COMPRESSED GAS ASSOCIATION, INC.
THE STANDARD FOR SAFETY SINCE 1913

GASES AND WELDING DISTRIBUTORS ASSOCIATION

21 CFR PROPOSED CHANGES CGA - GAWDA

FDA Public Workshop

FDA's White Oak Campus, Silver Spring, MD

December 15, 2017

Presenter: Michael Tiller, CGA President and CEO

OVERVIEW

- Background
- CGA Proposals for Regulation Change
  - 21 CFR Parts 210/211
  - 21 CFR Part 205
  - 21 CFR Part 201

Designated Medical Gases Background

- **CGA welcomes this opportunity to work with FDA to develop appropriate and effective medical gas regulations.**
- Today's workshop is the culmination of decades of interactions with FDA where we have agreed existing federal regulations are not a good fit for medical gases.
- On September 28, 1978, the final FDA CGMP regulations stated "the Commissioner intends to propose at future times CGMP regulations for specific classes of drug products such as . . . compressed medical gases." (43 Fed. Reg. 45026 (1978)).
- On June 30, 2015, FDA provided a report to Congress that stated that various FDA regulations "generally should not be applied to medical gases" and "are generally not well-suited for medical gases."

Designated Medical Gases Background

- **Executive Orders 13771 and 13777 provide the perfect opportunity to address long-standing FDA regulatory issues.**
- EO 13771: “it is essential to manage the costs associated with the governmental imposition of private expenditures required to comply with Federal regulations.”
- EO 13777: “It is the policy of the United States to alleviate unnecessary regulatory burdens placed on the American people.”

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Designated Medical Gases Background

- **Regulatory Review will also help meet statutory obligations.**
  - The Consolidated Appropriations Act of 2017 (Public Law 115-31) Section 756 requires "The Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs, shall issue final regulations revising the Federal drug regulations (as defined in section 1112(c) of such Act (21 U.S.C. 360dd note)) with respect to medical gases not later than July 15, 2017."
- **House and Senate Fiscal Year 2018 FDA appropriations report language**
  - FDA to hold a public meeting, provide a written report by December 31, 2017, and issue final regulations by July 15, 2018

FDA and Industry Standards in Basic Agreement

- Based on:
  - previous discussions in 2003/2004;
  - the fact FDA has shared industry voluntary consensus standards with their district offices; and
  - recent enforcement history.
- We are unaware of any difference of opinion on the merits of the suggested changes.

Designated Medical Gases Background

- **Based off a thoughtful review of FDA's regulations, we have grouped the changes we propose into essentially two categories:**
  1. SAFETY: Regulations where compliance would make medical gases unsafe
  2. REGULATORY BURDEN: Regulations where compliance is impossible or impractical and therefore creates a federal and/or state enforcement regulatory burden

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21 CFR Parts 210 and 211

Regulatory Review Changes
21 CFR Part 210

Section	Issue
§210.3 (23)	Add a definition of Designated Medical Gas to Part 210

Regulatory Review Changes
21 CFR Part 211

Safety Concerns

- The following section numbers need modifications to be effective and appropriate for medical gases because:
  - compliance with the regulations could cause safety risks to patients and/or personnel handling these products; or
  - the regulations would be safer with the proposed changes.
- Given these regulations are specific, they must be amended or a separate section of the regulations must be created for medical gas to address safety risks.
- Guidance represents “current thinking” and cannot alter regulatory obligations, therefore these changes must be made by regulation.
- State regulations require compliance with federal regulations, so federal enforcement discretion will not resolve the regulatory burden.

Regulatory Review Changes 21 CFR Part 211

- The following proposed changes/additions reflect directly impact Designated Medical Gas **SAFETY**:

