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

GASES AND WELDING DISTRIBUTORS ASSOCIATION

# 21 CFR PROPOSED CHANGES CGA - GAWDA

## FDA Public Workshop III

## FDA's White Oak Campus, Silver Spring, MD

## 11 May 2018

**Presenter: Michael Tiller, CGA President and CEO**

# OVERVIEW

- Address FDA's questions, comments, concerns on CGA-GAWDA's submissions for
  - 21 CFR Part 2XX/211
  - 21 CFR Part 201
  - 21 CFR Part 3XX/314
    - DMG Manufacturing and Distribution Scheme
- Address FDA's questions, comments, concerns on CGA-GAWDA's submissions for
  - 21 CFR Part 205
  - 21 CFR Part 207
- FDA Access to Experts with DMG Experience

# ADDRESS FDA'S QUESTIONS, COMMENTS, CONCERNS ON CGA-GAWDA'S SUBMISSIONS FOR: 21 CFR PART 2XX

# 21 CFR Part 2XX Sections

- 21 CFR Part 210
  - §210.3 (23) Definitions
- Subpart A—General Provisions
  - § 2XX.1 Scope
  - § 2XX.3 Definitions
- Subpart B—Organization and Personnel
  - § 2XX.22 Responsibilities of quality control unit
  - § 2XX.25 Personnel qualifications
  - § 2XX.34 Consultants
- Subpart C—Buildings and Facilities
  - § 2XX.42 Design and construction features
- Subpart D—Equipment
  - § 2XX.63 Equipment design, size, and location
  - § 2XX.65 Equipment construction
  - § 2XX.67(a) Equipment maintenance
  - § 2XX.67(b) Equipment cleaning for product contact surfaces
  - § 2XX.68 Automatic, mechanical, and electronic equipment
- Subpart E—Control of Components and DMG Drug Product Containers and Closures
  - § 2XX.80 General requirements
  - § 2XX.85 Testing and approval or rejection of designated medical gas components, containers, and closures
  - § 2XX.89 Rejected components, DMG drug product containers, and closures
  - § 2XX.94 DMG Drug product containers and closures

# 21 CFR Part 2XX Sections

- Subpart F—Production and Process Controls
  - § 2XX.100 Written procedures; deviations
  - § 2XX.101 Charge-in of components
  - § 2XX.110 Sampling and testing of in-process materials and DMG drug products
  - § 2XX.115 Reprocessing
- Subpart G—Packaging and Labeling Control
  - § 2XX.122 Materials examination and usage criteria
  - § 2XX.125 Labeling issuance
  - § 2XX.130 Packaging and labeling operations
- Subpart H—Holding and Distribution
  - § 2XX.150 Distribution procedures
- Subpart I—Laboratory Controls
  - § 2XX.160 General requirements
  - § 2XX.165 Testing and release for distribution for original and subsequent manufacturing operations
- Subpart J—Records
  - § 2XX.180 General requirements
  - § 2XX.184 Component, DMG drug product container, closure, and labeling records
  - § 2XX.186 Master production and control records
  - § 2XX.189 Production and control records for designated medical gases
  - § 2XX.192 Production record review
  - § 2XX.194 Laboratory records
  - § 2XX.196 Distribution records
  - § 2XX.198 Complaint files
- Subpart K—Returned and Salvaged DMG drug products
  - § 2XX.204 Returned DMG drug products
  - § 2XX.208 DMG drug product salvaging

