REVIEW ARTICLE

An Overview of Regulatory Guidelines for Medical Gases

Lakshmi Prasanthi Nori, Gudala Vasantha Lakshmi, Sushma Naidu M, Vyasam Vishnu Vardhan, Eda Sujan Wesly, K. S. Nataraj, K. Venkateswara Raju

Department of Regulatory Affairs, Shri Vishnu College of Pharmacy, Bhimavaram, Andhra Pradesh, India

Abstract

Direct administration or supply of medical gases to patients is dangeous. Regulatory guidance requirements of various regulatory agencies, the highest quality should be used in their manufacture and transfer. The manufacturer of medical gases requires a license or regulatory approval to manufacture the gases; thus, they must maintain the quality of the gases in accordance with standards or quality limitations established by the drug regulatory authorities. Medicinal gases are manufactured, packed, and designed for patient administration during anesthesia, therapy, or diagnostics. Oxygen, helium, carbon dioxide, nitrous oxide, medicinal air, and nitrogen are officially recognized therapeutic gases. These gases are usually administered preoperatively, intraoperatively, and postoperatively in surgical patients. This gas ignites supplied in an airtight, color-coded, and properly labeled container as required by the relevant regulatory authorities in each country or through the central line runs all over the hospital. Despite all the rules, they are reports on problems related to the production and use of medical gases. In this study, we tried to give a brief overview of regulatory guidelines for medical gases in India and USA.

Key words: Documentation, good manufacturing practice, medical gas, regulatory authorities, standards

INTRODUCTION

Medical gases

Definition

Medical gases are manufactured, packaged, and administered to a patient for anesthesia, treatment, or diagnosis.[1]

Types of medical gas

Gases used in hospital treatments are known as medical gases. Some are used for anesthetic, and treatment, and some are utilized to power medical equipment and tools.

There are seven kinds of gases commonly used: oxygen, nitrogen, nitrous oxide, argon, helium, carbon dioxide, and compressed air.[2]

Vacuum suction and anesthesia gas scavenging systems are further components of the medical gas system.

REGULATORY GUIDELINES FOR MEDICAL GASES IN INDIA

In India

Medical gases are regulated in India by the central drugs standard control organization and the Ministry of Commerce and Industry. There are several acts that can be used to reinforce regulations for medical gases, including the Gas Cylinder Regulations of 2004 and the Explosives Act of 1884, the Drugs and Cosmetics Act (D and C Act) of 1940, and the Medical Gas Requirements in Indian Pharmacopoeia. Sections 5 and 7 of the D and C

Address for correspondence:
K. Venkateswara Raju, Department of Regulatory Affairs,
Shri Vishnu College of Pharmacy,
Bhimavaram - 534 202, Andhra Pradesh, India.
Phone: +91-7702718782.
E-mail: venkateswararaju.k@svcp.edu.in

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Act authorized the proclamation of the 2004 Gas Cylinder Regulations to regulate the filling, possession, transportation, and importation of such gases. Manufacturers of medical gases are responsible for ensuring the uniformity of gases required by drug regulatory agencies.[3]

The Bureau of Indian Standards Act (1986) is significant for the general public, especially vulnerable communities, and those interested in pursuing education and awareness are made available to help facilitate the prompt and accurate dissemination of this data to the wider community. Organizations such as the national fire protection association and the department of transportation (DOT) support gas rules and standards. The approval process of medical gases is depicted in Figure 1.

GAS CYLINDER RULES

Schedules

- Schedule I: Types and standards of cylinders – contains cylinders, containers, and valves from different origins.[4]
- Schedule II: The Inspecting Authority's test and inspection certificates for cylinders and valves produced in accordance with approved design and specification
- Schedule III: Particulars submission to manufacture cylinders, valves, and other fittings
- Schedule IV: Requirement of facilities for cylinder testing
- Schedule V: The fee for the cylinders provision.

GENERAL PROVISIONS

A. Filling, possession, import, and transport of cylinders
Cylinders should not be filled with any compressed gas, imported, possess, or transport any cylinder unless it is approved by Chief Controller.

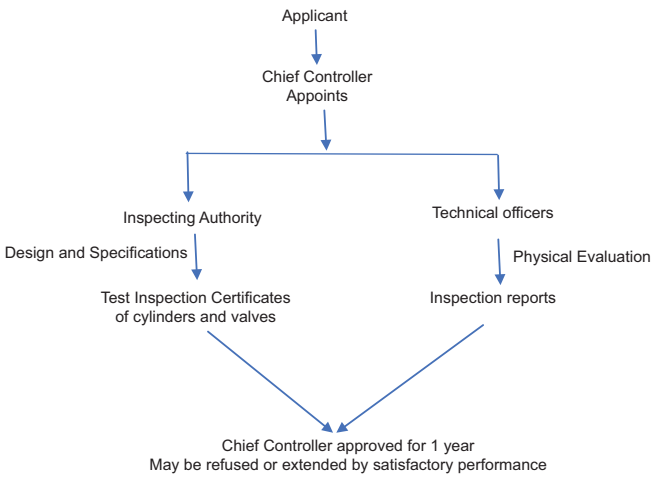

Figure 1: Approval process

The particulars are provided to the Chief Controller –

- The total quantity and serial numbers of the cylinders;
- The name and place of the manufacturers of the cylinders;
- Specification of the cylinders and the valves;
- if applicable, any prior approval;
- The certifications of test and inspection for the cylinders and valves;
- A scrutiny fee as per Schedule V.

