Guidelines for Good Manufacturing Practices of Medical Gases

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1. INTRODUCTION

The Medicines Act of the Kingdom of Bhutan 2003 mandates the Drug Regulatory Authority to safeguard the health of the consumers against harm ensuing from poor quality of medicinal products. Notably, in accordance with the definition of medicinal products as stated in the Bhutan Medicine Rules and Regulations 2019, medical gases can be classified as medicinal products.

As per the National Drug Policy 2007, the Government shall promote and support local manufacture of pharmaceuticals in order to promote self-sufficiency. The policy and the Bhutan Medicines Rules and Regulation 2019 also mandate DRA ensure compliance of manufacturing firms to the Good Manufacturing Practice standards.

Medical gases are generally regulated as finished pharmaceuticals and are subject to current Good Manufacturing Practices requirements regardless of the processing stage. Compliance with applicable cGMP requirements helps to ensure the safety, identity, strength, quality, and purity of medical gases. Medical gases that are not manufactured, processed, packed, or held according to applicable cGMP requirements can potentially cause serious injury or death.

Although the Guidance Document on Technical Authorization for Manufacture and Regulatory Certifications (DRA-G-D1-TA-08) specifies the requirements and procedures for obtaining Technical Authorization for Manufacturing from the DRA, these guidelines complement the requirements and procedures in relation to Good Manufacturing Practices. To assist the local Medical Gases Industry in comprehending and interpreting the overall requirements in relation to GMP, this guideline has been developed. It is primarily harmonized with the principles from the myriad of published guidelines while taking into account the capacity of the domestic medical gases industries and it is developed chiefly to pragmatize the requirements in our own context.

Ultimately, the guidelines are expected to foster better regulatory compliance and reduce the regulatory burden. Hence, this GMP guide may be used by all the domestic medical gases manufacturers to ensure high standards of quality management system during the manufacture of medical gases.

2. SCOPE

2.1. These guidelines apply to all the medical gases manufacturers and healthcare facilities equipped with provision to produce medical gases and, it focuses on production, quality control, storage and distribution of medical gases.

2.2. This shall NOT apply to:

2.2.1. GMP related to issuance of Technical Authorization for Manufacture which is covered by Guidance Document on Technical Authorization for Manufacture and Regulatory Certifications;

2.2.2. Oxygen concentrators for personal use;

2.2.3. Gases used for cosmetic or aesthetic purpose;

2.2.4. Gases used in laboratory (e.g. gas for freezing of tissue samples, calibration gas);

2.2.5. Recreational gases (e.g. oxygen gas for diving, mountain climbing); and

2.2.6. Industrial gases.

However, relevant parts of this guide may be used as a basis for such activities.

3. OBJECTIVE

3.1. To provide guidance on Good Manufacturing Practices for medical gas manufacturers.

4. NORMATIVE REFERENCES

The following documents, in whole or in part, are normatively referenced in these guidelines and are indispensable for its application.

4.1.1. The Medicines Act of the Kingdom of Bhutan, 2003;

4.1.2. Bhutan Medicines Rules and Regulation, 2019; and

4.1.3. Manufacturing of Medical Products in Bhutan: Guidance Document on Technical Authorization for Manufacture and Regulatory Certifications (DRA-G-D1-TA-08).

5. DEFINITIONS:

5.1. Act: It refers to the Medicines Act of the Kingdom of Bhutan, 2003

5.2. Air separation: It refers to separation of atmospheric air into its constituent gases using fractional distillation at cryogenic temperatures.

5.3. Authority: It refers to the Drug Regulatory Authority.

5.4. Bulk material: It refers to bulk gases intended for medical use that can be prepared by chemical synthesis or obtained from natural resources followed by purification steps if necessary (for example in an air separation unit). These gases could be regarded as Active Pharmaceutical Ingredients (API) or as bulk pharmaceutical products as specified by the authority.

5.5. Finished product: It refers to medical gas cylinders which have been filled, all quality control functions completed and recorded and formally released by the Qualified Person.

5.6. Cryogenic gases: It refers to gas which liquefies at 1.013 bars at temperatures below –150°C.

5.7. Manifold: It refers to equipment or an apparatus designed to enable one or more gas containers to be emptied and filled at the same time.

5.8. Manufacturer: It refers to the authorized firm manufacturing medical gases including filling of medical gases.

5.9. Medical gas: It refers to any gas or mixture of gases classified as a medicinal product. It includes oxygen, carbon dioxide, nitrogen, nitrous oxide and medical air.