# ADDRESS FDA'S QUESTIONS, COMMENTS, CONCERNS ON CGA-GAWDA'S SUBMISSIONS FOR: 21 CFR PART 201

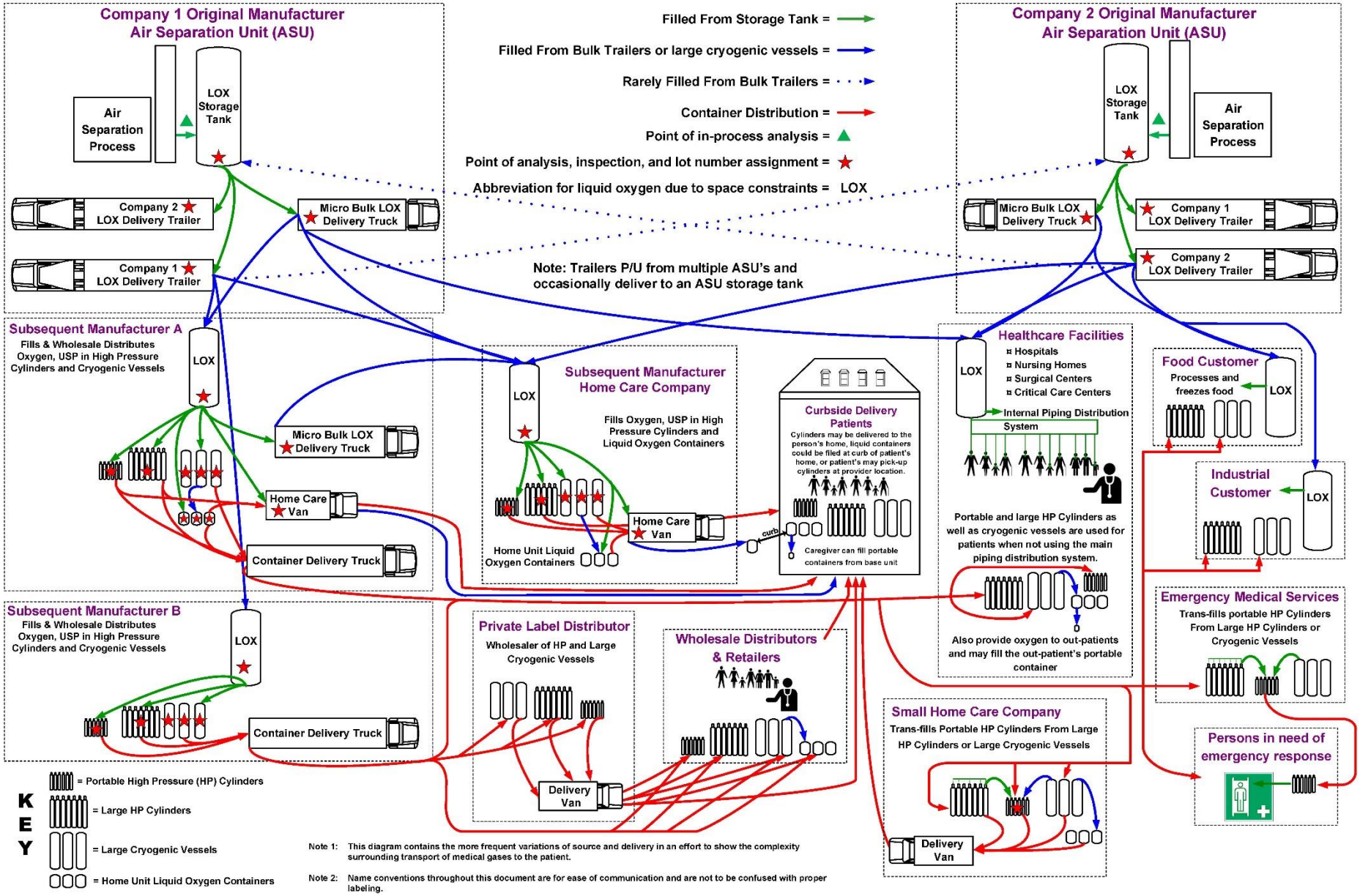
# Regulatory Review Changes 21 CFR Part 201

- Part 201 Labeling
  - § 201.1(b) Drugs; name and place of business of manufacturer, packer, or distributor
  - § 201.1(x) Drugs; name and place of business of manufacturer, packer, or distributor
  - § 201.1(d) Drugs; name and place of business of manufacturer, packer, or distributor
  - § 201.1(h) Drugs; name and place of business of manufacturer, packer, or distributor
  - § 201.100 Prescription drugs for human use
  - § 201.105 Veterinary drugs
  - § 201.128 Meaning of “intended uses”
  - § 201.161 Medical gases.
  - § 201.328(a) Labeling of medical gas containers

# 21 CFR Part 314/3XX

- DMG Manufacturing and Distribution Scheme
- Address FDA's questions, comments, concerns on CGA-GAWDA's submissions for: 21 CFR Part 314/3XX

