ 205.50(b)(1)).

Entry into areas where medical gases are held must be limited to authorized personnel (§ 205.50(b)(1)(iii)). We recommend areas where nitrous oxide is held be especially secure.

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

A manufacturer could use an alarm system to secure the building and keep loading docks secure, rather than open and easily accessible.

V. EQUIPMENT

A. Equipment Cleaning and Maintenance

Medical gases are subject to the requirements in § 211.67 - Equipment cleaning and maintenance.

Equipment must be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the medical gas beyond the official or other established requirements (§ 211.67(a)).

Written procedures must be established and followed (§ 211.67(b), (4), (5), & (6)), including maintenance and cleaning schedules, removal or obliteration of previous batch identification, protection of clean equipment from contamination prior to use, and inspection of equipment for cleanliness immediately prior to use.

We recommend that equipment used in the manufacture of medical gas (e.g., manifolds, pigtails, valve assemblies, hoses, and gauges) be cleaned at initial use and if exposed to a contaminant. We recommend that hoses used to fill cryogenic containers have protective end caps to prevent contamination from insects, dirt, debris, and other materials. 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).

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

B. Equipment Calibration

Medical gases are subject to the requirements in § 211.68 - Automatic, mechanical, and electronic equipment.

Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems can be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is used, it must be routinely calibrated, inspected, or checked according to a written program designed to ensure proper performance (§ 211.68(a)). Written records of those calibration checks and inspections must be maintained (§ 211.68(a)).

The Agency recommends that medical gas manufacturers use either the equipment manufacturer recommended calibration schedule or a schedule based on their own historical data. A company can reference the equipment manufacturer instruction manual in its written procedures if the manual is available for use at the manufacturing site.

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 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. Low pressure gauges and flow meters used in filling cryogenic home containers would not require calibration.

We recomment that thermometers be calibrated in accordance with manufacturer recommendations, and that the calibrations be documented in a separate log.

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.

C. Computerized Systems

Medical gases are subject to the requirements in § 211.68 - Automatic, mechanical, and electronic equipment.

Appropriate controls must be exercised over computer or related systems to ensure that changes in master production and control records or other records are instituted only by authorized personnel (§ 211.68(b)). Input to and output from the computer or related system of records or data must be checked for accuracy (§ 211.68(b)). The degree and frequency of input/output verification must be based on the complexity and reliability of the computer or related system (§ 211.68(b)).

The Agency recommends that computerized systems, including hardware and software, used in the manufacturing, processing, and holding of medical gases be validated. The depth and scope of the validation depends on the diversity, complexity, and significance of the computerized application. Commercially available software that has been qualified does not need the same level of testing as software that has been specifically developed for a company.

The Agency recommends that computerized systems have sufficient controls to prevent unauthorized access or changes to data and to preclude omissions in data. The Agency also recommends that records be kept of any changes made to data, including who made the change, when the change was made, and the previous entry.

We recommend that any change to computerized systems be made according to specified procedures and would be formally authorized, documented, and tested. We recommend that records of all changes, including modifications and enhancements made to hardware, software, and any other critical component of the system be kept as long as the manufacturer is still using that system.

VI. COMPONENTS, CONTAINERS, AND CLOSURES

A. General Recommendations

Medical gases are subject to the requirements in §§ 211.80 - 211.94: Control of components and drug product containers and closures.

Manufacturers must have written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and medical gas containers and closures (§ 211.80(a)). Containers and closures must at all times be handled and stored in a manner to prevent contamination (§ 211.80(b)).

Each medical gas container and closure, upon receipt and before acceptance, must be examined visually for appropriate labeling as to contents, container damage, and contamination (§ 211.82(a)). Containers and closures must be stored under quarantine until they have been tested or examined, as appropriate (§ 211.82(b)).

Medical gas containers and closures must be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit (QCU) (§ 211.84(a)). The containers must be opened, sampled, and resealed in a manner designed to prevent contamination (§ 211.84(c)(2)). Each medical gas container and closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant must be examined against established specifications for such contamination (§ 211.84(d)(5)).

Rejected containers and closures must be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable (§ 211.89).

Medical gas containers and closures must not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements (§ 211.94(a)). Container closure systems must provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product (§ 211.94(b)). Containers and closures must be clean (§ 211.94(c)). Medical gas containers and closures are used repeatedly and therefore play a critical role in ensuring that the drug product provided to the patient has the appropriate identity, strength, quality, and purity. Containers and closures used for medical gases are integral parts of the drug delivery system. We recommend they undergo strict inspections and examinations prior to the introduction of the drug product. In addition, we advise medical gas manfacturers to determine valve assembly compatibility prior to installation on a high-pressure cylinder and during the lifetime of the valve.

To avoid the possibility of contamination, we recommend that all high-pressure cylinders and cryogenic containers used for medical gases be dedicated to medical use only.

1. Prefill Inspections for Cylinders

We recommend that the following prefill inspections be performed on each medical gas cylinder prior to the start of the filling operation. Cylinders failing any of these procedures would be quarantined to prevent their use in any subsequent filling operation. We recommend that medical gas manufacturers document all prefill inspections on a batch production record.

Hydrostatic testing date inspection: Hydrostatic tests offer assurance of the integrity of a cylinder. Ultrasonic inspection of steel high-pressure cylinders can be performed instead of internal visual and hydrostatic testing. We recommend that manufacturers consult U.S. Department of Transportation (DOT) requirements pertaining to hydrostatic testing of certain cylinders as appropriate (see, e.g., 49 CFR 180.209).

External examination: We recommend that each cylinder be examined externally for dents, arc burns, dings, oil, grease, and other signs of damage, including fire or thermal damage, that can cause a cylinder to be unacceptable or unsafe for use. 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.

Venting or blowing down: If any gas is present in a cylinder, venting or blowing down a cylinder can be performed until atmospheric pressure occurs. We recommend that cylinders containing liquid be inverted and drained.

Odor test: The odor test is a very important prefill test for detecting the presence of any foreign gas or odor. Do not perform this test on carbon dioxide, nitrous oxide, toxic, or corrosive gases. If a cylinder is empty (contains no pressure), a medical gas can be introduced into the cylinder at a predetermined pressure, and an odor test can be performed on the resulting gas. Use only medical gases, as an industrial gas could contain industrial contaminants.

Do not confuse this odor test with the finished product odor test conducted under § 211.165(a) and required by the USP.

Hammer or dead ring test: One way to determine if a cylinder has internal corrosion is by performing a hammer or dead ring test. This test consists of lightly tapping the cylinder sidewall with a hammer-like instrument. A cylinder in good condition will make a clear bell-like ring, while a dull ring indicates possible internal corrosion. All cylinders that produce a dull ring would be quarantined until their suitability has been determined. This procedure cannot be performed on aluminum or fiber wrapped cylinders because the test would not indicate internal corrosion. A hammer test works best on empty unpressurized cylinders with a 10-year test date (stamped into the cylinder shoulder area). It is not necessary to test cylinders with a 5-year test date.

Valve assembly examination: The Agency recommends that the valve assembly be appropriate for the medical gas being dispensed and be examined for debris, oil, or grease. The inspection would examine whether any of the threads on the valve or on top of the valve stem are damaged; whether the handwheel or valve stem is bent; and whether there are indications of damage, corrosion inside the valve, or excessive heat or fire damage.

Color code examination: The following colors are used by the medical gas industry in the United States to aid in identifying a medical gas. We recommend manufacturers use them.

- Carbon Dioxide - gray;
- Helium - brown;
- Medical Air - yellow;
- Nitrogen - black;
- Nitrous Oxide - blue;
- Oxygen - green; and
- Blends of medical gases use a combination of the corresponding color for each component gas. For example, oxygen and carbon dioxide would be green and gray.

Color coding alone cannot be relied on for identification of the medical gas; use color coding in addition to examining the product label on the cylinder.

Label inspection: We recommend that the label on the cylinder be inspected and that obsolete labels or labels containing outdated lot numbers be removed. A label on an empty cylinder does not need to be removed if it is in good condition and is identical to the label that will be used for the filled cylinder. We suggest that you ensure that cylinders bear only one manufacturer or filler's label and that you not apply new labels on top of an old label.