B. Flowchart
For a physical evaluation to be included in the approval procedure for foreign producers, an additional fee must be paid. The Chief Controller grants a temporary permit pending a time of physical evaluation and once-every-5-year re-evaluation of the foreign manufacturer's unit.

C. Valve
The following specifications must be fulfilled by valves fitted to gas cylinders:

- An industrial gas cylinder IS0: 3224
- Medical gas cylinders, ISO: 3745
- Cylinders used with breathing apparatus, ISO: 7302

D. Safety relief devices

- Cylinders produced in India should be manufactured and maintained, provided they have safety-relieving devices
- No safety system should be provided for cylinders containing dangerous or hazardous gases
- Cylinders produced in foreign nations that have a license to use them there shall be maintained in accordance with the requirements of the standard to which they were actually made, provided that they are fitted with safety relief devices.[5]

E. Marking on cylinders

- Each gas cylinder must have a distinct, permanently labeled one
- If there is a danger of corrosion, soldering should not be used to attach the nameplate to the cylinder
- Sufficient areas should be provided in accordance with the original marking for the stamping of the test date during the periodic inspection.

F. Markings on the valve

- Cylinder valves should have clearly identified, durable valves.

G. Identification colors

- For medical cylinders, the cylinder is coated with suitable identification colors specified by ISO: 3933.[6] The color coding for medical gas cylinders were shown in Figure 2.

H. Labeling of cylinders

- Each cylinder should include the name and address of the person who filled it with gas as well as the name of the gas.

I. Restriction on delivery or dispatch of cylinders

- This can be accomplished by approving a license and is limited to the number of cylinders that will be dispatched.

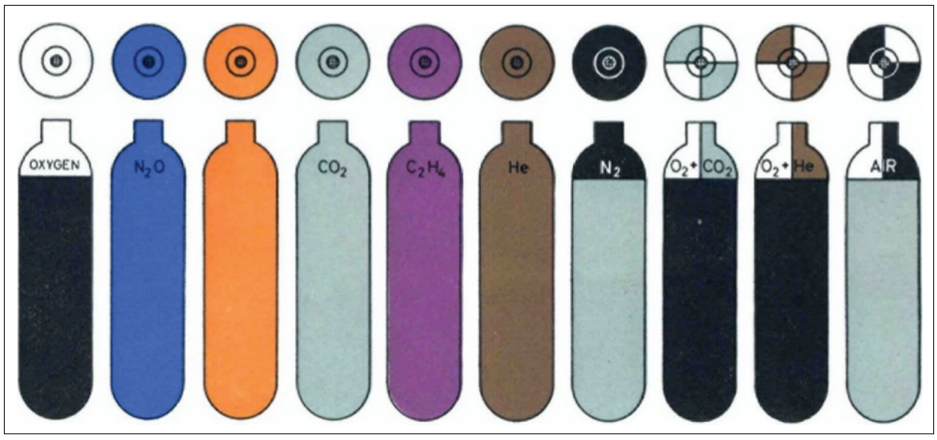

Figure 2: Color identification of cylinders

J. Restricting the employment of minors and intoxicated persons
- No one under the age of 18 or someone under the influence of alcohol should be responsible for loading, unloading, or carrying any compressed gas cylinder.

K. Restriction on lighting, fires, and other dangerous substances
- No one should smoke, be at risk for spontaneous combustion, cause a fire or communicate an explosion near to a location where combustible gas cylinders are being filled, stored, or handled.

L. General precautions
- A suitable neutralization or scrubbing system should be provided in the location where hazardous and corrosive gases are filled into and stored in cylinders.
- The dangerous, corrosive, and flammable gas storage shed should be equipped with the proper emergency handling systems or kits, as well as safety gear including hand gloves, gas masks, breathing apparatus, goggles, and gumboots.
- An suitable alarm with a switch that can be activated on-site should be installed in the hazardous and storage space for corrosive gas so that, in the event of an emergency, the control room can hear the alarm by activating the switch on-site.

M. Handling and use
- Conveyors, trolleys, and cradles with enough strength should be used to transfer the cylinders.
- Slide, drop, or play with cylinders is not allowed.
- Except while welding, cutting, or heating, open fires, lamps, cell phones, lighting fires, and smoking are not permitted next to any combustible gas-containing cylinder.

N. Storage of cylinders
- The storage area or shed, as well as the cylinders kept in a cool, dry, and well-ventilated location, should be fire-resistant against boilers, open fires, pipes of the steam, or other potential heat sources.

O. Purity of gas
- The Chief Controller shall ensure that purity complies with the applicable Indian Standard.

IMPORTATION OF CYLINDERS

- Anybody importing cylinders must have the required infrastructure, transit facilities, handling and storage capabilities, as well as a plan for emergency action and qualified technical personnel.
- It is necessary to have a license issued in Form F to store compressed gas in cylinders if the volume of imported cylinders exceeds the quantity.

