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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

9 Feb 2018

Presenter: Michael Tiller, CGA President and CEO

OVERVIEW

- Response to FDA Questions from Workshop 1:
  - Separate section(s) for Designated Medical Gases
- Common definitions
- CGA Proposals for Regulation Change
  - 21 CFR Part 314/3XX
  - 21 CFR Part 207
  - 21 CFR Part 210 and 211/2XX

Separate Sections for Designated Medical Gases

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- Considered separate sections for 201, 205, 207, 210, 211 and 314.
- Based on a review of the safety issues and regulatory burdens and the potential for unintended consequences to non-DMG, we believe separate sections would be most important for 211 and 314.
  - We refer to these as 2XX and 3XX later in the presentation
  - Could be argued 2XX and 3XX should be merged into one comprehensive DMG section
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Definitions of Medical Gas Operations 21 CFR Parts 201.1, 207.3, 2XX.3, 3XX.3

- Original Manufacturer:
  - means the person or entity that initially produces a designated medical gas by chemical reaction, physical separation, compression of atmospheric air, purification (e.g., re-processing an industrial gas into a medical gas), or other means.
  - Requires obtaining an NDA/NADA number
- Subsequent Manufacturer:
  - means the person or entity that fills a certified designated medical gas into containers by any one of the following methods:
    - Liquid to gas
    - Liquid to liquid (other than the filling of cryogenic containers at the final use customer's location)
    - Gas to gas
    - Mixing two or more certified designated medical gases
  - Does not obtain an NDA/NADA number
- Designated medical gas (DMG) curbside filler:
  - means a person or entity filling a DMG via liquid to liquid into a final use container at the point of use.
  - Does not obtain an NDA/NADA number

21 CFR PART 314/3XX

§314/ GOALS FOR §3XX

- Why CGA proposes §3XX
  - Adverse Events
    - In absence of NDA process, §3XX defines unexpected adverse drug experience for DMG based on label
    - Establishes logical reporting system:
      - Avoids reporting on millions of people who experience a serious adverse event (e.g. death) when on oxygen;
      - Avoids massive duplication of reporting an a single event;
      - Put responsibilities on original manufacturers to submit meaningful DMG adverse event reports provided by physicians, since DMG manufacturers made no medical claims and have no medical expertise to evaluate legitimacy of news articles or internet postings.
  - Approval of Designated Medical Gases (DMG)
    - Sets DMG Certification Process into regulation and establishes revision process, missing from current regulation and guidance

§3XX Overview

- Exemption for DMG per proposed §314.1(c)
- How did CGA develop 3XX
  - Definitions – will discuss twice: first for ADE and second for Certification
  - DMG Adverse Drug Experiences
  - Other Items (e.g. drug shortage, import/export)
  - Initial Certification
  - Revisions and Updates to Certification

Designated Medical Gas Adverse Drug Experiences and ADE Definitions

- Types of operations (previously discussed)
- How DMG ADEs differ from traditional pharmaceutical ADEs
- Adverse Drug Experience (ADE) (*Lines 68 – 73*)
  - Life Threating ADE (*Lines 75 – 78*)
  - Serious ADE (*Lines 79 – 86*)
  - Unexpected ADE (*Lines 87 – 92*)

ADVERSE DRUG EXPERIENCES

- Reporting of DMG ADEs §3XX.80
  - Review of DMG ADE *(Lines 262 – 274)*
    - Purpose of literature searches are to confirm or expand on contraindications listed on the NDA
    - Since DMG were approved without listed contraindications, original manufacturers of DMGs are not required to review literature but are required to report on adverse events communicated by physicians
  - Reporting Requirements *(Lines 275 – 320)*
    - 15-day alert reports and follow-up
    - Subsequent Manufacturers / DMG Curbside fillers
  - FDA Form 3500A *(Lines 321 – 336)*
    - Request FDA to update regulation consistent with electronic reporting requirements - paper form described in 21 CFR 314 is no longer accepted

ADVERSE DRUG EXPERIENCES

- Other requirements
  - Patient privacy *(Lines 337 – 343)*
  - Recordkeeping *(Lines 344 – 346)*
  - Withdrawal of certification *(Lines 347 – 350)*
  - Disclaimer *(Lines 351 – 359)*

OTHER REPORTS §3XX.81

- Applicability – Reports under section 505(k) of the Act *(Lines 361 and 362)*
- NDA Field Alert Reports *(Lines 365 – 375)*
- Notification of Discontinuance – Shortages *(Lines 382 – 475)*
- General requirements - Patient Identification *(Lines 477 – 485)*
- Withdrawal of certification *(Lines 486 – 488)*
- Annual Report exemption *(Lines 376 and 377)*