Residual gas removal: We recommend that residual gases be removed from medical gas cylinders by means of a vacuum pump prior to filling a medical gas.

All the above inspections can be documented on a batch production record.

2. Prefill Inspections for Cryogenic Home Containers

The FDA recommends that the following prefill inspections be performed on all cryogenic home containers (patient-specific containers):

- An external inspection for any signs of damage, oil, or grease that would cause the container to be unacceptable for use
- An inspection of the inlet and outlet connection for any signs of damage, oil, or grease
- An inspection of the volume or quantity of contents gauge to ensure that it is operating properly
- An inspection of the drug label to ensure correctness.

All the above inspections can be documented on a batch production record.

3. Dedication of Large Cryogenic Containers to Medical Use Only

To avoid the possibility of industrial contaminants, we recommend that large cryogenic containers used to contain medical gases be dedicated to medical service only.

4. Prefill Inspections of Large Cryogenic Containers

We recommend the following prefill inspections be performed on large cryogenic containers:

- An external examination for any signs of damage, oil, or grease that could cause the container to be unacceptable for use
- An inspection of the inlet and outlet connections for any signs of damage, oil, or grease and to ensure that they are the correct fittings for the corresponding medical gas. Permanently attach all connections or fittings to the container.
- An inspection of the label for correctness.
- An examination for a 360-degree wrap-around label applied on the sidewall of the cylinder, as close to the top portion of the container as possible, but below the top weld seam. These labels are designed to repeat the drug product name (e.g., Medical Oxygen) in the appropriate color around the entire container. See the "Color Code

Examination" discussed above under section *1. Prefill Inspections for Cylinders;* and in the Glossary under "Wrap-around" Label.

We recommend all the above inspections be documented on a batch production record.

5. Prefill Inspections for Permanently Mounted Cryogenic Containers

We recommend that the following prefill inspections be performed on permanently mounted cryogenic containers:

- An external examination for any signs of damage, oil, or grease
- An inspection of the inlet and outlet connections for any signs of damage, oil, or grease
- An inspection of the product label

B. Retesting of Containers

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

VII. PRODUCTION AND PROCESS CONTROLS

A. Written Procedures

Manufacturers must have written procedures for production and process controls designed to ensure that medical gases have the identity, strength, quality, and purity they purport or are represented to possess. These written procedures, including any changes, must be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the QCU (§ 211.100(a)).

Written production and process control procedures must be followed in the execution of the various production and process control functions and must be documented at the time of performance (§ 211.100(b)).

To guarantee batch uniformity and integrity of medical gases, written procedures must be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures must be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the drug product (§ 211.110(a)).

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.

Written procedures provide a basis for the uniform performance of a function and a step-by-step description of how to perform a specific task, function, or operation, regardless of its size or complexity. We recommend the procedures be readily available to all employees and be read, understood, and followed by them.

We recommend that a manufacturer or individual, especially a manufacturer filling multiple gases, have data on file demonstrating the amount of vacuum evacuation required to remove all contaminants from high-pressure cylinders. We also recommend that the manufacturer have data demonstrating that each different gas it fills would be removed by the established vacuum evacuation limit.

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.

We recommend that automated filling systems (that is, systems that fill from large cryogenic containers into high pressure cylinders) be validated to provide assurance that the filling is done to the correct pressure.

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):

- The batch must be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient (§ 211.101(a)).
- Components for medical gas manufacturing must be weighed, measured, or subdivided as appropriate (§ 211.101(b)).
- Each component must be added to the batch by one person and verified by a second person (§ 211.101(d)).

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.

1. Temperature/Pressure Readings (Boyle's Law)

A medical gas in a high-pressure cylinder increases in pressure as the temperature of the gas rises. Overfilled cylinders could reach dangerously high pressures if exposed to elevated temperatures, even if the pressure at room temperature is safe. This temperature rise can be properly compensated for during filling, so that the cylinder contents do not exceed the net content statement on the label. A temperature/pressure chart or other temperature/pressure calculation algorithms can be used to adjust the filling pressure so that the proper contents are achieved (this is usually stated as the pressure at 70°F with appropriate tolerances). We recommend that temperatures measured on the wall of a cylinder during filling operations not exceed 130°F. Before the filling is complete, the temperature and pressure reading would be recorded on the batch production record.

To ensure that high-pressure cylinders have the correct contents as indicated on the label, the manufacturer can attach a thermometer to one cylinder per manifold-filling sequence and adjust the temperature and pressure readings according to a temperature pressure chart. We recommend that, when filling cylinders one at a time (also known as the cascade method), each cylinder have a thermometer attached to it.

If a "+" symbol follows the hydrostatic testing date, the cylinder can be overfilled by 10 percent unless the valve is equipped with a fusible, metal-backed safety. It is critical not to overfill aluminum cylinders.

2. Valve Assembly Leak Testing

The Agency recommends that a valve assembly leak test be performed during the cylinder filling operation. Each valve assembly would be tested for valve packing leaks, safety plug leaks, and other valve leaks using an appropriate leak detection solution. The test would be performed while the cylinder is under pressure with the cylinder valve open. The leak detection solution would be sprayed on and around the entire valve assembly. A leak would be indicated when bubbles appear in the solution. We recommend the solution be oxygen compatible and not contain any hydrocarbons. Solutions containing soap are not recommended because they can corrode the valve stem and can leave a residue.

After the filling of high-pressure cylinders, and after all valves have been closed, we recommend a second valve assembly leak test be performed to detect any valve outlet leaks. If any leaks are detected, the cylinder would be removed from service and quarantined until repaired.

The two valve assembly leak tests provide assurance that the cylinder contents do not leak out during storage or shipment, resulting in a partially filled or empty cylinder that would not contain sufficient contents for a patient.

3. Heat of Compression

During the filling of high-pressure cylinders, we recommend a heat-of-compression check be performed by lightly touching the exterior of each and every cylinder. A warm cylinder indicates that the cylinder is filling properly; a cool or cold cylinder indicates that the cylinder may not be filling properly. Such a situation would be investigated.

C. Calculation of Yield

Actual yields and percentages of theoretical yield must be determined at the conclusion of each appropriate phase of manufacturing, processing, packing, or holding of medical gases. Such calculations must be performed by one person and independently verified by a second person (§ 211.103).

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

VIII. PACKAGING AND LABELING CONTROLS

A. Materials Examination and Usage

Medical gases are subject to the requirements in § 211.122 - Materials examination and usage criteria.

There must be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, and examination of labeling and packaging materials, and these written procedures must be followed. Labeling and packaging materials must be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a medical gas (§ 211.122(a)).

Records must be maintained for each shipment received of each different labeling indicating receipt, examination, and whether accepted or rejected (§ 211.122(c)).

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)).

Obsolete and outdated labels must be destroyed (§ 211.122(e)).

If cut labeling is used, labeling operations must include one of the following special control procedures (§ 211.122(g)):

- Dedication of labeling lines to each different strength of each different medical gas (§ 211.122(g)(1))
- Use of appropriate electronic or electromechanical equipment to conduct a 100 percent examination for correct labeling during or after completion of finishing operations

- Use of visual inspection to conduct a 100 percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination must be performed by one person and independently verified by a second person (§ 211.122(g)(3))

Upon receipt from the printer, labels would be counted to verify the quantity received and would be examined to ensure correctness when compared against the master label.

We recommend that labels be locked in a secure area with access limited to authorized personnel. Different medical gas labels would be stored separately. We recommend that industrial labels be stored in a separate area.

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. In light of recent deaths and injuries, this examination is critical to ensure that the correct label has been applied to a container of medical gas.

B. Labeling Control

Medical gases are subject to the requirements in § 211.125 - Labeling issuance.

Strict control must be exercised over labeling issued for use in medical gas labeling operations (§ 211.125(a)).

Labeling materials issued for a batch must be carefully examined for identity and conformity to the labeling specified in the master or batch production records (§ 211.125(b)).