Section	Safety Issue
§211.56(e)	Exemption from environmental controls that if enforced may lead to unsafe conditions for the manufacture and storage of medical gases. The external environment does not have an effect on medical gases' due to being maintained in closed pressurized systems.
§211.65(c)	Addition of appropriate controls related to equipment to prevent mix-ups
§211.68(c)	Addition of appropriate engineering controls for automatic, mechanical and electronic equipment used in the manufacture of medical gases where the current regulation is inadequate and failure to require the proposed information could have a negative impact on safety
§211.82(a) and (b), §211.84(f) and §211.85	The exemption provided in §211.82(a) and (b) and §211.84(f) and the added requirements under new section §211.85 for testing and approval of Designated Medical Gas components, containers and closures adds safety compliance requirements that are unique for the medical gas industry, where many aspects of the current §211.84 are inappropriate or inadequate for medical gases
§211.94(e)(1) and (2)	Modification of FDA's language regarding medical gas outlet connections to eliminate the base unit and modify the label and coloring requirements regarding where or inadvertent detachment.
§211.134(d)	Adds the requirement for critical 100% inspection of labeling during the container filling process as opposed to the inadequate sampling required by the current regulation, thereby assuring all medical gas product containers are properly labeled
§211.182	Clarifies the appropriate equipment cleaning and maintenance requirements for medical gases and associated documentation. The current regulations, if strictly followed significantly increases the risk of contamination. Batch or lot cleaning frequency is not necessary as medical gases are manufactured and stored using closed pressurized systems

Regulatory Review Changes 21 CFR Part 211

Relieving **REGULATORY BURDENS**

- The following section numbers need modifications to be effective and appropriate for medical gases because they are impossible or impractical for medical gas.
- Given these regulations are specific and impose a clear regulatory burden, these regulations must be amended or a separate section of the regulations must be created for medical gas.
- Guidance represents “current thinking” and cannot alter regulatory obligations, therefore these changes must be made by regulation.
- State regulations require compliance with federal regulations, so federal enforcement discretion will not resolve the regulatory burden.

Regulatory Review Changes
21 CFR Part 211

- Industry has been cited in federal or state cGMP inspections for failure to follow most of the listed regulations.

Section	Issue
§211.22(e)	Quality Control Unit for small manufacturers of medical gases
§211.28(a)	Personal health and sanitation habits not critical to medical gases
§211.42(e); §211.46(e); §211.67(b); §211.80(c); §211.101(b), (c), (d), (e); and §211.142(b)	Environmental conditions and medical gases in closed pressurized systems, impacting storage, incoming receipts, cleaning, production and analysis
§211.44	Regarding lighting
§211.80(d)	Exemption for incoming inspection of new and reused medical gas containers (100% inspection during fill)
§211.86	FIFO and commingling of components
§211.87	Medical gas components, containers, and closures not impacted by length of storage and other storage conditions
§211.101(a)	Formulating for 100% of “active” ingredients not appropriate for medical gases.
§211.103	Calculation of Yield
§211.105(c)	Dedicated equipment
§211.122(i)	Acceptability of reusing medical gas labels provided they meet all appropriate requirements.

Regulatory Review Changes
21 CFR Part 211

Section	Issue
§211.125(c) and (g)	Label reconciliation for medical gas lot labels and 360° degree wraparound "labels"
§211.130(f) and (g)	The unique reuse of product labels
§211.137(i); §211.150(a); §211.166(e); §211.180(a), (b); and §211.198(b)	Expiration Dating and its impact on FIFO, record retention and stability studies
§211.170	211.170(c) regarding exemption from reserve samples (moved from 211.170(b) at end of sentence)
§211.184(a) and (c)	Revised to exempt identifying and quantifying medical gas components, containers, and closures receipts and inventory records.
§211.186(b) and (c)	Long-standing industry practice regarding SOPs in lieu of traditional Master production and control records used in the traditional pharmaceutical industry
§211.188(c) and §211.189	The uniqueness of medical gases and the need for an appropriate separate section of the regulation to address medical gas batch production and control records
§211.192	Record review and container prefill and fill failures do not require investigation
§211.194(a)(4) and (5)	Type of analytical equipment used in the medical gas industry as it relates to visual outputs
§211.196	Adding dosage form to the existing exemption.
§211.204	Residual product in cryogenic medical gas containers not being considered "returned" drug product
§211.208	Salvaging of medical gases under certain conditions.

21 CFR Part 205

Regulatory Review Changes
21 CFR Part 205

- The changes listed are necessary to be consistent with other proposed changes or to be appropriate for medical gases.

Section	Issue
§205.50(a)(6)	Facility size, construction, lighting, HVAC, quarantine, cleanliness, pest control
§205.50(c)	Non-applicability of temperature control and other conditions of storage
§205.50(b)(2)	Establishes a minimum requirement upon the states to require firms to have after hours alarm systems. The proposed change adds flexibility to a security regulation for Designated Medical Gases that are not subject to theft or diversion.
§205.3	Adding a definition for Designated Medical Gas
§205.3	Allowing for emergency use oxygen
§205.50(h)	Limiting the reporting of duties to those related to wholesale distribution

- The National Association of Boards of Pharmacy (NABP) has a specific model rule for the wholesale distribution of Designated Medical Gases. Our proposed changes to 21 CFR Part 205 would harmonize the federal regulation with the NABP model rule.