5.10. Minimum pressure retention valve: It refers to a cylinder valve, which maintains a positive pressure above atmospheric pressure in a gas cylinder after use, in order to prevent any internal contamination of the cylinder.

5.11. Purge: It refers to removing the residual gas from a container/system by first pressurising and then venting the gas used for purging to 1.013 bar.

5.12. Production of medical gases: It refers to either the filling of medical gas cylinders or the production of the bulk medical gases as finished products or as a starting material for medical cylinder filling.

5.13. Regulation: It refers to the Bhutan Medicines Rules and Regulations 2019

5.14. Rejected product: It refers to any medicinal gas either as bulk medicinal gas or filled into medicinal gas cylinders where either it has been found to be outside the specification limit by the quality control checks or by the qualified person or has been identified by the end user as being of suspect quality.

5.15. Starting Material: It refers to the bulk product used to manufacture the finished product (such as ammonium nitrate for the production of nitrous oxide). In the case of medical cylinder filling, the starting material refers to the bulk medical gas supplied into the storage tank at the cylinder filling site.

6. ACRONYM

6.1. API: Active Pharmaceutical Ingredient

6.2. cGMP: Current Good Manufacturing Practices

6.3. DRA: Drug Regulatory Authority

6.4. GLP: Good Laboratory Practices

6.5. GMP: Good Manufacturing Practices

6.6. SOP: Standard Operating Procedure

6.7. QA: Quality Assurance

6.8. QC: Quality Control

6.9. QMS: Quality Management System

7. QUALITY MANAGEMENT SYSTEM

7.1. Any manufacturer of medical gases holding Technical Authorization for Manufacture, should ensure that medical gases manufactured are safe, of an appropriate quality, and efficacious so that they do not pose risk to the patients. The manufacturer should also comply with the requirements of their technical authorisation.

7.2. The firm should implement and document a quality assurance system, incorporating the principles of GMP and QC. The effectiveness of QA should be monitored on a regular basis. There should be adequate resources including competent personnel, suitable and sufficient premises, equipment and facilities.

7.3. Senior management should also assume responsibility for the quality of the medical gases manufactured, controlled, stored and distributed.

8. QUALITY ASSURANCE

8.1. It refers to quality Assurance is a wide ranging concept which covers all matters which individually or collectively influence the quality of the medical gases. It incorporates the principles of GMP as well as other factors outside the scope of this GMP Guide.

8.2. The manufacturer should ensure that:

a. The equipment and procedures used for the manufacture of medical gas are designed and developed as per the requirements of GMP;

b. Production and quality control operations are clearly specified and the principles of GMP and GLP are adopted;

c. Job responsibilities are clearly specified;

d. All necessary controls on starting and packaging materials, intermediate products, and any other in-process controls and validations are carried out;

e. The bulk medical gases and the filled medical gas cylinders are correctly processed and checked, according to the SOPs;

f. Medical gases are not supplied before they are released by a qualified person;

g. The medical gases are stored, distributed and subsequently handled so that safety and quality of the gas and the condition of the containers are maintained throughout their shelf life; and

h. There is a procedure for self-inspection or internal audit.

9. GOOD MANUFACTURING PRACTICE

9.1. GMP ensures that medical gases are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the technical authorization or product specification. It is concerned with the quality control of the production, filling and distribution of medical gases.

9.2. The manufacturer should ensure that:

a. Manufacturing processes are clearly defined and systematically reviewed so that they comply with their specifications.

b. Critical steps of the manufacturing processes and any significant changes to the process are reviewed and where possible validated

c. All necessary facilities, including following are provided:
   - » appropriately qualified and trained personnel;
   - » adequate premises and space to carry out all operations;
   - » suitable equipment and services;
   - » correct materials, containers and labels;
   - » approved SOP; and
   - » suitable store for finished product.

d. Operators are trained to carry out procedures correctly and their competency assessed as per SOP.

e. Records are made, manually or electronically during manufacture of the medical gases.

f. A system is available to recall and manage complaints of any batch of product, from sale or supply.

10. QUALITY CONTROL

10.1. Quality control is a part of GMP which is concerned with sampling, testing and specifications of medical gases. It is also concerned with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that medical gases are not released for patient use until their quality has been judged satisfactory.

10.2. The manufacturer should ensure that:

a. Adequate facilities, trained personnel and approved procedures are available for the sampling, inspecting and testing of starting materials, packaging materials, bulk medical gases and filled medical gas cylinders.

b. Test methods as specified in the pharmacopoeias are used. In case of different methods, the test should be validated.

c. The bulk medical gases and the filled medical gas cylinders comply with the qualitative and quantitative specification of the finished product and are correctly labelled.

