CURRENT REGULATION OF MEDICAL GASES IN INDIA AND FUTURE ASPECTS

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REVIEW ARTICLE

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ABSTRACT

Generally medical gases are administered or supplied directly to the patients. They should be manufactured and transferred with the highest quality possible as per standards and limits decided by the different regulatory authorities. In India medical gases are regulated by Ministry of Commerce and Industry and central drug standard control organization. Along with these various act are available for better regulation that are Explosives act 1884, Gas cylinder rules 2004, Drugs and Cosmetics Act and specifications of medical gases are given in Indian pharmacopoeias. Various facilities and requirements for the manufacturing and regulation of medical gases are covered. In spite of all the regulations, there are reports of problems associates with medical gas manufacturing and uses. What are steps should be taken for the solution of these problems.

Keywords: Medical gas, Regulations, Documentation, Good manufacturing practice, Standards.

INTRODUCTION

Under the Drug and Cosmetics Act, the regulation of manufacture, sale and distribution of Drugs is primarily the concern of the State authorities while the Central Authorities are responsible for endorsement of New Drugs, Clinical Trials in the country, setting down the standards for Drugs, control over the quality of imported Drugs, coordination of the activities of State Drug Control Organizations and providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act.

Drug Controller General of India is responsible for approval of licenses of specified categories of Drugs.

The Central Government in exercise of power under Section 5 & 7 of the said Act had proclaimed the rules namely Gas Cylinder Rules, 2004 to regulate filling, ownership, transport and import of such gases. The goal of these Rules is to ensure safety of the general population occupied with the activity of filling, ownership, transport and import of such gases. (1)

Manufacturing practice for Medical Gases (1-3)

The organization must be manufacturer of Medical Gases i.e. Medical oxygen IP, Nitrous oxide IP, Medical carbon dioxide, IP and should be have valid manufacturing license issued from the state Drug controller as per the provisions of the Drug and Cosmetic Act 1940 and rules there under.

General requirements

Location and surroundings: The facility for the manufacture of medical gases shall be so situated and shall have such measures as to avoid risk of contamination.

Personnel: The manufacturing shall be conducted under the direct supervision of competent technical staff with prescribed qualifications and practical experience in the relevant areas.

Buildings and premises: Facility shall be designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions provided in the Factories Act, 1948.

Production area: The production area shall be designed to allow the production preferably in uniflow and with logical sequence of operations.

In order to avoid the risk of cross-contamination, separate dedicated facilities shall be made available for the production of gases used in medical and pharmaceutical field.

Working and in-process space shall be adequate to permit orderly and logical positioning of equipment and materials and movement of personnel to avoid cross contamination and to minimize risk of omission or wrong application of any of manufacturing and control measures.

Pipe-work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid gathering of dust. Service lines shall be identified by colors and the nature of the supply and direction of the flow shall be marked/ indicated.

Quality Control area: Quality Control Laboratories shall be designed appropriately for the operations to be carried out in them. Appropriate space shall be provided to prevent mix-ups and cross contamination. Sufficient and suitable storage space shall be provided for test samples, retained samples, reference standards, reagents and records.

Manufacturing Operations and Controls: All manufacturing operations shall be carried out under the supervision of technical staff approved by the Licensing Authority. The contents of all vessels and containers used in manufacturing and storage during the various manufacturing stages shall be clearly visible labelling with the name of the product, batch no., batch size and stage of manufacturing. Each label should be initialed and dated by the authorized technical staff.

Equipment: Equipment shall be designed, constructed, adapted, located and maintained to suit the operations to be carried out. All equipment of an appropriate range, accuracy and precision and these should be calibrated and checked on a scheduled basis in accordance with Standard Operating Procedures and records maintained.

The parts of the production equipment that come into contact with the product shall not be additive, reactive or adsorptive to an extent that would affect the product's quality.

Documentation and records: Documentation is an essential part of the Quality assurance system and shall be related to all aspects of Good Manufacturing Practices (GMP). Its goal is to define the specifications for all materials, manufacturing process and process control, to ensure that all personnel concerned with manufacturing know the information required to decide whether or not to release a batch of a drug for sale and to provide an audit trail that shall permit investigation of the history of any suspected defective batch.