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)). However, this paragraph does not apply to the 360-degree wrap-around label that is applied to large cryogenic containers.

The Agency recommends that all labels be issued by authorized personnel only. Before release of issued labels to an employee, we recommend a representative label be checked against the master label to ensure correctness.

C. Packaging and Labeling Operations

Medical gases are subject to the requirements in § 211.130 - Packaging and labeling operations.

There must be written procedures designed to ensure that correct labels and labeling are used for medical gases; such written procedures must be followed. These procedures must incorporate the following features (§ 211.130):

- Prevention of mix-ups and cross contamination by physical or spatial separation from operations on other medical gases (§ 211.130(a))
- Identification of the medical gas with a lot or control number that permits determination of the history of the manufacture and control of the batch (§ 211.130(c))
- Examination of labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record (§ 211.130(d))

We recommend manufacturers consider each batch of medical gas a separate entity with unique filling procedures to help ensure that the batch is uniform and consistent. Assigning a single lot number to an entire day's production is not appropriate. 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.

In addition, we recommend each large cryogenic container containing liquid oxygen for delivery to patients at home, whether portable or permanently mounted in a van or a truck, be considered a lot and be assigned a unique lot number. 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 safety reasons, we recommend each medical gas container bear only one drug label containing the appropriate information. Do not place a current label on top of an obsolete label.

In accordance with 502(b)(2) of the Act, all medical gas cylinders and cryogenic containers must bear a label with an accurate statement of the net contents. We recommend that the net contents appear on the body label or shoulder label and not on (1) a removable tag, (2) a certificate of analysis, or (3) a small separate sticker.

If a medical gas company sells medical oxygen to emergency medical services for emergency use, the label would contain the statement:

> For emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation. For all other medical applications, Rx Only.[3]

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.

We recommend the labeling for large permanently mounted containers, trailers, and rail cars bear a statement consisting of "Name of the Medical Gas, Refrigerated Liquid USP or NF," such as "Oxygen Refrigerated Liquid USP."

[3] See September 19, 1996, citizen petition response in docket 87P-0167.

The Agency recommends the use of a 360-degree wrap-around label to identify medical gases in large cryogenic containers.

D. Drug Product Inspection

Medical gases are subject to the requirements in § 211.134 – Drug product inspection.

Labeled products must be examined during finishing operations to provide assurance that containers in the lot have the correct label (§ 211.134(a)).

A representative sample of units must be collected at the completion of finishing operations and must be visually examined for correct labeling (§ 211.134(b)).

Results of these examinations must be recorded in the batch production or control records (§ 211.134(c)).

Only one medical gas label would appear on a cylinder or container, and the manufacturer of the medical gas would apply the label in accordance with section 502(b) of the act.

E. Expiration Dating

Medical gases are subject to the requirements in § 211.137 - Expiration dating.

To ensure that a medical gas meets applicable standards of identity, strength, quality, and purity at the time of use, each container must bear an expiration date determined by appropriate stability testing described in § 211.166 (§ 211.137(a)).

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

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

New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations (§ 211.137(g)).

The Agency recommends that high-pressure cylinders stored for long periods of time, such as those provided to patients as a backup to their oxygen concentrator, be monitored to ensure they contain the correct net contents (i.e., pressure). We recommend that companies, especially home care companies and durable medical equipment suppliers, establish and follow a written plan to periodically verify the pressure (i.e., net content) of each high-pressure cylinder stored at a patient's home and that the results be documented.

IX. HOLDING AND DISTRIBUTION

A. Warehousing Procedures

Medical gases are subject to the requirements in § 211.142 - Warehousing procedures.

Manufacturers must develop and follow written procedures describing the warehousing of medical gases. Procedures must include (§ 211.142):

- Quarantine of medical gases before release by the QCU (§ 211.142(a))
- Storage of medical gases under appropriate conditions (§ 211.142(b))

The Agency recommends that separate areas be designated 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.

We recommend medical gas containers be stored under protective covering and not be subject to temperature extremes. Based on this recommendation, storage areas would be clean, dry, well ventilated, and free of combustible materials. Also all valve assemblies, hoses, and other relevant equipment would be protected from contamination such as insect infestation.

B. Distribution Procedures and Recalls

Medical gases are subject to the requirements in § 211.150 - Distribution procedures.

Manufacturers must establish and follow written procedures describing the distribution of medical gases (§ 211.150). They must include a system by which the distribution of each lot of the drug product can be readily determined to facilitate its recall if necessary (§ 211.150(b)).

We recommend that manufacturers have procedures to explain who would evaluate distribution information if a recall were necessary, how a recall would be initiated, who would be informed about the recall, and what would be done with the recalled product.

The Agency recommends that delivery vehicles have well-defined, separate areas for medical gases and industrial gases to prevent mix-ups from occurring. For example, medical and industrial gases can be separated physically in the delivery truck, or a manufacturer can use a unique identifier to distinguish medical gases from industrial gases. As mentioned above, the Agency recommends the use of a 360-degree wrap-around label to identify medical gases in large cryogenic containers. If a manufacturer applies a 360-degree wrap-around label to its large cryogenic containers, and the manufacturer has established adequate driver training, written procedures, and proper stock inventory systems, physical separation on a delivery vehicle is not critical.

We recommend that handheld computer devices or computers used during distribution operations be validated to ensure proper performance.

X. LABORATORY CONTROLS

A. General Controls

Medical gases are subject to the requirements in § 211.160 - Laboratory control general requirements.

The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by Subpart I of 21 CFR Part 211, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, must be drafted by the appropriate organizational unit and reviewed and approved by the QCU. The requirements in Subpart I of 21 CFR Part 211 must be followed and must be documented at the time of performance (§ 211.160(a)).

The Agency recommends that a manufacturer follow the specifications for the specific medical gas as described in the respective monograph of the current U.S. Pharmacoepia/National Formulary (USP/NF), or a manufacturer can establish its own specifications capable of producing equivalent or better-than-USP results.

Medical gases approved under a new drug application (NDA) or covered by an investigational new drug application (IND) would comply with the specifications established in the application.

Although a primary objective of the USP is to ensure the identity, strength, quality, and purity of a product, it is impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. Contaminants can arise from a change in the source of material or from a change in processing, or contaminants can be introduced from extraneous sources. We recommend that a manufacturer use tests suitable for detecting such occurrences in addition to the tests provided in the individual monograph (refer to the USP General Notices, Foreign Substances and Impurities).

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.

1. Sampling Plan

We recommend that a sampling plan describe the following:

- How many cylinders or cryogenic containers will be tested
- When the testing will occur
- What acceptance criteria will be used for selecting samples
- What action will be taken if test results are outside established specifications

2. USP Oxygen Monograph

Medical gas manufacturers can establish their own testing specifications that meet or exceed the requirements of the USP or can use the USP specifications.

USP Testing Specifications - Specifications recommend that the potency of oxygen not be less than 99.0 percent by volume. Oxygen produced by the air liquefaction process is exempt from tests for carbon dioxide and carbon monoxide. However, if there is no documentation that the oxygen is produced by the air liquefaction process, we recommend that two additional impurity tests for carbon dioxide and for carbon monoxide be performed.

Note: The official method is explained below. The Agency recommends that you check periodically with the USP to determine if the official method has changed or has been modified.

The ORSAT testing method uses a calibrated 100-ml buret, copper wire, and an ammonium chloride - ammonium hydroxide solution mixed together and equilibrated by agitation with the copper wire. Prior to the introduction of a sample from a pumped cylinder, a series of analyses (minimum of 3 runs) using a calibration standard would be performed to properly age the test solution and to eliminate any air bubbles that may have become trapped in the apparatus. The Agency recommends that a manufacturer not proceed with testing a filled or pumped cylinder until these analyses are completed. A 100-ml sample of the unknown gas would be drawn into the buret, agitated, and measured. An identification test, using a carbon dioxide detector tube, would be performed at the same time.

Note: The ammonium chloride - ammonium hydroxide solution used in this method would be expected to bear an expiration date supported by appropriate stability studies.