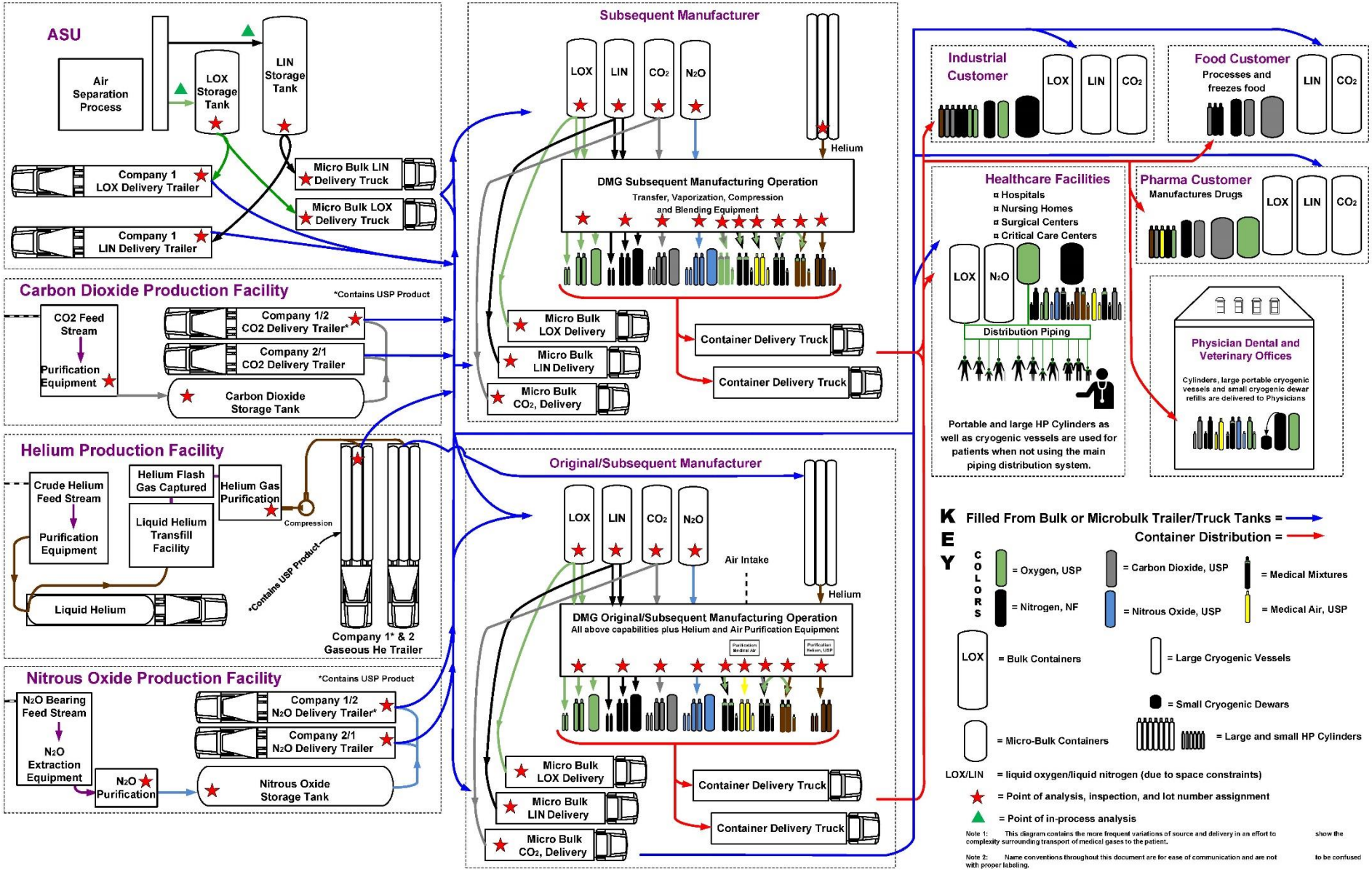
# Page 1 of 2: DMG Oxygen, USP Manufacturing and Distribution Scheme



# DMG Oxygen, USP Manufacturing and Distribution Scheme (Page 1)

- Original manufacturers:
  - Company 1 Original Manufacturer Air Separation Unit (ASU)
  - Company 2 Original Manufacturer Air Separation Unit (ASU)
- Subsequent manufacturers:
  - Subsequent Manufacturer A
  - Subsequent Manufacturer B
  - Subsequent Manufacturer Home Care Company
    - Also a DMG curbside filler
- Wholesalers and Customers:
  - Private Label Distributor
  - Wholesale distributor and retailers
  - Curbside delivery patients
  - Healthcare delivery patients
  - Small home care company
  - Healthcare facilities
  - Food customer
  - Industrial customer
  - Emergency medical service
  - Persons in need of emergency response