21 CFR Part 201

Regulatory Review Changes 21 CFR Part 201

- The changes to 201 include:
  - safety related issues;
  - issues not addressed by the changes in the 2016 Medical Gas Containers / Closure Rule;
  - those necessary to reflect current industry operations and to prevent violations when strictly enforced; and
  - those contingent on other changes.

Regulatory Review Changes 21 CFR Part 201

- Safety related issues

Section	Issue
§201.100(a)(1)(iv)	This change will permit persons to possess prescription Designated Medical Gases for purposes of purging and cleaning containers, including medical gas piping, to ensure that non-medical grade product is not used for purging and cleaning.
§201.161(a)(1)(iii)	Adds the Warning statement for medical air, that is a designated medical gas not currently addressed in 201.161. The labeling recommended is consistent with industry practice
§201.161(a)(2)	Adds to the existing required directions to include "transportation" and additional statements required by other federal agencies such as OSHA and DOT as specified in publication CGA C-7 and supplemental statements per the current USP
§ 201.328(a)	Eliminate the term "base unit" and other issues related to containers used by patients used within their home.

Regulatory Review Changes
21 CFR Part 201

- Changes needed to 201.161 not addressed by 2016 Medical Gas Containers / Closure Rule

Section	Issue
§201.161(a)	Eliminates a list of specific gas names, substituting Designated Medical Gases for the list and adds in a critical exemption from the "adequate directions for use" requirement of §201.5;
§201.161(g) new	Oxygen provided in liquid oxygen home units
§201.161(b)	Exemption of labeling for open topped nitrogen dewars
§201.161(h) new	Labeling of non-final use medical gas containers
§201.161(c)	Mixtures of Designated Medical Gases and replacing 201.100(b)(4) and 201.10(d)(2)
§201.161(d)	Medical container labeling reuse, lot number decals as ancillary decals, and replacing 201.100(b)(6)
§201.161(e)	Manufacturer name and replacing 201.100(e)
§201.161(f) and (f)(1) thru (f)(5)	Net quantity of contents labeling for various modalities and type of container of Designated Medical Gases and mixtures thereof

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EXAMPLES OF A BASE UNIT

Regulatory Review Changes
21 CFR Part 201

- Changes outside of 201.161 are necessary to reflect current industry operations and to prevent violations when strictly enforced.

Section	Issue
§201.1(b) and §201.1(d)	The manufacturing operations associated with Designated Medical Gases, including the concept of subsequent manufacturer.
§201.1(h)(2)	Permanent DOT markings on cylinders not considered "labeling" even though the stamped markings are "on" (actually stamped into) the container
§201.1(h)(7)	The use of "Property Of" stickers on Designated Medical Gas containers

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Regulatory Review Changes
21 CFR Part 201

- Depending on the changes to 201.161, the following may not be needed:

Section	Issue
§201.10(d)(2)	Percentages of ingredients ion designated medical gas mixtures
§201.18	Lot/ control numbers more correctly stated in 201.161
§201.51(i)	Net quantity of contents more correctly stated in 201.161
§201.56(e)	Labeling for "older" drugs
§201.100(b)	Prescriptions for drugs
§201.105	Labeling for veterinary drugs
§201.128	Exemption for Designated Medical Gases from labeling to indicate intended uses

WHY COORDINATION IS IMPORTANT

- The need to update FDA's regulation of medical gas has been recognized since 1978
- Medical gas manufacturing is unique in many ways as compared to other FDA regulated drug product categories
- CGA publication M-15 is a voluntary consensus standard that includes text that proposes updates to FDA's existing regulations for medical gases
- CGA and GAWDA stand ready to ensure FDA has the feedback and knowledge of the industry necessary to draft a comprehensive regulatory review for medical gases consistent with EO 13771 and 13777 and Section 756 of the Consolidated Appropriations Act of 2017.

ITEMS FOR FEBRUARY 9, 2018

- 21 CFR 207
- 21 CFR 314
- Others identified during this workshop and questions posed by FDA
- Other items FDA would like to discuss

THANK YOU FOR YOUR TIME

For questions regarding this presentation, please contact Michael Tiller at mtiller@cganet.com

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