11. PRODUCT QUALITY REVIEW (PQR)

11.1. Annual product quality review of medical gas should be conducted to verify the consistency of the existing process, the appropriateness of current specifications, to highlight any trends and to identify product and process improvements.

11.2. The review may include:

a. critical in-process controls, finished product testing results, and specifications of all batches that failed to meet established specification(s) and their investigation, if any

b. all significant deviations or non-conformances, their related investigations, and the effectiveness of corrective and preventative actions taken, if any

c. all product quality-related returns, complaints and recalls, and the investigations performed at the time, if any

d. the qualification status of relevant equipment used for fabricating and packaging medical gases.

11.3. The results of the review should be evaluated, and assessed whether corrective and preventive action or any revalidation should be undertaken. The review should be documented.

12. PERSONNEL

Principle

12.1. As per section 96 of the regulation, the Authority shall register the key personnel involved in manufacturing as Competent Person. The manufacturer of medical gases shall have an adequate number of personnel with the necessary qualifications and practical experience available to carry out all operations.

12.2. All medical gases manufacturer should recruit at least one competent person with adequate experience and/or necessary qualifications to oversee production and quality control activities.

12.3. Manufacturers of medical gases shall have an organization chart. All personnel in responsible positions shall have their specific duties recorded in their written job descriptions and adequate authority to carry out their responsibilities.

Responsibilities of Competent Person

12.4. The manufacturing firm should recruit key personnel with prescribed qualifications and/or experience to oversee production and quality control activities. A quality unit's size and complexity can vary with the size of the operation.

12.5. The responsibilities of competent personl includes:

12.5.1. Production Unit:

a. manufacture of medical gases and filling of medical gas cylinders follows the defined SOPs;
b. periodic maintenance of the equipment and premises are carried out correctly;
c. appropriate process validations are completed;
d. periodic trainings are carried out;
e. periodic self-inspection is carried out and associated corrective actions implemented accordingly;
f. validate production procedures;
g. authorize SOPs and other documents;
h. maintain and retain production documentation;
i. monitor compliance with the requirements of GMP; and
j. control of any changes to procedures or equipment, including any relevant validations.

12.5.2. Quality Unit:

a. approve or reject starting materials, packaging materials, intermediate bulk and finished product;
b. evaluate batch records;
c. all necessary testing is carried out;
d. approve specifications, sampling instructions, test methods and other QC procedures;

e. approve and monitor any contract analysis;
f. approve and monitor suppliers and materials;
g. periodic maintenance of the equipment and premises are carried out correctly;
h. ensure that the appropriate quality control validations are completed;
i. train quality control personnel;
j. validate the quality control procedures;
k. authorize SOPs and other documents;
l. maintain and retain quality control documentation;
m. monitor compliance with the requirements of GMP; and
n. control of any changes to procedures or equipment, including any relevant validations.

Training

12.6. All personnel must be trained in cGMP requirements on a continuing basis and with sufficient frequency to provide assurance that they remain familiar with the applicable requirements. Besides the basic training on the theory and practice of GMP relevant to the manufacture of medical gases, newly recruited personnel should receive training appropriate to the duties assigned to them.

12.7. The effectiveness of training should be periodically assessed and training records should be retained.

Personnel Protection and Hygienic Practices

12.8. For safety reasons, every person entering the manufacturing areas shall wear protective garments appropriate to the operations to be carried out.

12.9. Separate facilities shall be provided for personnel for eating, drinking or smoking and it should be remote from any production and quality control areas.

12.10. Any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.

12.11. Visitors or untrained personnel should not be taken into the production and quality control areas. If this is unavoidable, they should be closely supervised and given the appropriate information in advance, particularly about personal hygiene and the prescribed protective clothing.

13. PREMISE AND EQUIPMENT

Principle

13.1. Premises and equipment for the manufacture of medical gases and the filling of medical cylinders shall be located, designed, constructed and maintained to suit all of the relevant operations. The layout and design of the premises and equipment shall be done to minimize the risk of errors and also permit effective cleaning/maintenance which ensures the quality of the medical gases.

13.2. The manufacture of medical gases should be carried out in closed pipework, containers and tanks. The closed system for manufacture of medical gases should ensure minimal contamination of the medical gases.

Premises

13.3. The layout and design of the premises should aim to minimize the risk of errors, mix-ups, contamination and cross-contamination. In addition, it should allow for effective cleaning and maintenance without any adverse effect on the quality of the product.