A. Importation by sea
- Any ship's master who intends to import compressed gas cylinders into India must provide the port's conservator not less than (NLT) 48 h notice of the ship's anticipated arrival.
- A Form A written statement bearing the pilot's signature must be delivered by the master of any ship carrying cylinders before it enters port.

CYLINDER INSPECTION AND TESTING

A. Periodicity of cylinder testing and inspection
- It is necessary to test the cylinder using hydrostatic or hydrostatic stretch testing.
- The initial period of the cylinders testing station's permit is 1 year, and it can later be extended for a maximum of 5 years.[7]

B. Condemning of cylinders
- A cylinder is deemed unfit for use and terminated by flattened it as a whole or breaking it into pieces that cannot be put back together again if it fails a periodic inspection or test, loses more than 5% of its tare weight, or exhibits another defect.

FILLING AND POSSESSION

- A license in the form of E should be issued for filling gas cylinders.
- A form B and C application must be submitted to the Chief Controller in order to apply for approval or renewal of a license.

- Documentation required for the licensing authorities to obtain in order to approve the manufacture of cylinders –
  - An application for the manufacturing of cylinders, along with all appropriate documentation;
  - The ISO certification, or equivalent certification, issued by any reputable organization;
  - A list of available technical books, codes, and specifications that are significant;
  - Evidence of ownership for actual possession and legal purpose;
  - Detail report on manufacturers, testing, and inspection;
  - Officially certified design drawings of the cylinders, valves, and regulators that are intended for fabrication from reliable third-party inspecting organizations;
  - The applicant's organizational structure, specifically referencing the personnel's qualifications and experience;
  - Any other documentation the Chief Controller may require.

The duration of a license that may be issued or renewed

Form D – Granted for a period of 1 year

Form E, F, or G – Remain in force till the 30th day of September of the year

Granted or renewed for a period of 10 years

ACCIDENTS AND INQUIRIES

Accident notifications must be sent through fax, email, and letter to the Chief Controller within 24 h. They must also be sent to the relevant district authority and the officer in charge of the local police station.

REGULATORY GUIDELINES FOR MEDICAL GASES IN USA

Under sections 201 (g) (1) and 503 (b) (1) of the federal food, drug, and cosmetic act (FD and C Act) and the United States Pharmacopoeia National Formulary (USP-NF), which provide standards for consistency, strength, and purity for all medical gases, medical gases are considered prescription medications. Over the past few years, incidents involving the handling of medical gases that caused patient harm or even death have raised concerns about their safety. The FD and C Act can be effectively implemented by recognizing medical gases as pharmaceuticals under the 21 Code of federal regulations (CFR), which is used by the Secretaries of the Treasury and Health and Human Services. Medicinal gases are often subject to cGMP requirements and are controlled as finished medicines at 21 CFR sections 210 and 211. The standards must be met by manufacturers of medicinal gases in accordance with 501 (a) (2) (B). According to section 505 of the FD and C Act, these gases are normally regarded as finished products and are sold in accordance with a new drug application (NDA) or the approval procedure described in section 576.[8] The regulatory authority information of medical gases is given in Table 1 and the color identification in Table 2.

GMP REQUIREMENTS

Organization and personnel

A. Quality unit (QU)

Manufacturers are required to keep a QU in place that has the responsibility and authority for approving or rejecting components. Under section 21 CFR part 211.22, the QU develops, oversees, and implements a quality system for approving or rejecting drug products.

a. Responsibilities
   - Each personnel must follow the policies and guidelines established by this unit

Table 1: National regulatory authorities responsible for regulation of medical gases

Regulatory Aspect	India	USA
The authority	Ministry of commerce and industry. Drugs control authority of state	FDA/CDER
The act	Explosives act 1884/gas cylinder rules 2004 Drugs and cosmetics act	Federal food and drug cosmetics act/ compressed medical gas guideline 1989
The official listing of the country	Indian pharmacopeia	USP, USP-NF

Table 2: Medical gas cylinder colors (as per food and drug administration)

Medicinal gas	Colour
Medical air	Yellow
Carbon dioxide	Grey
Helium	Brown
Nitrogen	Black
Nitrous oxide	Blue
Oxygen	Green
Mixture or Blend	Colours corresponding to each component gas

- Each staff member must receive training and certification to carry out the QU functions (21 CFR 211.25).

b. Quality Agreements with Suppliers
- Written quality agreements with manufacturers describe the cGMP's responsibilities as well as the reporting procedure for issues with drug quality.

c. Supplier Qualification
- Manufacturers must depend on a supplier's qualifications, which must include a certificate of examination (COA)
- Manufacturers are required to routinely evaluate authorized suppliers' credentials and assess how quickly they respond to customer concerns.

B. Personnel requirements
- All personnel must possess the necessary training, expertise, and experience to perform the duties given to them (21 CFR 211.25)
- Manufacturers must hold regular CGMP training sessions and keep training records with entries for attendance and time.