Documents designed, prepared, reviewed and controlled, wherever applicable, shall comply with these rules.

Documents shall be signed, approved and made effective by placing date by appropriate and authorized persons.

Documents shall specify the title, nature and purpose. They shall be laid out in an orderly fashion and be easy to check. Reproduced documents shall be clear and legible. Documents shall be regularly reviewed and kept up to date. Any alteration made in the entry of a document shall be signed and dated.

Master Formula Records: There shall be Master Formula records relating to all manufacturing procedures for each product and batch size to be manufactured. These shall be prepared and endorsed by the competent technical staff i.e. head of production and quality control.

Batch Processing Records: It shall be based on the relevant parts of the currently approved Master Formula. The method of preparation of such records included in the Master Formula shall be designed to avoid transcription errors.

Standard Operating Procedures (SOPs) and Records, regarding:

1. Receipt of materials
2. Sampling
3. Batch Numbering
4. Testing
5. Records of Analysis

Labels and other Printed Materials: Labels are absolutely necessary for identification of the gases and their use. The Printing shall be done in bright colors and in a legible manner. The label shall carry all the prescribed details about the product.

All containers and equipment shall bear appropriate labels. Different colour coded tablets shall be used to indicate the status of a product (for example under test, approved, passed, rejected).

Prior to release, all labels for containers, cartons and boxes and all circulars, inserts and leaflets shall be examined by the Quality Control Department of the licensee.

Quality Assurance: This is a wide-ranging concept concerning all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that products are of the quality required for their intended use. The system of quality assurance appropriate to the manufacture of pharmaceutical products shall ensure that -

(a) the pharmaceutical products are designed and developed in a way that takes account of the requirement of Good Manufacturing Practices (herein referred as GMP) and other associated codes such as those of Good Laboratory Practices (hereinafter referred as GLP).

(b) Adequate arrangements are made for manufacture, supply and use of the correct starting and packaging materials.

(c) Adequate controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out.

(d) The finished product is correctly processed and checked in accordance with established procedures;

(e) The pharmaceutical products are not released for sale or supplied before authorized persons have certified that each production batch as been produced and controlled in accordance with the requirements of the label claim and any other provisions relevant to production, control and release of products.

Self-Inspection and Quality audit: It may be useful to constitute a self-inspection team supplemented with a quality audit procedure for assessment of all or part of a system with the specific purpose of improving it.

To evaluate the manufacturer is compliance with GMP in all aspects of production and quality control, concept of self-inspection shall be followed. The manufacturer shall constitute a team of independent, experienced, qualified persons from within or outside the company, who can audit objectively the implementation of methodology and procedures evolved. The procedure for self-inspection shall be documented indicating self-inspection results; evaluation, conclusions and recommended corrective actions with effective follow up program. The recommendations for corrective action shall be adopted.

Written instructions for self-inspection shall be drawn up which shall include the following:

(a) Personnel
(b) Premises including personnel facilities.
(c) Maintenance of buildings and equipment
(d) Storage of starting materials and finished products
(e) Equipment
(f) Production and in-process controls
(g) Quality control
(h) Documentation
(i) Sanitation and hygiene
(j) Validation and revalidation programs
(k) Calibration of instruments or measurement systems.
(l) Recall procedures
(m) Complaints management
(n) Labels control
(o) Results of previous self-inspections and any corrective steps taken.

Specification for product containers and closures: All containers and closures intended for use shall comply with the pharmacopoeial requirements. Suitable validated test methods, sample sizes, specifications, cleaning procedure and sterilization procedure, wherever indicated, shall be strictly followed to ensure that these are not reactive, additive, absorptive, or leach to an extent that significantly affects the quality or purity of the drug. No second hand or used containers and closures shall be used.

Distribution records: Prior to distribution or dispatch of given batch of a drug, it shall be ensure that the batch has been duly tested, approved and released by the quality control personnel. Pre-dispatch inspection shall be performed on each consignment on a random basis to ensure that only the correct goods are dispatched.

Validation and process validation: Validation studies shall be an essential part of Good Manufacturing Practices and shall be conducted as per the pre-defined protocols. These shall include validation of processing, testing and cleaning procedures.