13.4. The premise should provide sufficient space for manufacturing, quality control testing and storage operations.

13.5. Cylinder filling areas shall be well lit, particularly where visual, on-line controls are used to inspect cylinders. The cylinders for medical gases should be checked, prepared, filled and stored in a separate area from non-medical gases, and there should be no exchange of cylinders between these areas. However, in exceptional cases, the principle of campaign filling in the same area can be accepted provided that specific precautions are taken and necessary validation is done to ensure that there is no confusion between medical and non-medical gas cylinders.

13.6. Premises used for the filling of medical gas cylinders should be laid out in a manner to allow a logical flow through the process in the area. Cylinder filling areas should be of a sufficient size and have an orderly layout (as shown in Figure 1).

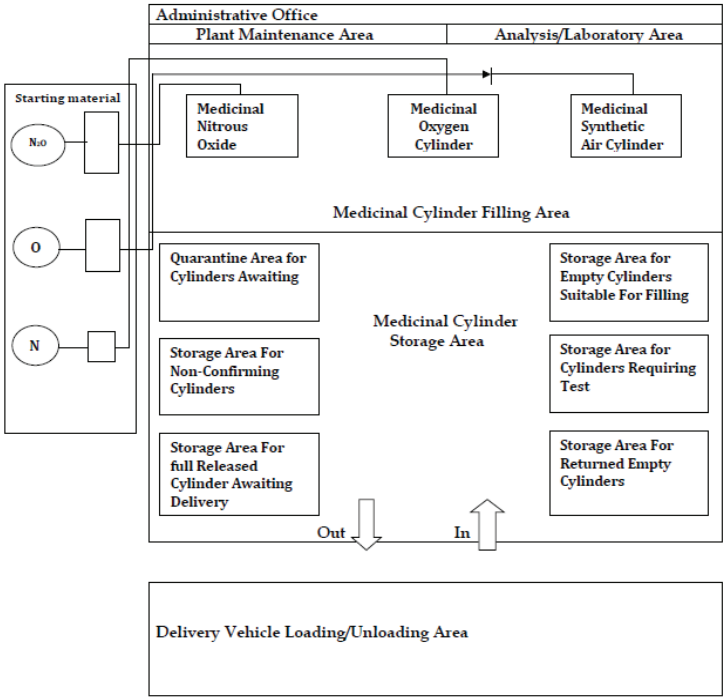

Figure 1: Layout of a typical medicinal gases plant (source: DRA-G-D1-TA-08)

13.7. Steps should be introduced to prevent the entry of unauthorized personnel to production, cylinder filling, storage and quality control areas.

13.8. Premises should provide sufficient space for manufacturing, testing and storage operations to avoid the risk of mix-up. Premises should be designated to provide:

a. separate marked areas for different gases;

b. clear identification and segregation of cylinders at various stages of processing (e.g. “empty cylinders awaiting checking”, “awaiting filling”, “quarantine”, “certified”, “rejected“, “prepared deliveries”).

13.9. The method used to achieve these various levels of segregation will depend on the nature, extent and complexity of the overall operation. Marked-out floor areas, partitions, barriers, signs, labels or other appropriate means may be used.

13.10. The empty and filled cylinders should be stored in its appropriate storage conditions in a clean and well ventilated area.

13.11. Storage areas should be kept clean, dry, well ventilated, protected from harsh effects of weather conditions and free of combustible materials to ensure that cylinders remain in an appropriate condition.

13.12. Cylinder storage areas shall be clearly identified and provide suitable segregation to allow distinction between the various stages reached by given cylinders, including:

a. empty cylinder storage area where cylinders returned from customers can be stored prior to cylinder sorting;

b. empty cylinder sorting area where cylinders can be segregated into those suitable for refilling and those requiring either statutory testing or rectification prior to refilling;

c. empty cylinder storage area for cylinders suitable for refilling;

d. quarantine area for filled cylinders awaiting quality control and formal release;

e. full cylinder storage area for released cylinders; and

f. rejected non-conforming cylinders.

13.13. Ancillary areas should be easily accessible but separated from production, cylinder filling, quality control and storage areas.

13.14. Maintenance workshops should be separate from production and cylinder filling areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

Equipment

13.15. All critical equipment should be qualified prior to its use, preferably at the temperature and pressure used during filling. Manifold valves (e.g., appropriately designed to prevent mix-ups during medical gas filling operations and shown to prevent contamination of medical gas) and other valves that are critical to the prevention of contamination, such as check valves used in filling systems, should be qualified for use.

13.16. Defective equipment shall be clearly labelled as defective and, if possible, be removed as soon as possible from the production or laboratory areas.