Buildings and facilities

- Buildings must contain sufficient space for sequential processes, such as clearly defined regions for the distribution of delivered medical gas cylinders, containers, processing equipment, rejected gas cylinders, and controlled delivery systems, as well as gas cylinders filling section, quarantine, for gas cylinders and filled gas cylinders section (21 CFR 211.89)
- Areas are distinguished from other places created by the maker using identifiers such as signs, floor demarcation, or marking (21 CFR 211.42).[9]

Equipment

A. Filling equipment qualification
- Equipment to be qualified while being filled at the applied pressure and temperature
- Inspection and manifold valves must be suitable for use.

B. Equipment cleaning and maintenance
- Equipment used to manufacture medical gases should be cleaned both before and after usage
- To prevent contamination, the producer must make sure that the open ends are correctly sealed
- Product containers and closures need to be handled and kept properly to prevent contaminating other elements
- Equipment needs to be properly cleaned and maintained (21 CFR 211.67).

C. Equipment calibration
- Vacuum gauges need to be checked frequently to make sure the needle resets to zero in the absence of vacuum or pressure
- The vacuum and pressure gauges need to be calibrated annually
- At least once a year, thermometers are calibrated

D. Computer-based systems
- Validation is required for all components of hardware and different types of software involved in the creation, gas cylinder processing, and storage of medicinal gas cylinders.
- Any modifications to a digitalized system must be made and properly documented in accordance with the established processes.

Container closure systems and components

A. Components
- Containers and closures materials for the gas cylinder shall be handled, stored, checked, and adhered to in accordance with written protocols.
- Before labels, broken seals, or other container damage or contamination have been checked.
- Materials, gas cylinder containers, and sealing mechanisms should all be verified before acceptance or rejection.

B. Containers and container closure system

i. The general
- The closure systems for containers and containers must be reviewed, re-examined, and approved or rejected by the QU
- Both before and after exposure, these systems need to be clean
- The manufacturer is required to implement suitable cleaning and retesting processes if the container's intended use is changed from industrial-grade gas to medicinal gas
- Manufacturers should not employ vapor recovery systems when delivering carbon dioxide because they risk drawing in impurities from the storage tank or container's gaseous head space.

ii. Prefill Inspections
- Before filling, suppliers must perform gas cylinder prefill inspections to ensure that the cylinder containers and container closing systems are appropriate for use, and they must correctly document their observations.

a. External Inspection
- Container
  - Each container should be checked for dents, oil, grease, burns, dings, and other damage indications
  - Any container found in violation of these conditions needs to be quarantined.
- Valves, inlets, connectors, and outlets
  - Carefully examine valves, inlets, outlets, gauges, connectors, and anything else that could be damaged by fire, abnormal wear, corrosion, debris, oil, or grease.

b. Label Inspection
- Check the label on each container for consistency and legibility. On medical gas containers, product labels can be reused
- Every portable cryogenic container shall bear a 360° wraparound label in bold lettering that reads For Medical Purpose, Medical Gas, or a statement of a like nature on the side wall of the container, above the top weld seam but below the marking
- The gas name must be constantly written across the wraparound label of 360°, and the lettering must be at least 2 inches high
- Containers that only hold one gas are labeled with a contrast backdrop or text, or with the label's letters in the proper color
- When exposed to ambient conditions, labels, and goods used in medical gas canisters should be durable, fade-resistant, and not easily dissolve in water.

C. Color Code Inspection
- The medical gas cylinder must have the relevant gas it contains colored on the shoulder.[10]

D. High-Pressure Medicinal Gas cylinder Prefill Inspection
- High-pressure medicinal gas cylinders should be inspected before the date of DOT requalification
  - Each high-pressure cylinder's date stamp is examined before use by the US DOT.
  - Except in cases where DOT guidelines have been satisfied or the cylinder has been withdrawn from the inventory, it is advisable to quarantine the cylinder.
- Hammer Dead-Ring Examination
  The hammer or dead-ring inspection of steel cylinders reveals information on interior corrosion. Because of damage to the cylinder wall, this test is not performed on aluminum or composite cylinders. Instead, it is done by pounding the cylinder sidewall with a tool resembling a hammer.
- Odor inspection
  - An odor test is used to identify any odors or foreign gases present in the container. This test does not apply to gases such as carbon dioxide, nitrous oxide, or hazardous or dangerous gases.
  - The odor test is carried out on nitrogen if nitrogen is added to an empty cylinder.
- Cylinder ventilation
  - When refilling high-pressure cylinders, any remaining gas should be evacuated or blown out.
  - This can be avoided if the cylinder contains residual pressure and is equipped with a proper residual pressure valve.

E. Stock Rotation
- The majority of medical gas cylinders and container closure mechanisms are repurposed, and they undergo years of prefill testing.
- Manufacturers should take steps to ensure that containers and container closure mechanisms are still appropriate.

Production and process controls

A. Testing and sampling
Medical gas quality control protocols must be created, and production process effectiveness must be validated.

B. Evacuation of high-pressure cylinders by vacuum
Manufacturers must use a vacuum of at least 25 inches of mercury (Hg) for the vacuum evacuation of residual gases in high-pressure cylinders. The information must be recorded if a vacuum of less than 25 Hg is required to remove any residual gases.