# Page 2 of 2: Other DMG Manufacturing and Distribution Scheme



# Other DMG Manufacturing and Distribution Scheme (Page 2)

- Original manufacturers:
  - ASU
  - Carbon Dioxide
  - Helium
  - Nitrous Oxide
- Subsequent manufacturer:
  - Single component filler
  - Mixture manufacturer
- Original/Subsequent manufacturer:
  - Same as above subsequent manufacturer, except:
    - Helium purification
    - Air by compression
- Customers:
  - Healthcare facilities
  - Industrial customers
  - Food customers
  - Pharm customers
  - Physician, Dental, and Veterinary Offices

# DMG Manufacturing and Distribution Scheme

- Many points of analysis during manufacturing/distribution;
  - ▲ Triangle reflects point of in-process analysis
  - ★ Star reflects point of analysis, inspection, and lot number assignment
- Comingling in all liquid containers
  - Storage tanks
  - Cryogenic Delivery trailers
  - Micro Bulk Delivery [trucks]
  - Large Cryogenic Containers
- SWAPS
  - where one company will pick up product from another company and comingle it with their product.
  - Company 1 trailer at Company 2's ASU or Production site
  - Company 2 trailer at Company 1's ASU or Production site

# EXAMPLES OF A BASE UNIT

# Address FDA's questions, comments, concerns on CGA-GAWDA's submissions for: 21 CFR Part 314/3XX

# 21 CFR Part 3XX Sections

- § 314.1 Scope
- Subpart A—General Provisions
  - § 3XX.1 Scope
  - § 3XX.2 Purpose
  - § 3XX.3 Definitions
- Subpart B—Certification of designated medical gases
  - § 3XX.50 Requesting a certification
  - § 3XX.70 Amendments and other changes to an approved certification
  - § 3XX.XX Responsibilities of Subsequent Manufacturers of Designated Medical Gases and Curbside Fillers
  - § 3XX.100 FDA Review of Certification Requests
  - § 3XX.102 Communications between FDA and certification requestor
  - § 3XX.105 Approval of a request for certification
  - § 3XX.125 Refusal to approve a request for certification
  - § 3XX.150 Revocation of Certification; Withdrawal or Suspension of Approval Withdrawal of approval of an application
  - § 3XX.152 Notice of withdrawal of approval of a certification
- Subpart J—Adverse Drug Experiences
  - § 3XX.80 Reporting of designated medical gas adverse drug experiences
  - § 3XX.81 Other reports
- Subpart G—Miscellaneous Provisions
  - § 3XX.410 Imports and exports of DMGs or combinations of DMGs
  - § 3XX.170 Adulteration and misbranding of a designated medical gas

# ADDRESS FDA'S QUESTIONS, COMMENTS, CONCERNS ON CGA-GAWDA'S SUBMISSIONS FOR: 21 CFR PART 205

# Regulatory Review Changes
# 21 CFR Part 205

- 21 CFR § 205
  - § 205.3(i) Definitions
  - § 205.3(j) Definitions
  - § 205.50(a) Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.
  - § 205.50(b) Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.
  - § 205.50(c) Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.
  - § 205.50(h) Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.

- 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.

# ADDRESS FDA'S QUESTIONS, COMMENTS, CONCERNS ON CGA-GAWDA'S SUBMISSIONS FOR: 21 CFR PART 207

# Overview of Proposed System Modifications

- No proposed regulatory changes to Part 207
- Meet with eDRLS staff to address current workarounds for almost 50% of facility inventory
- Changes are needed to the eDRLS system used to implement these regulations for DMGs
- Develop guidance once modification are made.

# Overview of Proposed System Modifications

- Modifications needed to address various workarounds when using the electronic drug registration and listing system (eDRLS) to address the uniqueness of Designated Medical Gases and Designated Medical Gas Mixtures.
  - NDA numbers for Subsequent Manufacturers; and DMG Curbside Fillers
  - Active Ingredient Issues in mixtures
  - Medical Air Issues
  - Concentration fields to allow for ranges
  - Package type and volume – package code;
  - Label for Bulk containers;

# FDA Access to Experts with DMG Experience during Rulemaking

# Access to Experts with DMG Experience

- During the December 15th Workshop there was a discussion of FDA's interest in having access to DMG regulatory experts during rulemaking
- We are committed to ensure FDA has the information and access to resources to complete the rulemaking process consistent with the Administrative Procedures Act
- Options:
  - Hiring a DMG consultant
  - Engaging in Negotiated Rulemaking