13.17. Ensure that every equipment is accompanied with respective SOPs at the place where it is stationed.

13.18. Ensure that equipment used in the manufacture of medical gases (e.g., manifolds, pigtails, valve assemblies, hoses, gauges) is cleaned before initial use and after exposure to a contaminant (e.g., industrial gas impurities).

13.19. Cleaning and purging of filling equipment and pipelines shall be carried out according to SOPs. This is especially important after maintenance, repair

or breaches of system integrity. Checks for the absence of contaminants or cleaning materials shall be carried out before the line is released for use.

13.20. Closed pressurized systems used for filling medical gases (e.g., manifolds) need not be cleaned between batches, unless exposed to a contaminant. To prevent contamination, manufacturers should ensure that open ends are appropriately covered (e.g., with physical caps).

13.21. The medical gas manifolds should be dedicated to a single gas or single pre-mixed mixture or to any given mixture of gases to different concentrations. Where a change of gas mixture is required, the manifold and the appropriate lines shall be cleared by means of purging or evacuation following an approved SOP.

13.22. Pipework and storage tanks are also required to be purged following the decision to convert the equipment from one gas service to another or as a means of removing atmospheric contamination.

Equipment Calibration and Maintenance

13.23. Manufacturers must establish an appropriate schedule or frequency for equipment calibration and maintenance. Critical instruments used for measuring, weighing, recording and controlling equipment shall have specific calibration periods using appropriate validated methods.

13.24. Detailed records of all of the calibration tests values shall be maintained along with the history of equipment.

13.25. Medical gas manufacturers that use automated, mechanical, or electronic equipment such as computer systems must ensure these systems are routinely calibrated, inspected, or checked according to approved SOPs to ensure proper performance.

13.26. Repair and maintenance operations shall not adversely affect the quality of medical gases produced. The manufacturing and cylinder filling equipment should be designed to ensure easy and effective cleaning and evacuation to remove any internal contamination.

Computerized Systems

13.27. Computerized systems, including hardware and software used in the manufacturing, processing, and holding of medical gases must be validated for their intended use. The depth and scope of the validation depend on the complexity and significance of the computerized system.

13.28. Computerized or automated systems must have sufficient controls to prevent unauthorized access or changes to master production control records or other records to ensure record integrity.

13.29. Any changes to a computerized or automated system should be made according to approved procedures, and it should be documented.

13.30. The pipework should not have inter-connections unless there is suitable backflow protection and appropriate validated procedures in place.

14. CONTAINERS & CONTAINER CLOSURE SYSTEM

Principle

14.1. The quality unit must examine, re-examine as appropriate, and approve or reject containers and container closure systems.

14.2. Rejected containers and container closure systems must be segregated and labelled.

14.3. Containers and container closure systems must be clean and must not be reactive, additive, or absorptive so as to alter the safety, identity, strength,

quality, or purity of a medical gas beyond the established specifications. In addition, if converting a container's use from industrial grade gas to medical gas, or if there is reason to believe there was a previous industrial use, manufacturers must implement appropriate cleaning and retesting procedures. The same should be documented.

14.4. The cylinders and valves should be made of appropriate materials and must be compatible with the medical gases contained in it.

Color Coding of Cylinders

14.5. Cylinders must be colored in the color or colors that correspond to the gas held in the cylinder as shown in table 1.

Gas	Color of cylinder's shoulder
Oxygen	White
Nitrous oxide	Light blue
Nitrogen	Black
Medical air	Black and white
Carbon dioxide	Grey

Table 1: Medical gases cylinder colour code

Valves, inlets, outlets, connectors and adapters

14.6. Each container's valve assembly, connectors, and fittings should be inspected carefully to ensure that they are appropriate for the medical gas. The valves, inlets, outlets, gauges, and connectors should be examined carefully for signs of damage, unusual wear, corrosion, or the presence of debris, oil, or grease. This inspection should cover any connections that are brazed, welded, or equipped with a locking device.

14.7. For safety reasons, manufacturers should avoid the use of adapters of any kind to circumvent the specific medical gas valves and connections associated with a specific medical gas.

14.8. The maintenance and repair operations of cylinders, mobile cryogenic vessels and valves are the responsibility of the manufacturer of the medical product. If subcontracted, they should only be carried out by approved subcontractors, and contracts including technical agreements should be established.

15. PRODUCTION

Principle

15.1. Incoming starting material shall be physically or administratively quarantined immediately on receipt or after processing, until they have been formally released for use.