C. Filling procedure checks
a. Measurements of the temperature and pressure
- The high-pressure cylinder's temperature rises as pressure increases.
- One cylinder in each multiple-filling series needs to have a thermometer attached for high-pressure cylinders to fill properly.
- On the batch production record, the producer must accurately record the values for temperature and pressure.

b. Valve Assembly Leak Testing Leak Checking for Valve Assembly
When filling-
- The solution for leak detection should be sprayed or brushed on and around each valve assembly to check for leaks.
- This test needs to be performed with the cylinder valve open when the cylinder is under pressure. The presence of bubbles indicates a leak. Overstuffed and disconnected if any leaks are found, a second inspection for the valve assembly should be performed, and the cylinder should be quarantined.

c. Heat-of-Compression Check
- By slightly rubbing each cylinder's outside, heat-of-compression tests on high-pressure cylinders should be performed during or directly after filling.
- The cylinders can be filled properly with a warm cylinder but not with a cool or cold cylinder.

Controls for packing and labeling

A. Material testing and use
Before being used for medical gas labeling, the sample of new labels and other labeling materials should be compared to the master label to ensure uniformity. It is essential to get rid of any extraneous or unneeded marks.

B. Labeling control
- Check that the amount of labels provided matches the amount of labels inserted to prevent problems.

- Electronic or electromechanical equipment or visual examination should be used to prevent improper labeling.

C. Packaging and labeling operations
- For each batch, a lot or control number should be assigned. Trans fillers that receive shipments of medicinal gases should be given a fresh lot number.
- A medical gas batch's lot number might be marked with a distinctive label or decal.
- The net content of the container may also be marked on a separate sticker.

D. Expiration dating

Stability studies must be included with a medical gas label that includes an expiration date.

Holding and distribution

The distribution of medical gas must be specified in documented protocols, which manufacturers must define and follow.

The steps should be described, including who will examine the shipment information, how the recall will be started, who will be made aware of it, and what will be done with the recalled product.

Laboratory controls

A. General requirements
- Laboratory controls should be recorded at the time of performance and should provide an explanation for any variances.
- Testing and screening are both required when turning industrial-grade gas into medicinal gas to ensure compliance with the relevant USP-NF.

B. Equipment Calibration
- A written schedule for a routine instrument, equipment, gauge, and recording device calibration must be included in the laboratory controls.
- The calibration gas COA must be particular to the calibration gas cylinder that was obtained and must contain the following details.
  - The name of the provider and contact information.
  - The name of the calibration gas.
  - The lot number or other special identifying number.
  - A brief information of the analytical procedure used for the calibration gas analysis.
  - Quantitative representations of analytical results (e.g., 99.9% nitrogen).
  - Declaration of traceability of the calibration gas to a recognized national standard.
  - The signer's name, along with the date they signed.

C. Testing and sampling of medicinal gases

Testing includes sampling
- For every batch, the number of units should be sampled and verified.
- Material sampling and testing must be done in accordance with the acceptance requirements.
- If the test's results are OOS (out of specification), the appropriate action should be done.

i. Multiple-outlet cylinder manifold filling

The identification and power of one high-pressure gas cylinder from each continuous filling series should be checked.

ii. Individually filled cylinders

The identity and strength of one high-pressure gas cylinder per continuous filling series should be checked.

iii. Mixtures

For combinations of two gases and three gases
- One high-pressure cylinder from each batch should go through tests to determine its composition for the second and third gases, as well as tests to determine its composition and strength for one of the two gases.
- The type and amount of oxygen should be checked in each cylinder used for mixtures containing oxygen.

iv. Suppliers of Medical Gas

After delivery or before the generated lot is released, the batch of medical gases ordered from suppliers should be examined for compliance with the required specifications. Whenever a COA is obtained from a supplier, identity, and purity tests have to be done.

D. Validation of test methods and alternative test methods

The analytical test methods or development methods are approved if a test included in the NDA is approved.

The USP-NF monograph should be followed during the evaluation and validation procedure. A copy of the exhaustive validation of the test method should be kept on file if the USP-NF monograph does not provide the test procedures.

E. Stability testing

The specified expiration date for a batch should be documented, and a stability testing schedule should be followed.

Records and reports

A. Basic prerequisites

i. Record retention

Records for products having an expiration date should be kept for a year beyond the batch's expiration date, and records for certificates of authenticity must be kept for 3 years. Moreover, training logs must be recorded.

ii. Record review

A sample of annual batch reports, complaint files, audits, medicine recalls, and returns to determine

whether changes to the requirements for drug products for development or control methods are required.

iii. Records providing information on machine and process validation, controls, inspections, and equipment calibration should be kept up to date.

B. Equipment cleaning and use of logs
Separate reports should be kept for equipment maintenance and cleaning.

C. Records for components, container closure systems, and labeling
- Records must include the provider's name, the lot number, and the initial date of receipt. They also need to contain information on freshly acquired containers' serial numbers and closing systems.
- To ensure that labels and labels conform with the criteria, they should be examined and recorded.

D. Master records of output and control
- These documents give an explanation of medicinal gas cylinders, container closing systems, and packaging items, along with a copy or sample of each label.
- Complete production and control orders, processes for sampling and checking, specifications, special considerations, and safety precautions to be taken.
- These documents should be created, dated, and signed by one person; then, they must be checked, dated, and signed separately by a second person.