Other Items in §3XX

- Miscellaneous Provisions (§3XX.410)
  - Imports *(Lines 493 – 499)*
  - Exports *(Lines 500 – 501)*
  - Adulteration and misbranding (similar to §314.170) *(Lines 503 – 506)*

Definitions related to Certification

- Types of Operations (previously discussed)
  - Original manufacturer (*Lines 56 – 58*)
  - Subsequent manufacturer (*Lines 60 – 67*)
  - DMG curbside filler (*Lines 53 – 55*)
- For Purposes of Designated Medical Gases
  - Certification (*Line 43 – 48*)
  - Designated Medical Gas (DMG) (*Line 49 – 52*)

INITIAL CERTIFICATION §3XX.50

- Who should submit (*Line 97 – 105*)
- Who should not submit (*Line 106 – 111*)
- What information is submitted (*Line 112 – 149*)
  - Requestor information
  - Type of Submission – generally an original certification request
  - Description of the Medical Gas for which certification is sought
  - Facility information
    - Where manufactured, DUNS, FDA Establishment
    - Brief description of manufacturing or processing used
  - Affirmation
- Where and how to submit (*Line 150 – 154*)

FDA Responsibilities Regarding Certification

- FDA responsibilities
  - Review (§3XX.100)
  - Communication (§3XX.102)
  - Approval, refusal to approve, revocation of approval and notice of approval withdrawal (§3XX.105, §3XX.125, §3XX.150, §3XX.152)

AMENDMENTS TO CERTIFICATIONS §3XX.70

- To amend/update granted certifications
  - Original manufacturer submits update to its eDRLS data with the appropriate changes within 5 days of the change.

- This would include when an original manufacturer:
  - Closing a site
  - Opens a new site
  - Ceases production of a specific DMG at one or more sites
  - Starting production of a specific DMG
  - Change of ownership

Subsequent Manufacturers and DMG Curbside Fillers

- Annual Verification and documentation of DMG certified source
- Listing of NDA/NADA numbers on their drug listing
  - via the eDRLS process per 21 CFR Part 207

21 CFR Part 207

Overview of Proposed Changes to 21 CFR Part 207

- In our September 10, 2013 letter to the Agency we identified 12 proposed changes to Part 207, most of which reflected changes where the regulation was obsolete at that time.
- On January 10, 2014, CGA and GAWDA held a meeting with Paul Loebach and the FDA registration and listing team. During our January 10th meeting with the Agency to discuss the electronic registration and listing process, the Agency indicated that it was in the process of revising Part 207 for all drugs.
- On August 31, 2016 FDA published a Final Rule based its 2006 Proposed Rule. CGA had commented on the proposed rule at the time and FDA responded to some comments in the preamble to the Final Rule.
- Changes to Part 207 are needed for definitions. It may be possible to use guidance to address some of our other issues but would like to discuss them now for your consideration.

21 CFR Part 207

- Part 207 is generally an administrative regulation - no real safety issues.
- DMG firms need 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.
- We would like to address and fix some specific issues:
  - Definitions;
  - Package type and volume – package code;
  - Label;
  - NDA numbers for Subsequent Manufacturers;
  - Medical Air Issues; and
  - Active Ingredient Issues – Mixtures.

Recent Enforcement Changes Regarding 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.

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21 CFR Part 210 and 211/2XX

21 CFR Part 2XX Examples of Specificity and Exemptions Avoided

- Examples of Improved Specificity:
  - Cylinder and valve pre-fill inspection;
  - Comingling;
  - QCUs;
  - COAs;
  - Stronger focus on avoiding mix-ups;
  - Color coding;
  - Brazed locked connections;
  - DMG Labeling;
  - Cylinder markings;
  - Production/Control records differ based on continuous operation vs batch vs transfilling vs filling liquid at customer site; and
  - Container closure systems.
- Examples of necessary exemptions avoided in 21 CFR 211:
  - Expiration dates;
  - Stability studies;
  - Calculation of Yield; and
  - Periodic cleaning/sanitizing.

21 CFR Part 2XX Sections

- 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
- 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
- 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

21 CFR Part 2XX Sections

- 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

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?

FDA Public Workshop 3

- Detailed discussion on industry proposal for §2XX and §3XX
- Any further questions on:
  - §201;
  - §205; and
  - §207.
- Any additional questions posed by FDA

THANK YOU FOR YOUR TIME

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