15.2. Where applicable, such as in nitrous oxide production, checks on yields of the manufacturing process shall be carried out to ensure that there are no discrepancies outside acceptable limits and no unwanted by-products are produced.

15.3. For the manufacture of liquid medical oxygen using an air separation plant, it is not appropriate to perform plant yield calculations from a medical gas manufacturing perspective.

15.4. At all times during processing, all bulk containers and cylinder filling equipment shall be appropriately labeled, with an indication of the medical gas being processed or stored.

15.5. Any deviation outside acceptable limits shall be recorded, investigated and appropriate corrective actions agreed and implemented.

Process Validation

15.6. Separation, purification and other critical steps shall be validated and monitored.

15.7. Where necessary in-process controls should be placed to monitor the effectiveness of the production process.

15.8. Processes and procedures shall undergo periodic re-validation of critical steps to ensure that they remain capable of achieving the intended result.

Starting Materials

15.9. Starting materials shall only be purchased from approved suppliers and, where possible, they should be purchased directly from the manufacturer.

15.10. Only starting material which has been released by the quality control shall be used for the production.

Bulk Medicinal Gases

15.11. All separation and purification steps shall be designed to operate at optimal effectiveness.

If applicable, limits for process parameters, including temperatures and pressures, shall be documented and the relevant in-process monitoring include measurement of critical parameters.

15.12. There shall be a system in place to ensure batch traceability of the bulk gases.

Medical Gas Cylinder Filling

15.13. To ensure that the correct medical gas is filled into cylinders, manifolds should be dedicated to a single medical gas or to a given mixture of medical gases to different concentrations.

15.14. There shall be a system in place to ensure traceability of the medical gas cylinders within a batch.

15.15. For filling of medical gas cylinders, the filling batch shall be defined and documented.

15.16. In order to prevent contamination of cylinders in service from either atmospheric contamination or back-feeding from the customer's process, it is recommended that minimum pressure retention valves are fitted to all medical gas cylinders.

Cylinder Testing

15.17. Cylinders shall be cleaned, tested and maintained in an appropriate manner. New cylinders and cylinders shall be subjected to an internal inspection to ensure that the cylinder is dry and free from contamination, prior to the cylinder valve being fitted.

Pre-fill Inspection

15.18. Pre-fill inspections shall be conducted to provide assurance that containers and container closure systems are acceptable for use before filling.

15.19. Any prefill inspections performed must be properly documented.

15.20. Containers and container closure systems that fail prefill inspections must be quarantined until the container, container closure system, or valve has been repaired, cleaned, or replaced, as appropriate, and determined to pass re-inspection.

15.21. Each container should be carefully examined for dents, burns, dings, oil, grease, and other signs of damage or contamination that can cause a container to be unsafe for use. Any container found to have any of these conditions must be quarantined until its suitability has been determined.

15.22. When inspecting cylinders, following prefill inspections shall be conducted in addition to the previously mentioned prefill inspections:

a. Hammer or Dead-ring Test:

Manufacturers should conduct a hammer or dead-ring test to provide information about internal corrosion of steel cylinders. The test consists of lightly tapping the cylinder sidewall with a hammer-like instrument. The hammer or dead-ring test should not be performed on aluminum or composite cylinders because the test would not indicate internal corrosion and could damage the cylinder wall.

b. Venting or Blow Down of Cylinders:

High-pressure cylinders that are received for refilling should be vented or blown down appropriately to remove any gas remaining in the cylinders. However, the test can be omitted if the cylinder is equipped with a qualified residual pressure valve and has residual pressure.

Post-fill Inspection

15.23. When inspecting cylinders, following post-fill inspections shall be conducted and post-fill checks shall include checks to ensure all containers in the batch:

a. Have been filled: An indication that a cylinder has been filled is that the exterior of the cylinder is warm to the touch immediately after filling.

b. Are not leaking, using an appropriate leak test method. Leak testing can be achieved by either using a proprietary leak detection device or using an appropriate leak detection fluid. Where leak detection fluids are used, care is needed to ensure that any leak detection solution is not left in the valve outlet which can contaminate the medical gas.

c. Are fitted with an appropriate product label.

16. LABELLING

16.1. Each cylinder need not necessarily be labelled, so long the cylinders released into the market is traceable. However, for every batch a representative sample of the product label should accompany the products.

16.2. Each container should be examined for legibility and accuracy of labels.

16.3. The printing on product labels shall be clear, legible and resistant to fading when exposed to daylight.

16.4. Labels that are obsolete or outdated must be removed.

16.5. Labels or leaflets shall be securely stored to prevent unauthorized access and mix-ups.

16.6. Only labeling that meets appropriate written specifications may be approved and released for use.

16.7. Labels shall only be issued for use by an authorised person following an approved SOP.

16.8. When a revised version of a label or leaflet is approved for use, all obsolete labels or leaflets shall be removed from the filing and storage areas and destroyed.