E. Records for Master production and control
- Each batch of medical gas produced should have a batch production report prepared, which should include comprehensive information on the production and management of each batch.
- These documents properly represent the processes and environment that were in place at the time of production.
- Each lot number in the batch manufacturing, labeling, testing, and release records should be traceable.

F. Records for production record reviews and investigations
- before batch release for packaging and labeling, all medical gas production and control papers should be reviewed by QU.
- Third-party consignees should refrain from releasing medicinal gas through the consistency system.
- When a filling is completed off-site, the QU is responsible for inspection and approval before delivery.

G. Laboratory Records
It contains-
- A summary of the sample, the lot number, the place where it was taken, and the dates it was obtained for testing.
- A description of each methodology used to assess the sample.
- A record of all measurements performed as part of the test, including their measuring units, conversion factors, and equivalency factors.
- The test findings should be documented and compared to the component's identity, strength, effectiveness, and purity standards.
- The signatures of the personnel doing each test, the dates on which the tests were conducted, and the accuracy, comprehensiveness, and conformance of the reviews with the required requirements.

H. Distribution records
The product name and strength, description information of the dose type, the consignee's name and address, the date of shipment, and the quantity shipped must all be included in the delivery records. Distribution records do not have to include batch numbers for medical gases.

I. Complaint files
Records for complaints should include—
- Name and batch numbers of the medical gas
- Name and contact information for the claimant
- A full justification for the existence of the complaint
- Any analysis to investigate if the allegation also serves as a negative incident\
- A answer to the complainant, along with the date it was delivered
- The QU team must review and look into each and every complaint, both verbal and written. The investigation's record includes the complaint's issuance date, action-takers' names, action dates, and the issue's resolution.

J. Certificate of Analysis
The following details should be included in the COAs-
- The manufacturer's complete name and address
- The supplier's complete name and address
- The product's name (e.g., Oxygen USP)
- The serial number for the lot, or another unique identification number
- Results of all monographs and other studies using USP-NF
- Analysis was carried out using a test approach
- The producer's or supplier's signature and the date.

Returned medical gas

For returned medicinal gases, the cylinder needs to be vented.

Adapters

Despite the fact that using rigorous control adapters to fill mixes of medical gases should be avoided, adapters are frequently used.

FDA CERTIFICATION PROCESS FOR DESIGNATED MEDICAL GASES

Introduction

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted. Three

parts of Title XI, Subtitle B of FDASIA, Medical Gas Products Regulation, address the regulation of medical gases (sections 1111-1113). In December 2012, there was mention of the proposed guidance on medical gases eligible for the certification procedure. The FD and C Act, which provides a licensing procedure for specified medicinal gases, has been amended to include new sections 575 and 576.[11]

Medical gases that comply with the requirements of an official compendium are designated as oxygen, nitrogen, nitrous oxide, carbon dioxide, helium, carbon monoxide, and medical air, according to Section 575 of the FD and C Act.An approved NDA under section 505 (21 U.S.C. 355) or an approved new animal drug application (NADA) under section 512 (21 U.S.C. 360b) of the FD and C Act is deemed to be in effect if a designated medical gas certification is issued, according to section 576(a)(3) of the FD and C Act. The designation process of medical gases was depicted in Figure 3.

The designated medical gases are certified under section 576 only for the following indications:

- Hypoxemia or Hypoxia - Oxygen
- Testing for hypoxic challenges - Nitrogen
- Analgesic activity- Nitrous oxide
- Extracorporeal membrane respiratory stimulation therapy or oxygenation therapy -Carbon dioxide
- Treatment of increased airway resistance or upper airway obstruction - Helium
- Reducing the condition of hyperoxia - Medical air
- Slung diffusion testing - Carbon monoxide

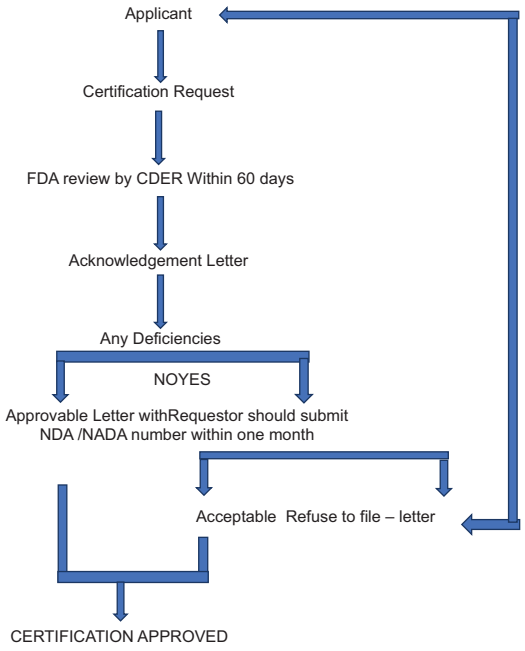

Figure 3: Flowchart: Certification of designated medical gases

Labeling revisions

- The label for the medicinal gas contains a caution regarding the use of the gas in finished pharmaceutical products. (Sec. 576(a)(3)(A)(ii)).
- The labeling for carbon dioxide, helium, nitrous oxide, mercury, medicinal air, and carbon monoxide must include a clear warning statement in accordance with 21 CFR 201.161(a).
- The caution statement required by section 576(b)(2)(B) must be printed on the oxygen label.