The USP Oxygen Monograph requires a finished drug product odor test to be performed on each container undergoing testing.

The Agency recommends that USP tests not be performed on an industrial gas in an attempt to convert it to a medical gas.

The accuracy of the USP procedure is $\pm$0.1 percent.

936
937 *3. Calibration of Instruments*
938
939 Laboratory controls must include the calibration of instruments, apparatus, gauges, and recording
940 devices at suitable intervals in accordance with an established written program containing
941 specific directions, schedules, limits for accuracy and precision, and provisions for remedial
942 action in the event accuracy and/or precision limits are not met (§ 211.160(b)(4)).
943
944 Oxygen analyzers and other instruments can be calibrated at intervals specified in the
945 instructions from the equipment manufacturer. The FDA recommends that gas manufacturers
946 not use other medical or industrial gases as the basis for calibrating their instruments.
947
948 We recommend that standards be certified to ensure the proper level of precision and accuracy as
949 reported on the certificate of analysis (COA).
950
951 We also recommend that each COA for a medical gas calibration standard be specific for that
952 cylinder and provide the following information:
953
954 • Name and address of the calibration standard supplier
955 • Name of the product
956 • Lot number or unique identification number specific for each cylinder
957 • Analytical methodology used to assay the calibration standard
958 • Actual analytical results (for example, 99.9 percent nitrogen)
959 • The responsible person's signature and the date signed
960
961 **B. Testing and Release for Distribution**
962
963 Medical gases are subject to the requirements in § 211.165 - Testing and release for distribution.
964
965 For each batch of medical gas, there must be appropriate laboratory determination of satisfactory
966 conformance to final specifications, prior to release (§ 211.165(a)).
967
968 The Agency recommends that each manufacturer determine the specific testing to be performed
969 on any incoming medical gas and on medical gases delivered to a consignee, customer, or
970 patient. We recommend that testing methods conform to official specifications (i.e., the USP
971 testing methodology or a validated test procedure capable of producing equivalent or better-than-
972 USP test method performance).
973
974 If batch results do not conform to specifications, retesting is not recommended unless a thorough
975 investigation is performed in accordance with established written procedures.[4]
976
977 For high-pressure cylinders filled on a multiple outlet manifold, the Agency recommends that
978 one or more cylinders from each manifold filling sequence be assayed for identity, strength, and

[4] A draft guidance, on *Investigating Out-of-Specification Test Results for Pharmaceutical Production* was issued on September 30, 1998.

odor. For high-pressure cylinders filled individually, one cylinder per uninterrupted filling sequence can be tested for identity, strength, and odor.

1. Liquid-to-Liquid Filling: Oxygen Only

This section pertains to the filling of liquid medical oxygen into cryogenic home containers, either at a patient's home (curbside), or on site. Due to the unique nature of this operation, the Agency recognizes that testing for conformance to final specifications prior to release is impractical. Therefore, FDA recommends using the following procedures.

a. Testing of the incoming liquid oxygen

In lieu of testing, the home care company (HCC) can (1) witness the testing for identity and strength of the large cryogenic container(s) performed by the supplier for each container received, (2) document that the testing has been witnessed, and (3) obtain a valid COA for each container. The employee responsible for witnessing the testing would have been trained on the analytical methodology used by their supplier. Training would be documented by the employee's company.

If the testing is not witnessed and the HCC chooses to rely on a valid COA, the Agency recommends that the HCC perform a specific identity test. The HCC would also periodically verify the reliability of the supplier's analysis. This can be done by (1) visiting the supplier to verify that the supplier is following appropriate written testing procedures, (2) observing the supplier's analytical testing, including calibration of the analyzer, and (3) documenting that steps 1 and 2 have been taken. Alternatively, to periodically verify the reliability of the supplier's analysis, the HCC can submit to a third party a sample from a recent delivery to be analyzed for conformance with the USP requirements or established specifications.

If an HCC does not follow the above methods or chooses to test the large cryogenic containers, the Agency recommends that full testing on the incoming medical oxygen (each large cryogenic container) be performed.

b. Testing of an oxygen storage tank used to fill large vehicle-mounted cryogenic containers

If a new shipment of oxygen is combined in a storage tank with a previously received, tested, and approved lot, we recommend that the manufacturer test the combined product and approve it before use. If the storage tank is located on the company's premises and is used to fill vehicle-mounted containers or cryogenic home containers, the Agency recommends an identity and strength test be performed by sampling from the storage tank after each oxygen delivery and prior to the filling of any cryogenic containers.

After the storage tank has been tested, the company can forego testing a large cryogenic container filled from the storage tank if:

- No other storage tank is located on the premises

- The container is dedicated to the delivery of medical oxygen for home care use only
- 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
- A valid COA is received with each delivery and is maintained on file

c. Testing of cryogenic home containers

It is important to exercise control over the home container during the filling operation. We recommend that appropriate methods be developed to control situations where external contamination may occur, such as failing to cap or cover the ends of a filling hose to prevent dirt, debris, or insect infestation.

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
- The container is filled by the company that owns it

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.

If cryogenic home containers are filled by another individual or another company prior to release to the patient, we recommend that the manufacturer distributing the containers inspect each container to ensure that a correct label including a lot number has been applied.

2. Liquid-To-Gas; Filling Large Cryogenic Containers

This section pertains to medical gas companies, such as welding supply companies, who fill multiple gases, both industrial and medical. In this situation, the potential for mix-ups is greatest. The Agency recommends that the incoming product be tested for full USP or established specifications immediately after each lot is received. 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.

Each filled large cryogenic container would be tested prior to release. Cryogenic containers usually contain a residual product and a commingling of new and old product would result in a new batch or lot. This new batch or lot would be analyzed and assigned a new batch or lot number. A valid COA would be provided with each cryogenic container.

3. Liquefied (gas on top of liquid) Compressed Gas

The pressure in a closed container containing carbon dioxide or nitrous oxide increases as the temperature rises. A cylinder filled at a safe pressure at normal temperatures can reach a dangerously high pressure at high ambient temperatures. Therefore, the Agency recommends that nitrous oxide and carbon dioxide be filled individually as liquids on a scale where the pressure does not indicate the amount filled. Instead, we recommend these cylinders be filled individually, and the weight not exceed 68 percent of the weight of water the cylinder will hold at 60°F (15.6 C).

The Agency recommends that one of the cylinders filled during an uninterrupted filling sequence be tested for conformance with specifications prior to release. For both carbon dioxide and nitrous oxide, a specific carbon dioxide identification test would be conducted concurrently with the assay in accordance with USP monograph.

4. Gas Mixtures

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. In addition, an identity test for the other gas would be performed on one cylinder from the manifold filling sequence. For product mixtures containing three gases, each cylinder of the blended product would be tested for the identity and strength of two of the gases, and one cylinder from each manifold filling sequence would be tested for the identity of the third gas.

5. Liquid Nitrogen

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:

- A valid COA is received with each delivery and the product is designated Nitrogen NF
- The filling system has dedicated lines, and these supply lines are traceable from the storage tank to the filling manifold. If there is a possibility that another gas, either industrial or medical, could be introduced and could contaminate the product, we recommend that USP testing and a test for the absence of the contaminating gas be performed.
- Testing for the lack of oxygen (less than or equal to 1.0 percent) is performed with an oxygen analyzer that has been validated against the USP methodology
- 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.

To ensure that they receive medical nitrogen, we recommend that manufacturers use suppliers registered with FDA.

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.[5]

C. Alternate Testing Methods

The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the manufacturer must be established and documented. We recommend that such validation and documentation be accomplished in accordance with § 211.194(a)(2).

We recommend that any alternative testing method (e.g., spectrophotometer, handheld analyzers) used to analyze a medical gas be compared against the official testing methodology.

We also recommend that each medical gas manufacturer maintain a copy of the entire validation study, including the actual data generated for each analyzer by model number that demonstrates USP equivalence and any changes made to the analytical methodology, such as a different column length or a different carrier gas. Validation of alternate methods can be performed in accordance with USP Validation of Compendia Methods.