16.9. There shall be adequate checks to ensure reconciliation between the number of labels issued and number of labels used or returned.

16.10. Depending on the type of medical gas containers, the following minimum information should be provided:

a. Name and physical address of the manufacturer

b. Batch number

c. Production or filling date

d. Expiry date (where applicable)

e. Brand or proprietary name of the product

f. Hazard Statement or Precautionary Statement

g. Color Code of the gas type

h. Storage conditions based on the properties of the gas.

17. QUALITY CONTROL

17.1. Each batch of medical gas shall be manufactured and tested in accordance with the current pharmacopoeial standard.

17.2. The sampling plan and the analysis to be performed should comply, in the case of cylinders with the following requirements:

a. In the case of a single medical gas filled via a multi-cylinder manifold, the gas from at least one cylinder from each manifold filling cycle should be tested for identity and assay each time the cylinders are changed on the manifold.

b. In the case of a single medical gas filled into cylinders one at a time, the gas from at least one cylinder of each uninterrupted filling cycle should be tested for identity and assay. An example of an uninterrupted filling cycle is one shift's production using the same personnel, equipment, and batch of gas to be filled.

c. In the case of a medical gas produced by mixing two or more gases in a cylinder from the same manifold, the gas from every cylinder should be tested for assay and identity of each component gas. For excipients, if any, testing on identity could be performed on one cylinder per manifold filling cycle (or per uninterrupted filling cycle in case of cylinders filled one at a time). Fewer cylinders may be tested in the case of a validated automated filling system.

d. Premixed gases should follow the same principles as single gases when continuous in-line testing of the mixture to be filled is performed.

17.3. Final testing on mobile cryogenic vessels should include a test for assay and identity on each vessel. Testing by batches should only be carried out if it has been demonstrated that the critical attributes of the gas remaining in each vessel before refilling have been maintained.

17.4. Cryogenic vessels retained by customers (hospital tanks or home cryogenic vessels), which are refilled in place from dedicated tankers do not need to be sampled after filling, provided that a certificate of analysis on the contents of the tanker accompanies the delivery. However, it should be demonstrated that the specification of the gas in the vessels is maintained over the successive refilling.

17.5. Manufacturers receiving a batch of medical gas from suppliers should test for conformance to established specifications after receipt or before the manufactured lot is released. This can be done either by sampling directly from the storage tank or by testing one container from the first batch of medical product filled.

17.6. For medical oxygen, all batches of product should be subject to test for identification and assay but the frequency of test for impurities can be subject to the risk and trends of test results conducted for assay. Nevertheless, tests for impurities should be conducted for all batches for the first one week of production after issuance of Technical Authorization for Manufacture, following which if the purity of the medical oxygen is maintained at a level of more than 99.5 % v/v, then a test for impurity may be conducted on a monthly basis. However, in the event, when purity is found to be less than 99.5% v/v then all the tests should be followed by a test for impurity until the purity of the oxygen reaches 99.5 % v/v.

17.7. All filled cylinders shall be held in quarantine until they have been released by the competent person for supply.

17.8. Released cylinders shall be stored in a designated filled medical gas cylinder storage area. Storage arrangements should permit segregation of different gases and rotation of stock to allow for a 'first in, first out' system.

17.9. Rejected filled cylinders shall be clearly marked or labelled and stored separately in a defined restricted area. Any corrective actions taken shall be approved by an authorized person and recorded.

18. DOCUMENTATION

Principle

18.1. Good documentation practices are those measures that collectively and individually ensure documentation, whether paper or electronic, is secure, attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate ("ALCOA"+). Good documentation is an essential part of any QA system used for the production, quality control operation and storage of medical gas cylinders in compliance with the GMP.

18.2. Clearly written and retained documentation prevents errors and permits the tracing of batch history. All specifications, SOPs and records shall be controlled and available to all of the relevant personnel either in written or electronic format.

18.3. The document control procedure shall ensure that only the current version of any document is available and all superseded documents are destroyed or archived. All records related to production, quality control, or distribution should be retained for at least 5 years after the batch distribution date.