Warnings

- Administration of (gas name) may be harmful or inappropriate
- Only to be used by or under the direction of a qualified practitioner who is knowledgeable with the signs, symptoms, dosages, procedures, duration and frequency of administration, risks, side effects, and contraindications, as well as the precautions to be taken for (name of gas)
- "Uninterrupted use of significant amounts of oxygen over a long length of time without managing its impact on arterial blood oxygen content can be dangerous," according to the instructions for using oxygen tanks.

The current list of designated medical gases

The term "official compendium" is used under Section 201(j) of the FD and C Act to refer to the official U.S. Pharmacopeia (USP), official U.S. Homeopathic Pharmacopeia (HPUS), official NF, or any modification to any of them.[12]

USP monograph the requirements and standards

OXYGEN (O_2):

- According to the USP monograph "Oxygen," oxygen comprises NLT 99.0% by volume of oxygen.
- Another USP monograph, Oxygen 93%, characterizes a product as having an O_2 content of NLT 90.0% by volume and not more than 96.0% by volume, with the remainder primarily made up of Argon (Ar) and Nitrogen (N_2).

Nitrogen (N_2): The NF monograph entitled Nitrogen contains NLT 99.0% by volume of N_2

Nitrous oxide (N_2O): The Nitrous Oxide contains NLT 99.0% by volume of N_2O

Carbon dioxide (CO_2): The Carbon dioxide contains NLT 99.0% by volume of CO_2

Helium (He): The Helium contains NLT 99.0% by volume of He.

Medical air: It contains NLT 19.5% and NMT 23.5% by volume of O_2.

Carbon monoxide (C_{11}): It contains the labeled amount of ^{11}C expressed in Mega Becquerel (MBq) or Mill Curie (mCi) at the time specified in the labeling, respectively, NLT 90.0% and NMT 110.0%.

Certification process

- A person or organization should apply for certification before introducing or delivering a recognized medicinal gas into interstate commerce. The certification requirements of the FD and C Act are not applicable to anyone or any entity that produces gases only for industrial or other non-medical purposes
- Applications for certification should be submitted separately for each specified medicinal gas
- The certification procedure for certified medicinal gases intended for both human and animal medication use is the same
- A person or entity requesting approval outside the parameters of this certification should go through a different network (21 CFR 314 and 21 CFR 514).[13]

Information to be submitted-

Requestor Information:
- The name and address of the sponsor.
- The name, address, and, if relevant, any contact details of an authorized U.S. agent.
- Contact information (phone and email).

Type of Submission:
- Original Certification Request for either brand-new medications for humans or animals or both
- FDA responds to the requester with an acknowledgment letter that includes an NDA or NADA number. In all subsequent submissions relating to the gas to which that certification request pertains, the requestor must include their NDAnumber.

Description of Medicinal Gas:
It contains the gas's name and details demonstrating that it complies with the requirements listed in an official compendium.

Facility Information:
- The name and address of the facility or facilities where the medicinal gas is being manufactured or will be manufactured must be provided by the requestor in accordance with Section 576(a)(1)(C).
- Each facility's data universal numbering system number, together with the facility's FDA Establishment Identification, if one exists, and any other relevant data, should be included in the request.

Certification Request for Updated or Corrected:
The requestor should revise their certification request if the information is erroneous or incomplete by sending a new, fully completed form along with a cover letter that specifically calls out the amended or corrected information.

APPLICATIONS OF MEDICAL GASES

Oxygen

The most essential gas for life is oxygen, which is given to patients who are anemic as a supplement.[14] High-purity oxygen should not be directly inhaled by humans. An average long-term oxygen concentration is between 30 and 40%. Patients well typically inhale oxygen with an oxygen flow meter, while severely ill individuals inhale oxygen through a ventilator.

Moreover, oxygen gas is used in high-pressure tanks to treat diving injuries, gas poisoning, and pharmaceutical nebulization.

A. Types of oxygen delivery systems
There are three main types of oxygen delivery systems
- Compressed gas cylinders
- Cryogenic containers for liquid oxygen
- Oxygen concentrators

B. Hyperbaric oxygen therapy.

Carbon dioxide

Carbon dioxide therapy, also known as carboxytherapy, is a straightforward procedure that involves injecting carbon dioxide gas into the treatment area to enhance blood flow. It is a non-invasive method for treating wrinkles, warts, and different surgical procedures.

Carbon dioxide can be used as an insufflation gas to widen and stabilize body cavities during minimally invasive procedures including laparoscopy, endoscopy, and arthroscopy to increase surgical field visibility.[15] For cryotherapy or local analgesia, liquid medicinal carbon dioxide can be used to obtain temperatures as low as −76°C.

Carbon, also known as Meduna's mixture, is a mixture of oxygen and carbon dioxide gases that contains 95% O_2 and 5% CO_2. It is used to treat respiratory conditions as well as early-stage central retinal artery blockage.

Hydrogen

Inhaling hydrogen gas is a simple therapeutic procedure. Inhaling hydrogen gas using a facemask, nasal cannula, or ventilator circuit is more effective and provides better protection from acute oxidative stress.[16]

Nitrogen

For cryotherapy, nitrogen is mostly used.