# Access to Experts with DMG Experience

- Hiring a DMG consultant
  - If FDA determines that hiring a DMG regulatory consultant during the rulemaking process is the best solution, we can provide a list of DMG regulatory experts we are aware of in this space

# Access to Experts with DMG Experience

- Engaging in Negotiated Rulemaking
  - 5 U.S. Code Subchapter III
  - Congress authorized agencies to establish negotiated rulemaking committees when:
    - "it enhances the informal rulemaking process"
    - "there are a limited number of identifiable interests that will be significantly affected by the rule"
    - "there is a reasonable likelihood…[participants] are willing to negotiate in good faith to reach a consensus on the proposed rule"

# Access to Experts with DMG Experience

**5 U.S. Code § 563 - Determination of need for negotiated rulemaking committee**

**(a)Determination of Need by the Agency.**—An agency may establish a negotiated rulemaking committee to negotiate and develop a proposed rule, if the head of the agency determines that the use of the negotiated rulemaking procedure is in the public interest. In making such a determination, the head of the agency shall consider whether—

(1) there is a need for a rule;

(2) there are a limited number of identifiable interests that will be significantly affected by the rule;

(3) there is a reasonable likelihood that a committee can be convened with a balanced representation of persons who—

(A) can adequately represent the interests identified under paragraph (2); and

(B) are willing to negotiate in good faith to reach a consensus on the proposed rule;

(4) there is a reasonable likelihood that a committee will reach a consensus on the proposed rule within a fixed period of time;

(5) the negotiated rulemaking procedure will not unreasonably delay the notice of proposed rulemaking and the issuance of the final rule;

(6) the agency has adequate resources and is willing to commit such resources, including technical assistance, to the committee; and

(7) the agency, to the maximum extent possible consistent with the legal obligations of the agency, will use the consensus of the committee with respect to the proposed rule as the basis for the rule proposed by the agency for notice and comment.

# OTHER TOPICS

# Nitrogen Open Topped Dewars

- Concept of Requiring locations delivering into open top dewars to register
  - What safety improvement is expected since there have been no safety issues related to delivering liquid nitrogen into dewars?
- Adds burden
  - Registering with eDRLS;
  - Register with state as a manufacturer with related state regulatory requirements and fees;
  - Adds federal regulatory requirements under today's 21 CFR Part 211 (lot numbers, labeling, QCU, final product testing, etc.);
  - Staffing a federal or state inspection.
- Potential consequences of added burden
  - Companies may decide not to have their delivery locations provide product;
  - Delivery locations may require customers to fill their own containers utilizing less experienced individuals.
- Conclusion: This change adds burden with no safety improvement
  - Cannot improve existing safety record
  - Change could result in injury as less trained people transfer cryogenic temperature product from one container to another.

# EMS and Health Care Facilities Filling Locations

- Emergency Medical Services and Health Care Facilities performing manufacturing or subsequent manufacturing functions
  - Not required to be registered/listed
  - Not subject to routine inspections
  - Often not following important CGMP provisions
    - QCU, training, equipment calibration, control of components, evacuation, labeling, records, lot number, finished product testing, release, recall systems
  - Often not following industry standards protecting their personnel from unsafe practices
    - Pre-fill inspection steps of containers, replacing washers
  - Often filling cylinders without permission of the owner (in violation of DOT regulations) and performing subsequent manufacturing operations yet leaving prior manufacturer's labels on container.
  - Serving most highly vulnerable patient population – most in need of CGMP protections
- Concern for safety of EMS and HCF personnel as well as product integrity through following:
  - CGA P-2.5, *Transfilling of high pressure gaseous oxygen used for respiration,* for gaseous
  - CGA P-2.6, *Transfilling of Liquid Oxygen Used for Respiration,* for liquid

# Additional Topics Identified by FDA in FR Notice to be discussed

- FDA has also indicated interest in discussing medical gases as drugs and the intersection of those regulations with:
  - regulations for animal drugs?
  - regulations for medical devices?
  - 93% oxygen?

# FINAL THOUGHTS

- Any further questions on the CGA – GAWDA proposals for modification and separate regulations
- Any additional questions posed by FDA

# THANK YOU FOR YOUR TIME

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