D. Stability Testing

Medical gases are subject to the requirements in § 211.166 – Stability Testing.

There must be a written testing program designed to assess the stability characteristics of medical gases. The results of such stability testing must be used in determining appropriate storage conditions and expiration dates. The written program must be followed and must include (••211.166(a)):

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

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

An adequate number of batches of each medical gas must be tested to determine an appropriate expiration date, and a record of such data must be maintained (§ 211.166(b)).

The Agency recommends that the testing program take into account the compatibility of the valve assembly, the acceptability of the valve packing and the valve seal used, the type of cylinder, and any other factor that can have an effect on the stability of the medical gas. Each medical gas would be tested for stability in the exact container closure system that it is marketed

[5] Compressed Gas Association, Inc., Saftey Alert (SA-6) Use of Nitrogen NF for Surgical Air Tools.

in, such as steel high-pressure cylinders, aluminum high-pressure cylinders, and cryogenic containers.

E. Reserve Samples

Reserve samples of compressed medical gases do not need to be retained (§ 211.170).

XI. RECORDS AND REPORTS

Medical gases are subject to the requirements on records and reports in §§ 211.180 - 198.

A. Record Retention

Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of medical gas must be retained for at least 1 year after the expiration date of the batch (§ 211. 180(a)).

All records required under this part, or copies of such records, must be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred (§ 211.180(c)). The records or copies thereof are subject to photocopying or other means of reproduction as part of such an inspection (§ 211.180(c)). Records that can be immediately retrieved from another location by computer or other electronic means will be considered as meeting the requirements of this paragraph (§ 211. 180(c)).

Records required under this part may be retained either as original records or as true copies such as photocopies or other accurate reproductions of the original records (§ 211.180(d)).

Records can be kept on paper or electronically. Electronic records must comply with the requirements of 21 CFR part 11.

Medical gas manufacturers are required to maintain a number of documents and records including:

- Equipment cleaning and use logs (§ 211.182)
- Computer and process validation data (§ 211.68)
- Analyzer validation studies and data (§ 211.194)
- Label reconciliation logs (§ 211.184)
- Master production records (§ 211.186)
- Batch production records (§ 211.188)
- Analytical equipment calibration logs (§ 211.194(d))
- Testing records (§ 211.194)
- Stability studies (§ 211.194(e))
- Complaint files (§ 211.198)

The Agency recommends that medical gas manufacturers also maintain training records and certificates of analysis.

B. Equipment Cleaning and Use Log

Medical gases are subject to the requirements in § 211.182 – Equipment cleaning and use log.

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use must be included in individual equipment logs that show the date, time, product, and lot number of each batch processed (§ 211.182). In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use must be part of the batch record (§ 211.182). The persons performing and double-checking the cleaning and maintenance must date and sign or initial the log indicating that the work was performed (§ 211.182).

Equipment cleaning and use logs can be maintained for trailers, rail cars, and storage tanks, especially those installed at a health care facility or a hospital.

C. Component, Drug Product Container, Closure, and Labeling Records

Medical gases are subject to the requirements in § 211.184 - Component, drug product container, closure, and labeling records.

These records must include the following (§ 211.184):

- The identity and quantity of each shipment of each lot of medical labeling
- The results of any test or examination performed (including those performed as required by § 211.82(a), ••211.84(d), or § 211.122(a)) and the conclusions derived therefrom
- Documentation of the examination and review of labels and labeling for conformity with established specifications in accordance with §§ 211.122(c) and 211.130(c)
- The disposition of rejected medical gas containers, closures, and labeling

D. Master Production and Control Records

Medical gases are subject to the requirements in § 211.186 – Master Production and Control Records.

To ensure uniformity from batch to batch, master production and control records for each medical gas, including each batch size thereof, must be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person (§ 211.186(a)). The preparation of master production and control records must be described in a written procedure, and the written procedures must be followed (§ 211.186(a)).

Master production and control records must include (§ 211.186(b)):

- A description of the medical gas containers and closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling (§ 211.186(b)(8))

- Complete manufacturing and control instructions, sampling, and testing procedures, specifications, special notations, and precautions to be followed (§ 211.186(b)(9))

The Agency recommends that a manual containing all of the above be on site and available to personnel to ensure that individuals are able to perform their assigned functions

E. Batch Production and Control Records

Medical gases are subject to the requirements in § 211.188 – Batch Production and Control Records.

Batch production and control records must be prepared for each batch of medical gas produced and must include complete information relating to the production and control of each batch. These record must include (§ 211.188):

- An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed (§ 211.188(a))

- Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including (§ 211.188(b)):

  --Dates (§ 211.188(b)(1))
  --Inspection of the packaging and labeling area before and after use (§ 211.188(b)(6)
  --Complete labeling control records (§ 211.188(b)(8))
  --Description of medical gas containers and closures (§ 211.188(b)(9))
  --Any sampling performed (§ 211.188(b)(10))
  --Identification of the persons performing and directly supervising or checking each significant step in the operations (§ 211.188(b)(11))
  --Any investigation made according to § 211.192 (§ 211.188(b)(12))
  --Results of examinations made in accordance with § 211.134 (§ 211.188(b)(13))

The Agency recommends that the records include documentation of the following:

- Prefill inspections
- Number and size of the cylinders or cryogenic containers filled
- Filling inspections
- Post-fill inspections
- Lot number assigned
- Final temperature and pressure results
- Initials of the filler and/or analyst

- Signature of the individual who checked the entries for accuracy and completeness

Historically, the industry has used pumper's logs or filler's logs as batch production records. This is appropriate as long as the logs contain all of the relevant information. A batch production record acts as a snapshot of the actual production at the time of its performance. One batch production record would document the filling of high-pressure cylinders and a separate record would document the filling of cryogenic containers.

Based on the requirements of § 211.188, batch production records would include an item-by-item entry. A manufacturer would not use a single entry to indicate that all of the significant steps have been performed, nor a check mark or other symbol when an actual value should be recorded, such as temperature and pressure readings, purity, and identity results.

F. Production Record Review

Medical gases are subject to the requirements in § 211.192 – Production record review.

All medical gas production and control records, including those for packaging and labeling, must be reviewed and approved by the QCU to determine compliance with all established, approved written procedures before a batch is released or distributed (§ 211.192). Any unexplained discrepancy or the failure of a batch to meet any of its specifications must be thoroughly investigated (§ 211.192). A written record of the investigation must be made and must include conclusions and follow-up (§ 211.192).

Any test result that is outside of the established limits would be considered an unexplained discrepancy or the failure of a batch to meet its specifications.

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

For ASUs where filling occurs at night, the ASU's QCU would be responsible for the release of the product, prior to distribution. For swap agreements, the manufacturer having its trailers filled would be responsible for and would have its own QCU review and approve the cleaning of any trailers that have contained industrial product, prior to filling with a medical gas.

G. Laboratory Records

Medical gases are subject to the requirements in § 211.194 – Laboratory records.

Laboratory records must include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays, as follows (§ 211.194(a)):

- 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))

- A statement of each method used in the testing of the sample. The statement must indicate the location of the data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested (§ 211.194(a)(2))

- A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific medical gas and lot tested (§ 211.194(a)(4))

- A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors (§ 211.194(a)(5))

- The initials or signature of the person who performs each test and the date(s) the tests were performed (§ 211.194(a)(7))

- The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards (§ 211.194(a)(8))

Complete records must be maintained of any modification of an established method employed in testing (§ 211.194(d)). Such records must include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method (§ 211.194(b)).

Complete records must be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions (§ 211.194(c)).

Complete records must be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by § 211.160(b)(4) (§ 211.194(d)).

Complete records must be maintained of all stability testing performed in accordance with § 211.166 (§ 211.194(e)).

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.

The suitability of all testing methods must be verified under actual conditions of use (• •211.194(a)(2)).