18.4. SOPs for production, quality control operation and storage of medical gases should be approved, signed and dated.

18.5. The manufacturer shall maintain documented information and SOPs covering following but not limited to:

a. Production of medical gases;
b. Purging of cylinders, pipelines and storage tanks;
c. Filling of cylinders;
d. Pre-fill and Post fill inspection of cylinders;
e. Sampling and Testing of medical gases: Identity, purity or assay and impurity tests;
f. Calibration and maintenance of equipment;
g. Packaging and labeling;
h. Cleaning and sanitization of premises and equipment;
i. Training and personal hygiene;
j. Complaints, recalls, and returns;
k. Internal audit or self-inspection.

18.6. However, the above mentioned SOPs may be incorporated into the Batch Manufacturing Record to foster better implementation.

Batch Manufacturing Record

18.7. Data included in the records for each batch of cylinders or mobile cryogenic vessels must ensure that each filled cylinder is traceable to significant aspects of the relevant filling operations. As appropriate, the following should be entered:

a. the name of the product;
b. batch number;
c. the date and the time of the filling operations;
d. identification of the person(s) carrying out each significant step;
e. line clearance;
f. quantity of cylinders or mobile cryogenic vessels filled;

g. pre-filling operations performed;

h. In-process Quality Control;

i. results of appropriate checks to ensure the containers have been filled;

j. sample of the batch label;

k. specification of the finished product and results of quality control tests;

l. Quantity of rejected cylinders or mobile cryogenic vessels with reasons for rejections, if any;

m. details of any problems or unusual events, and signed authorization for any deviation from filling instructions;

n. Certification statement by the Authorized Person, date and signature; and

o. Distribution record.

19. OUTSOURCED ACTIVITIES

Principle

19.1. Any outsourced activities relating to manufacture and analysis of medicinal gases shall be formally agreed, correctly specified and controlled by means of a contract. The contract conditions shall ensure that the contracted arrangements are carried out correctly and that there are no misunderstandings which could lead to substandard product.

19.2. There shall be a written contract between the contract giver and the contract acceptor which clearly establishes the duties and responsibilities of each party.

20. COMPLAINT & PRODUCT RECALL

Principle

20.1. All complaints and other information concerning potentially defective products must be carefully reviewed according to SOPs. In addition, a system should be in place to recall the products from the market.

Complaints

20.2. There should be a SOP to identify the cause of the complaint and the corrective measures to limit its impact. Upon receipt of a complaint, depending on the criticality, a detailed investigation shall be employed and proposed corrective actions shall be implemented accordingly. The SOP shall include all the actions to be taken in the event of receipt of complaint concerning the quality of medical gases.

20.3. All details concerning the original complaint, subsequent investigations, corrective actions taken shall be documented and retained as a record.

Product Recall and Returns

20.4. There should be a SOP detailing the actions to be taken if a product has to be recalled or returned due to quality or any other associated issues.

20.5. The recall SOP shall be regularly reviewed and updated when necessary, to ensure that the recall procedure is effective.

20.6. The Authority should be immediately informed if products are intended to be recalled.

20.7. The distribution records should be readily available and should contain sufficient detail for the information to reach wholesalers and directly supplied customers, including exported products.

20.8. Recalled products should be identified and stored separately in a secure area while awaiting a decision and records of recalled procedures should be documented accordingly.

21. SELF-INSPECTION

Principle

21.1. Self-inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

21.2. Self inspections should be conducted in an independent and detailed way by designated competent person(s). Independent audits by external experts may also be useful.

Self-inspection Programme

21.3. There shall be a formal self-inspection programme agreed that reviews the compliance of at least the following aspects of the quality assurance system:

- requirements for nominated personnel and their training needs;
- layout of the premises; • equipment used for medicinal gas manufacture and cylinder filling;
- batch records and other formal documentation;
- bulk manufacture and cylinder filling of medicinal gases;
- quality control of the production processes;
- distribution of the medicinal products; and
- arrangements for dealing with complaints and recalls.

21.4. The self-inspection programme shall be carried out at an agreed intervals and used to verify the conformity of the quality assurance system with the principles of Good Manufacturing Practice.

21.5. All self-inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals

for corrective measures. Statements on the actions subsequently taken should also be recorded.

22. REFERENCES

22.1. PIC/S GMP guide part I : Basic Requirements for medicinal products
22.2. PIC/S GMP guide: annexes
22.3. US FDA cGMP for medical gases
22.4. AIGA Good Manufacturing Practices guide for medical gases
22.5. Health Canada Good Manufacturing Practices guide for medical gases
22.6. WHO guide for Guidance on good data and record management practices.

Drug Regulatory Authority

We commit to provide consistent regulatory operations with risk based planning and continual improvement in compliance with the recognized standards to meet our consumers' satisfaction and confidence.

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