Processes and procedures shall be established on the basis of validation study and undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Critical processes shall be validated, prospectively for retrospectively.

Product Recalls: There shall be an established written procedure in the form of Standard Operating Procedure for effective recall of products distributed by the licensee. Recall operations shall be capable of being initiated promptly so as to effectively reach at the level of each distribution channel.

Complaints and Adverse Reactions: All complaints thereof concerning product quality shall be carefully reviewed and recorded according to written procedures. Each complaint shall be investigated /evaluated by the designated personnel of the company and records of investigation and remedial action taken thereof shall be maintained.

Site Master File: The licensee shall prepare a succinct document in the form of Site Master File containing specific and factual Good Manufacturing Practices about the production and/or control of pharmaceutical manufacturing preparations carried out at the licensed premises.

The firm should have in-house facility for testing/trace impurities in P.P.M/P.P.B range for CO, NO; Phosphines, Polymers, SO2 and argon etc. and the facilities should be open to scrutiny by the Authorities.

- The Firm should perform Dragger Test as per I.P.-2010

- Filling the gas in CCOE-approved cylinders in CCOE-licensed premises and FORM E & F (rules 50, 51 and 54) for License to fill compressed gas in cylinders and License to store compressed gas in cylinders respectively. The license in Form-F is granted by respective Circle offices of the Department of Explosives. But when storage shed of cylinders is attached to the gas filling plant, the license is granted for storage of cylinder in the filling plant along with license for filling by the Chief Controller of Explosives, Nagpur

- SCHEDULE VI - (See rule 20)-TRANSPORT OF CYLINDERS -Gas Cylinder Rules-Rule 20. Loading, unloading and transport of cylinders: - Cylinders filled with any compressed gas shall be transported duly complying with the provisions laid down in Schedule VI and also observing the relevant provisions of other statutes as applicable

- Facility for periodic examination and testing of compressed gas cylinders as per rule 35 and 36 of gas cylinder rules 2004. Periodicity of examination and testing of cylinders- (1) No person shall fill any cylinder with any compressed gas unless the cylinder has been examined and subjected to hydrostatic test or hydrostatic stretch test, as the case may be, and other tests set forth in Schedule IV within such period as is specified in IS: 15975 issued by Bureau of Indian Standards or as approved in writing by the Chief Controller. (2) Any testing station desiring to obtain recognition for periodical testing and examination of cylinders shall provide the facilities set forth in Schedule IV and shall submit to Chief Controller the particulars of the facilities provided and a scrutiny fee specified in Schedule V.

- The firm shall have to supply the medical gases in the cylinders (duly tested with relevant documents) if they are available in the hospital. Howsoever any additional requirements of various type of cylinder will have to be met by the vendor.

CYLINDERS (4-6)

- Cylinders are IS marked to IS 7285(Part2):2004 duly approved from CCOE Nagpur. Cylinder marking as per IS 7285(Part-2):2004 includes Test pressure and date of the

hydrostatic stretch test, Colour coding (ISO) e.g.: Neck-white; body-black, Capacity of gases, Water capacity, Maximum working pressure at 150 celsius, Minimum Pressure at supply (kgf/cm^2) at ambient conditions. "Marking on the valve as per IS 3745 (2006)" IS 3745 (2006): Yoke Type Valve Connection for Small Medical Gas Cylinders.

Specifications of Medical Gases as per Indian Pharmacopoeias (7)

1. Medical Oxygen - Medical grade IP 2010 - Certified safe for human use. - Purity 99-100% - Carbon monoxide less than 5 PPM - Carbon-di-oxide not more than 300 PPM - Free from halogen, polymer & oxidizing substance & moisture. - Should not cause any damage to the materials of cylinders, Gas pipeline, Anesthesia machine and ventilators.

2. Nitrous Oxide - Medical grade IP 2010 - Certified safe for human use. - Purity 99-100% in liquefied form - Humidity and other impurities zero percent Free from hydrogen sulphide. Free of all forms of reducing and oxidizing substances. - Should not cause any damage to the materials of cylinders, Gas pipeline, Anesthesia machine and ventilators. - Each batch must have passed tests for alkalinity, arsenic, phosphate and ammonia.

3. Carbon dioxide - Medical grade Latest IP - Certified safe for human use. - Should not damage any instrument used with it.