When testing is done by a gas chromatographic method specified in a USP monograph (such as the assay method for Nitrogen NF), the Agency recommends the chromatographic system used be adjusted to meet all system suitability requirements listed in the monograph. We recommend that after tests are run to verify that the requirements have been met, the results be documented. For monograph methods that lack specific system suitability requirements, the section on system suitability in USP "Chromatography" can be used as a guide.

When an alternative testing methodology is employed, we recommend that the methodology be validated against an official test method and the method be carried out under substantially the same conditions that prevailed during the validation study. If the testing environment is substantially different, some additional on-site "spot check" tests of the method, perhaps with a small number of standard gases, would help show that its performance has not been affected by local conditions. For example, paramagnetic oxygen analyzers can give inaccurate readings when used at high altitudes unless special adjustments are made. We recommend such an on-site spot check also be made if the analyzer is installed as part of a control or alarm system. The results of these tests would be fully documented. 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.

H. Liquid Supply (Certificate of Analysis (COA))

The medical gas industry routinely relies on COAs to reduce the amount of finished product testing performed. For example, if a COA lists all of the impurities tested for by a supplier, then it would be unnecessary for a manufacturer to perform a test for the listed impurities on the finished drug product. If no COA is received, the Agency recommends that the finished drug product testing include all impurities listed in the USP monograph or established specifications for each medical gas.

In addition, the COA for medical oxygen usually contains the *air liquefaction statement* as required by the USP, and as a result, it would be unnecessary for a manufacturer to test for carbon dioxide and carbon monoxide impurities. If a manufacturer does not maintain the air liquefaction statement for its medical oxygen, the Agency recommends that the manufacturer perform testing for carbon dioxide and carbon monoxide impurities.

We also recommend that a COA contain the following information and would accompany all incoming deliveries of liquid medical gas:

- Supplier's name and complete address
- Name of the product (e.g., oxygen USP, carbon dioxide USP, nitrogen NF, nitrous oxide USP, helium USP, or medical air USP)
- An air liquefaction statement, where appropriate
- Lot number or other unique identification number
- Actual analytical results for full USP monograph testing, (e.g., 99.5 percent oxygen)

- Test method used to perform the analysis. If an analyzer is used, the specific model number is indicated.
- Supplier's signature and the date
- Signature of the employee witnessing any testing at a supplier, if applicable

If a company relies on a COA to reduce the amount of testing required by the USP, we recommend the company establish the reliability of the supplier's analysis at appropriate intervals. This can be accomplished by the manufacturer, by a third party, or by a contract-testing laboratory.

I. Distribution Records

Medical gases are subject to the requirements in § 211.196 – Distribution records.

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).

A manufacturer must establish and follow written procedures that include a system whereby the distribution of each lot of a medical gas can be determined if a recall becomes necessary, as required in § 211.150. For compressed medical gases, distribution records are not required to contain lot or control numbers.

J. Complaint Files

Medical gases are subject to the requirements in § 211.198 – Complaint files.

Written procedures describing the handling of all written and oral complaints regarding a medical gas must be established and followed (§ 211.198(a)). Such procedures must include provisions for review by the QCU, of any complaint involving the possible failure of a medical gas to meet any of its specifications and, for such a medical gas, a determination as to the need for an investigation in accordance with § 211.192 (§ 211.198(a)). Such procedures must include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience, which is required to be reported to the Food and Drug Administration in accordance with § 301.305 (§ 211.198(a)).

A written record of each complaint must be maintained in a file designated for medical gas complaints (§ 211.198(b)). The file regarding such medical gas complaints must be maintained at the establishment where the medical gas involved was manufactured, processed, or packed, or the file may be maintained at another facility if the written records in the file are readily available for inspection at that other facility (§ 211.198(b)).

The Agency recommends that complaint records include, where known:

- Name of the drug product
- Name and address of complainant

- Name (and, where appropriate, title) and telephone number of the person submitting the complaint
- Nature of the complaint
- Date the complaint is received
- Action initially taken, including dates and identity of person taking the action
- Follow-up action taken
- Response provided to the originator of complaint, including the date the response was sent
- Final outcome regarding the issues raised by the complaint

Where an investigation under § 211.192 is conducted, the written record must include the findings of the investigation and follow-up (211.198(b)(2)). The record or copy of the record of the investigation must be maintained at the establishment where the investigation occurred in accordance with § 211.180(c) (§ 211.198(b)(2)).

K. Reporting Deaths and Injuries

The following is intended to clarify current adverse event reporting requirements.

In accordance with § 310.305, manufacturers of prescription medical gases must establish and maintain records and must make reports to FDA of all serious, unexpected adverse drug experiences, such as deaths or life-threatening adverse events, associated with the use of their medical gases. More information can be obtained on FDA's web site, at http://www.fda.gov/medwatch/report/mfg.htm.

According to § 310.305(b) Definitions – an adverse drug experience is any adverse event associated with the use of a drug in humans, whether or not considered drug related. This would include problems with valves, such as valve seat combustion resulting in a release of chlorine gas, contamination from cleaning solutions, and mix-ups that result in an adverse event to a patient.

We also encourage hospitals, nursing homes, and other health care facilities dispensing medical gases to report serious adverse events and product problems associated with the use of those gases. They can report adverse events directly to the medical gas manufacturer. Or, they can report to **MedWatch**, the FDA's voluntary reporting program, in one of the following four ways:

- Online at http://www.accessdata.fda.gov/scripts/medwatch/
- By telephone at 1-800-FDA-1088
- By FAX at 1-800-FDA-0178
- By mail to:

  MedWatch
  Food and Drug Administration (HF-2)
  5600 Fishers Lane
  Rockville, MD 20857-9787

XII. RETURNED AND SALVAGED DRUG PRODUCTS

A. Returned Drug Products

Medical gases are subject to the requirements in § 211.204 – Returned drug products.

Returned medical gases must be identified as such and held (§ 211.204). If the conditions under which returned medical gases have been held, stored, or shipped before or during their return, or if the condition of the drug product, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the medical gas, the returned medical gas must be destroyed unless examination, testing, or other investigations prove the medical gas meets appropriate standards of safety, identity, strength, quality, or purity (§ 211.204).

B. Drug Product Salvaging

Medical gases are subject to the requirements in § 211.208 – Drug product salvaging.

Medical gases that have been subjected to improper storage conditions must not be salvaged and returned to the marketplace (§ 211.208).

XIII. AIR SEPARATION PLANTS OR UNITS (ASU)

ASUs separate atmospheric air into the constituent gases of oxygen, nitrogen, and argon by using a purification process of cleaning, compressing, and cooling. ASUs are generally highly computerized and have very few employees in attendance during operations, which usually take place 24 hours a day, 7 days a week. ASUs are drug manufacturers and as such must comply with all relevant CGMP regulations.

The Agency recommends that an ASU that receives deliveries of a drug product into its storage tanks from outside sources perform finished product testing on the incoming supply, prior to accepting the delivery. Appropriate COAs would be maintained.

The Agency plans to develop and publish a separate guidance on the validation of the manufacturing process and computerized systems at ASUs.

XIV. STORAGE TANK INSTALLATIONS AT HEALTH CARE FACILITIES

This section pertains to the installation of a storage tank that will contain a medical gas, usually oxygen, at a hospital, nursing home, or long-term health care facility. During the installation of a storage tank and associated equipment (i.e., equipment used for the delivery of medical gases — usually oxygen — to hospitals, nursing homes, clinics, and long-term health care facilities), following CGMP would be very important for manufacturers or individuals installing the storage tank. CGMP would also be important any time the system is exposed to a possible contaminant

or impurity, such as installation of a new valve or piping. The company would determine the stage of the installation where problems or contamination may occur and ensure compliance. CGMP would be applicable to activities involving all equipment that is part of the medical gas storage and delivery mechanism, including the storage tank that holds the drug product, all related equipment such as piping and valves, and all other equipment up to the wall leading into the facility.