The local or broad application of low temperatures in medical therapy is known as cryotherapy, commonly referred to as cold therapy. A number of tissue lesions can be treated by cryotherapy. particularly for cryosurgery or cryoablation, a type of surgical treatment. The most prevalent use of cryosurgery, which uses extremely low temperatures to eliminate aberrant or diseased tissue, is to treat skin diseases.[17]

Nitrous oxide

As an anesthetic or laughing gas, nitrous oxide is employed. Anesthesia typically has analgesic or anesthetic effects.[18] Nitrous oxide therapy's main limitation should be kept to 24 or a maximum of 48 h due to the possibility of leukopenia. To relieve discomfort during childbirth and heart attacks, nitrous oxide, and oxygen are mixed in a 1:1 ratio. For temporary pain management, midwives use a mixture of 50% nitrous oxide and 50% oxygen called Entonox. Nitrous oxide and carbon dioxide are the two most often utilized compressed gases for surgery.

Medical air

Aerosol drug therapy, which involves delivering medicine, humidification, or both to the body through the lungs, is the most popular application of Medical Air. Aerosol treatments typically last for 15–20 min and absorb 4–8 lpm of medical air.

For the care of child resurrection, medical air is used. 1-8 lpm of heated and humidified medical air, USP (also known as medical grade vapor), is given through the nasal cannula to hold the infant's airways open and to lessen the child's breathing work because 10% of infants have difficulty extending their lungs during their initial breath.[19]

BRIEFING ON MEDICAL GAS TRAGEDIES

The FDA's advice document offers suggestions to assist hospitals, nursing homes, and other healthcare clinics in preventing disasters caused by medical gas mix-ups.[20]

The following instances are those that led to the FDA's warning:

On December 7, 2000, a nursing facility in Bellbrook, Ohio, reported two patient fatalities and eight patient injuries due to a problem with their oxygen supply system. Two of the four cryogenic vessels that were shipped to the nursing home supposedly contained medical-grade oxygen. But a cryogenic vessel of nitrogen of industrial quality was delivered as well. An employee of maintenance was sent to connect a fresh oxygen vessel to the system of oxygen delivery because the nursing home was running low on oxygen. When the worker made the nitrogen vessel selection, he correctly realized that he could not attach it to the oxygen delivery system because the oxygen vessel connectors are designed specifically to work with oxygen delivery systems only. The worker attempted to assist by removing a fitting from an empty oxygen vessel and installing it on the nitrogen vessel.

On April 22, 1998, a hospital in Idaho discovered that a sizable cryogenic vessel of industrial nitrogen had been attached to the oxygen system supplying the operating rooms, labor and delivery rooms, and emergency department. The hospital discovered that the medical gas delivery person had initially been unable to connect the incompatible nitrogen vessel output connection to the oxygen system and had instead used a wrench to remove the nitrogen fitting from the oxygen system and replace it with an oxygen fitting. This medical gas mix-up resulted in the deaths of two patients.

In October 1997, a few cryogenic containers of medical-grade oxygen were delivered to a hospital in Nebraska. The shipmen's kit had one cryogenic vial filled with industrial-grade argon that was properly labeled. A maintenance worker was assigned by the hospital to attach an oxygen vessel to the oxygen delivery system since the facility was running low on oxygen. The employee chose the argon tank without first reading the label. When he realized he could not connect the argon vessel to the oxygen supply system, he removed a fitting off an empty oxygen vessel, put it on the argon vessel, and connected the deadly material to the oxygen system. A patient undergoing minor surgery was given argon. The patient passed away.

On December 2, 1996, New York children's home reported nine patients had negative reactions after breathing carbon dioxide. When instructed to attach a sizable cryogenic vessel of medical-grade oxygen, a home employee mistakenly chose a carbon dioxide container from the home's inventory. He pointed out that the connector on the oxygen system did not fit the fitting on the carbon dioxide vessel. However, he installed the oxygen fitting on the carbon dioxide vessel, connected it to the oxygen gas supply system, and removed the oxygen fitting from an empty vessel. Four patients suffered varying degrees of respiratory difficulty, while two patients suffered critically from injuries.

CONCLUSION

Medical gases have been used since the beginning of science and are still used today throughout the world. This has been the case for more than a century. A number of specifications are adopted for medical gases to harmonize the needs, as standardization has long been acknowledged as a crucial factor for the protection of patients and others as a consequence of many tragedies. Medicinal gases, which were in use long before the FD and C Act was created in 1938, are the most commonly prescribed drugs. Further guidelines on medical gas legislation, including advice and industry standards, have been developed by regulatory agencies in

various nations. Pharmacopoeia monographs are the primary tool for developing industrial processes appropriate for the generation of medical gases, and GMP guidelines are also becoming more important as a result of the globalization of medication production and manufacturing by national authorities.[21] To lower the rate of morbidity and death, strict standards for the control of medicinal gases must be created. Medical gases are subject to regulatory norms and laws in the U.S. and Europe. The globe is currently moving towards a universally agreed-upon standard for cylinders, and strict regulation of medical gas as well as the harmonization of these standards may happen for a better healthcare system.

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