Liquid Medical Oxygen (LMO) (6, 7)

Installation of LMO -site requirements. Firm should obtain the site location details from the hospital authorities. It should then procure the necessary site approval from the Petroleum and Explosives Safety Organization. The site should be located inside a fenced compound, be accessible to the road tankers. All hazardous buildings, flammable materials, public access, vehicles and surface water drains must be at least 5 m and in some cases 8 m from the nearest point of the compound. The compound directly in front of the fill connection must be concrete and should be designed to contain any liquid spillage as risk of fire is increased in case of liquid spillage. Tar and asphalt should never be used in the vicinity as they form an explosive mixture when in contact with liquid oxygen. The firm will be responsible for routine check, maintenance & demonstration of functioning of LMO & preventive measure to be adopted in case of emergency to Technical staff of the hospital at their own cost. Unit should be of latest version internationally. The unit should be fitted with standard accessories as minimum and should have undergone standard inspection requirement. A certificate to that effect has to be submitted. The liquid oxygen tank will remain under the ownership of the supplier. The license for the Liquid Oxygen Tank installation will technically be in the name of the authority of the hospital, however, the responsibility of safe and secured maintenance of the entire infrastructure will belong to the LMO supplier.

The vessel should be maintained in such a way to keep natural evaporation rate less than 1%. LMO Vessel Capacity: 990 liters (Single tank) / 2600 litres/5 kL/ 6 kL/10 kL tanks. Depending on the LMO consumption volumes -Liquid Medical Oxygen should be supplied through mobile vehicles- Configuration- Vertical - Operating working pressure 8-12 to 16 kg/cm2 (approx.) - Should have compact unit including vessel and vaporizer. - Vessel should be of standard material and technology keeping in view of safety & International standard. - Telemetry facility. -Dimension of Vessel- Vendors are requested to visit/Inspect the site so that the tank of requisite dimension can be provided by them to meet our requirement. - Purity-99-100%.-Medical grade I.P. 2010. - Certified safe for human use. -Should not cause any damage to gas pipeline, anesthesia machine and ventilators. -Should have content indicator and preferably low liquid level alarm with safety system in case of emergency/unnatural calamities.

Challenges faces by India

Medical gases are essential for the healthcare systems. They should be manufactured and transferred with the highest quality possible as per standards and limits. In different countries their regulatory body drafted additional guidance regarding regulations of medical gases in order to provide more compliance for industry. These guidelines provide recommendations and clarify industry requirements.

According to Federal Food, Drug, and Cosmetic Act, "a medical gas that meets the definition of a drug (referred to in this guidance as simply a medical gas) is deemed to be adulterated under section 501(a)(2)(B) of the FD&C Act if 'the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice."

In case of India there is various regulations for the medical and pharmaceutical gases but not in specified manner. There should be separate guidance for manufacturing of medical gases, specific and separate rules for the only medical gases because all the type of gases covered in the gas rules. In spite of all the regulations, precautions put down by the regulatory authorities, there are still reports of medical gas mix ups which even resulted in death of the patients. Even though the mistake done is not intentional it puts the patient's life at jeopardy. So, eventually who is to be blamed for the mix up, the regulatory authority, the manufacturer, the distributor, the physician or the nurse? Well it is a rhetorical question which still remains unanswered. These reports emphasize the need of regular monitoring from their manufacture until their administration.

CONCLUSION

In India CDSCO that monitors the manufacture and use of the medical gases. Regulatory authority emphasizes the proper color coding, labeling, warning and safety procedures on the containers to facilitate easy identification and to avoid mixing. They also insist that the handling of these gases should be done only by a trained professional. India included the medical gases and their containers in their monograph so as to follow the specific standards throughout the country. Despite of all the regulation by authorities there are still reports of tragedy due to improper manufacturing of the gases around the world. There might be so many un-documented cases across the world especially in the third world countries where there are weak regulatory mechanisms and poor documentation practice. Every country has a law that ensures safety, but the question is how soundly it is implemented. For better health care system of India there should be specific guidance and guideline for medical gases should be drafted and implemented.

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CONFILCTS OF INTEREST

The authors declare that there are no conflicts of interest.

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