For storage tank filling, we recommend a focus on the following aspects of CGMP:

- Establish a QCU and written procedures
- Perform training for service technicians in their job functions and in CGMP
- Qualify all equipment for medical use, including delivery vehicles and storage tanks
- Audit contracted cleaning firms
- Develop and follow detailed written procedures
- Calibrate testing equipment
- Test finished products prior to introduction of the drug product into the supply system
- Use USP equivalent testing methodology
- Log equipment cleaning and use, especially for storage tanks
- Maintain batch production records
- Provide COAs to the receiving facility with each delivery
- Maintain documentation

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

XV. MEDICAL GAS MIX-UPS

FDA has investigated a number of deaths and injuries resulting from medical gas mix-ups. In all of these incidents, the injuries and deaths could have been prevented if the manufacturer had followed the CGMP and industry standards.[6] Specific CGMP deviations noted repeatedly included:

- § 211.100(a & b): Failure to establish and follow adequate written procedures
- § 211.25(a): Failure to provide adequate CGMP training to all persons involved with the handling and delivery of a medical gas
- § 211.42(c): Inadequate storage areas on delivery vehicles for the storing of medical gases and industrial gases

[6] See CGA standards.

In particular, over the past several years, FDA has received reports from separate hospitals, nursing homes, and clinics involving 7 deaths and 15 injuries to patients who were thought to be receiving medical oxygen when in fact they were receiving a toxic industrial gas, (e.g., nitrogen). The Agency recommends the following steps to help prevent similar deaths or injuries from occurring:

- Ensure that all employees involved in the manufacturing, processing, packaging, or holding of medical gases have the education, training, and experience, or any combination thereof, to enable them to perform their assigned functions.
- Ensure that employees understand that they are handling a drug. Make sure they learn how to examine the label on each container before delivering the container or connecting the container to a supply system. Make sure employees know what to do if a label does not match the invoice or the connections do not fit (e.g., possibly not accept the product and/or notify their supervisor immediately).
- Be aware that most fittings or connectors are permanently attached on all large cryogenic containers used to deliver medical gases.
- Never remove fittings and connectors. If an employee is unable to connect a container to a supply system, he or she would contact the supplier immediately. This is especially true for oxygen.
- Ensure that written procedures are developed and followed. Train employees regularly on how to perform the procedures.
- Ensure that separate storage areas for medical and industrial gases are identified and used on each delivery vehicle.
- Make sure that all large cryogenic containers are dedicated to medical use and are not used for industrial gases.
- Ensure that all cryogenic containers have clear labeling, such as a 360-degree wrap-around label on the sidewalls. The wrap-around label would be placed as close to the top portion of the container as possible, but below the top weld seam, and would contain and repeat the product name (e.g., *Medical Oxygen Medical Oxygen Medical Oxygen)* and be the appropriate color (e.g., green for oxygen).
- Make sure only one drug label is applied to a container. Never apply a label on top of another label.
- Provide each consignee (e.g., hospital, nursing home, and clinic) with a copy of FDA's Public Health Advisory, *Guidance to Hospitals, Nursing Homes, and Other Health Care Facilities*.

XVI. CARBON DIOXIDE AND HELIUM MANUFACTURERS AND WHOLESALE DISTRIBUTORS

Manufacturers of medical carbon dioxide and medical helium also are subject to CGMP requirements. The Agency recommends that manufacturers perform process and computer systems validation and have a written agreement with the raw material manufacturer to be notified of any changes in the manufacturing process or the quality of the raw material. We also recommend that manufacturers perform an initial *fingerprinting* or characterization of the incoming raw material for any contaminants or impurities that could affect the quality, strength, purity, or identity of the finished drug product.

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:

- Process validation and computer systems validation (§ 211.68)
- Establishment of a QCU and written procedures (§ 211.22)
- In-process testing (§ 211.110)
- Lot numbering (§ 211.80(d))
- Written operating procedures (§§ 211.80(a) and 211.100)
- Calibration of analytical equipment (§ 211.160(b)(4))
- Testing of the finished product via USP or equivalent testing methodology (§ 211.165)
- Batch production records (§ 211.188)
- Maintaining documentation (§ 211.180)

The Agency also recommends that carbon dioxide and helium manufacturers, as well as shippers, wholesale distributor jobbers, and transporters that fill these medical gases into or out of rail cars, storage tanks, trailers, and containers, do the following:

- Conduct training, including for CGMP
- Test residual gas in tankers, trailers, and rail cars prior to filling

The Agency recommends that all tankers or trailers used for the delivery of carbon dioxide be dedicated to medical use only.

XVII. EMERGENCY MEDICAL SERVICE (EMS)

An EMS can follow this guidance to comply with CGMP when filling small high-pressure cylinders. Given the limited nature of the operation, an EMS would emphasize:

- CGMP training
- Operating procedures
- Procedures for accurate labeling
- Receiving oxygen from reliable sources
- Performing pre-fill inspections
- Traceability, so that a recall can be performed if necessary

XVIII. GAS-TO-GAS ADAPTERS

For safety reasons, ***avoid the use of*** gas-to-gas adapters of any kind to circumvent the specific medical gas valves and connections associated with a specific medical gas. The Agency recommends that companies only use adapters that reduce or expand the connection size for a specific medical gas while still maintaining the proper connection system. This practice would be described in written procedures.

Adapters can be used when filling mixtures or blends. However, documented written procedures detailing a system of checks will help prevent mix-ups or contamination. We recommend that adapters be under strict control and be kept under limited access.

XVIX. ALTERNATIVE APPROACHES

As noted, this guidance represents FDA's current thinking on CGMP for medical gases. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach can be used if that approach satisfies the applicable statutes and regulations. In the event you have ideas, questions, or concerns regarding an alternative approach, we encourage you to contact the Director of the Division of Manufacturing and Product Quality in the Office of Compliance of the Center for Drug Evaluation and Research at FDA.

ATTACHMENT: MEDICAL GAS MIX-UPS

The purpose of this section is to highlight the serious consequences of failing to follow CGMP in the production and delivery of medical gases.

On December 7, 2000, a nursing home in Bellbrook, Ohio, reported the death of two patients and the injury of eight patients following a mix-up in the nursing home's oxygen supply system. The nursing home had received a shipment from their supplier of four cryogenic containers supposedly containing medical oxygen. Included in the delivery, however, was a cryogenic container of industrial nitrogen that bore two different labels. The nursing home was running low on oxygen and sent a maintenance employee to connect a new oxygen container to the oxygen supply system. The employee selected the nitrogen container and discovered, correctly, that he was unable to connect the container to the oxygen system. The employee removed a fitting from an empty oxygen container and installed it on the nitrogen container. He then connected the deadly product to the oxygen system. Several days later, two more patients died from exposure to industrial nitrogen, bringing the death toll from this one incident to four.

On December 6, 2000, an industrial nitrogen container was connected to the oxygen supply system at a Medical Center in Springerville, Arizona. The nitrogen container was properly labeled and had the correct nitrogen fitting. The supplier removed the nitrogen fitting and replaced it with an oxygen fitting. A female who had been undergoing a hysterectomy was coming off anesthesia when a ventilator alarm sounded. The anesthesiologist immediately removed the ventilator and started her on an ambu bag. The patient demonstrated no ill effects.

On July 12, 1999, a patient in a California hospital was undergoing dialysis treatment. Since he required a continuous supply of oxygen he was connected to the wall oxygen source during the procedure. Upon completion of dialysis, the oxygen connection was removed from the wall source and reattached to a portable cylinder. The cannula was attached to the patient's existing tracheostomy and the patient was transported to the Intensive Care Unit (ICU). When the patient arrived at the ICU, he was in ventricular fibrillation, became apneic and sustained a cardiac arrest. The patient died. An investigation found that the patient had been attached to a cylinder of carbon dioxide, not oxygen. This cylinder had a green top, was labeled for CO2 and had the specific CO2 valve.

On April 22, 1998, a hospital in Idaho discovered that a large cryogenic container of industrial nitrogen had been connected to their oxygen system supplying the operating rooms, labor and delivery rooms, and the emergency room. When the supplier's truck driver was unable to connect the incompatible nitrogen container fitting to the oxygen supply system, he used a wrench to disconnect the nitrogen fitting and replaced it with an oxygen fitting. Two patients died as a result of this medical gas mix-up.

In October 1997, a hospital in Nebraska received a shipment of large cryogenic containers which were supposed to contain medical oxygen. The shipment included one cryogenic container of industrial argon that was labeled as argon. The hospital was running low on oxygen and sent a maintenance employee to connect a new oxygen container to the oxygen supply system.

Without examining the label, the employee selected the argon container, and, discovering he was unable to connect the container to the oxygen supply system, he removed a fitting from an empty oxygen container, installed it on the argon container, and connected the deadly product to the oxygen supply system. Argon was administered to a patient undergoing minor surgery. The patient died.

On December 2, 1996, a children's home located in New York reported adverse reactions experienced by nine patients due to the inhalation of carbon dioxide. An employee of the home, asked to attach a large cryogenic container of medical oxygen, unknowingly selected a carbon dioxide container from their inventory. He noted that the fitting on the carbon dioxide container was not compatible with the connector on the oxygen supply system. He removed an oxygen fitting from an empty container, installed it on the carbon dioxide container, and attached it to the oxygen supply system. Two patients were injured critically, four patients experienced varying stages of respiratory distress, and three patients recovered with no lasting side effects.

In March of 1996, 11 deaths were associated with contaminated oxygen delivered to a hospital during installation of a new storage tank. A 500-gallon cryogenic container was temporarily connected to the hospital's oxygen supply system with a 50-foot hose. An analysis of the 50-foot hose tested positive for the presence of trichloroethylene (TCE), a standard cleaning chemical that is very toxic to humans.

In December of 1993, a home care company (HCC) that filled liquid oxygen containers authorized an inadequately trained employee to obtain from their supplier a container (GP-45) of medical oxygen. The supplier's employees did not accompany the HCC employee to the loading dock to pick up the medical oxygen. The home care company's employee who failed to examine the label selected a container of argon instead of a container of medical oxygen. The employee loaded the container into the van and went to three patients' homes to fill their containers. When he attempted to fill the cryogenic containers containing oxygen, the discharge line was not compatible with the container fittings. The employee removed a fitting from an empty oxygen container and attached it to the container containing argon, and was able to fill the patients' containers with argon. The next day, the employee became aware of the argon mix-up and retrieved all three containers before the patients used the gas.

In July of 1986, a large welding supply company filled four gray-colored oxygen cylinders with carbon dioxide (CO_2). The cylinders were subsequently sent to a hospital and administered to two patients undergoing surgery. One patient's death was attributed to CO_2 exposure; the other patient was seriously injured. The cylinders had the proper medical oxygen label and the correct oxygen valve. Some hospitals paint their cylinders a certain color to designate a specific unit or room located within the hospital. In this case, the gray-colored cylinders denoted cylinders to be delivered to the surgery rooms only.

In May of 1983, a large welding supply company delivered and connected to a hospital a large cryogenic container thought to contain medical oxygen. The gas was administered to a premature infant, a 46-year-old male, and a 27-year-old female in three separate areas of the hospital. All three patients died. Analysis of the container found that it contained argon instead of oxygen, and the container bore two labels, one label read "Liquid O" while a second label on

the opposite side of the container read "Argon"; the fill line of the container had an argon fitting; and the discharge line had an oxygen fitting.

GLOSSARY

The following terms and definitions are provided to assist the reader in using this guidance document.

Cascading: This operation pertains to gas-to-gas filling of high-pressure cylinders only, and consists of a supply cylinder unit (usually called a *bank*) containing a group of *H* or *K*-sized cylinders, a receiving cylinder unit, a filling manifold, and a vacuum evacuation pump. The first supply cylinder's valve is opened and the gas flows into the smaller cylinder(s) to be filled until equilibrium or the correct net contents is reached. If the smaller cylinder is not full and requires additional pressure or contents, the second supply cylinder's valve is opened and the gas is allowed to flow into the smaller cylinder. This process is repeated to the third, and fourth, etc., supply cylinder until the desired pressure or contents is reached in the smaller cylinder(s). Individual cylinders in the bank are replaced sequentially as their respective pressures or contents are diminished to levels that are ineffective for the transfilling operation.

Certificate of analysis (COA): A single document provided with each shipment of incoming liquid medical gas that undergoes further processing (filling, transfilling). A COA contains all of the required information that would allow the receiving manufacturer to determine if the medical gas is acceptable. A COA can also reduce the amount of finished product testing a manufacturer performs by allowing the manufacturer to rely on the contaminants or impurities testing performed by the supplier and documented on the COA. Otherwise, a manufacturer would test each finished drug product for all contaminants and impurities required by the USP or the manufacturer's established specifications. See above for details.

Cryogenic containers: Containers used to hold a low-temperature, low-pressure liquid product that are similar in design to an insulated thermos bottle with a vacuum between the inner and outer container. They may be portable or permanently mounted in a vehicle, and are commonly known as VGLs (vertical gas liquids), GPs (gas packs), or PLCs (portable liquid containers), or HL119s, MDX 60s, 80s, and 190s. This does not include tankers, trailers, or rail cars.

Cryogenic home containers: Containers designed to hold liquid oxygen at a patient's home under low pressure and very low temperature.

Distributor: An individual or a manufacturer that receives liquid and/or compressed gas in labeled high-pressure cylinders or cryogenic containers and does not manipulate or apply a label to the product. The product is then delivered to a patient or consignee.

Emergency medical services (EMSs): EMSs include fire departments, ambulance companies, and rescue squads that are usually government-affiliated emergency services. EMSs transfill medical oxygen for their own use (no other gases are filled on site other than compressed breathing air) and administer medical oxygen to patients and/or victims in emergency situations.

Handheld oxygen analyzers: Oxygen analyzers that operate on the fuel cell, electrochemical cell, galvanic cell, or polarographic principle. When properly calibrated, these analyzers provide

a specific oxygen identification test result only. They do not have the required USP accuracy for determining potency. We recommend they be validated.

Home care company/home respiratory care company (HCC): Manufacturers that sell durable medical equipment and usually supply liquid oxygen to patients at their home. They may also fill high-pressure cylinders by means of cascading as a back up for their oxygen concentrators.

Oxygen for environmental use: Oxygen that meets USP specifications and is used to support life artificially in environments that are normally deficient. This includes, but is not limited to, space and space simulation capsules, deep submersibles, and scuba systems. This definition excludes oxygen used in chambers or devices. This product is not to be used for inhalation or the medical therapeutic treatment of humans or animals.

Oxygen for industrial use: Oxygen not intended for inhalation or therapeutic treatment of humans or animals. Because of the many contaminants and impurities associated with industrial oxygen, industrial oxygen is not appropriate for breathing purposes.

Oxygen for aircraft use (Aviators Breathing Oxygen (ABO)): Oxygen in fixed or portable oxygen containers or systems intended for commercial or private aircraft use. ABO meets USP specifications for oxygen and has special moisture and/or other limiting characteristics. We recommend against the use of ABO for recreational inhalation or medical therapeutic treatment of humans or animals.

Process validation: Documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (see the FDA guidance, *General Principles of Process Validation*).

Storage tank or stand tank: A large cryogenic stationary holding tank with a capacity of several thousand to several million gallons/liters of a liquid product.

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.

United States Pharmacopeia /National Formulary (USP/NF): A reference containing a select list of articles in the form of monographs. Included in each monograph are the standards for determining the identity, strength, quality, and purity of the articles. Except for medical gases approved under a new drug application or an investigational new drug application, manufacturers can use the specifications for single medical gases described under the individual medical gas monograph. Medical gas mixtures are not listed in the USP.

Wrap-around label: A 360-degree label that encircles and is applied to the top of large cryogenic containers. We recommend the lettering on the label be at least 2¾ inches high and

contain the name of the medical gas. The Agency recommends that the medical gas name be repeated so that the name can be visible when viewed from all angles. We also recommend one of the following: (1) the name of the medical gas (text) in the standard color for that medical gas with a white background or (2) the background in the standard color for that medical gas with the name of the medical gas (text) in white (See Color Code examination).