World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO good manufacturing practices for medicinal gases

Please send your comments to **Dr Steve Estevao Cordeiro**, Technical Officer, Norms and Standards for Pharmaceuticals , Technical Standards and Specifications (estevaos@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int) before **31 August 2021**. Please use the "Table of Comments" document for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/current-projects) for comments under the "*Working documents in public consultation*" link. If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.

SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/21.875:

WHO good manufacturing practices for medicinal gases

Description of Activity	Date
Following a recommendation by several teams in WHO dealing with the COVID-19 emergencies and the oxygen supply, the WHO Secretariat triggered action towards the development of a new guidance on good manufacturing practices for medicinal gases.	December 2020
Preparation of first draft working document.	January 2021
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	February 2021
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	June 2021
Discussion of comments in the virtual meeting on *Good practices for health product manufacture and inspection.*	28 June – 2 July 2021
Preparation of working document for next round of public consultation.	July 2021
Mailing of revised working document inviting comments, including to the EAP, and posting the working document on the WHO website for a second round of public consultation.	July – August 2021
Consolidation of comments received and review of feedback. Preparation of working document for discussion in the ECSPP.	September – October 2021
Presentation to the Fifty-sixth meeting of the ECSPP.	TBD
Any other follow-up action as required.	

WHO good manufacturing practices for medicinal gases

Introduction

1.1. Arising from an increased demand for medicinal gases, in particular the use of oxygen in the treatment of patients with Coronavirus disease 2019 (COVID-19), the World Health Organization (WHO) Health Products Policy and Standards Department (formerly Essential Medicines and Health Products) and other departments involved in the supply of oxygen and the inspection of production sites of medicinal gases, raised the urgency for the preparation of the *WHO good manufacturing practices for medicinal gases* guidance text.

1.2. There is an urgent need to scale-up the production of medicinal gases, in particular oxygen, meeting the required quality specifications. Where the standards for medicinal gases are not followed in the production and control of Industrial oxygen, the purity and content of industrial oxygen could be affected. The possible contamination of industrial oxygen with viable and non-viable particulate matter, including other impurities, could result in risks to patients when applied for medicinal use. Industrial oxygen should not be used as a medicinal gas.

1.3. Although there are other published guidelines, such as those in the European Union (EU) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S), the COVID-19 pandemic resulted in a urgent and increased need for the rational use of oxygen and medicinal gases in many WHO Member States.

1.4. Whilst the urgent supply of medicinal gases is necessary, we must be certain that appropriate standards in all countries are followed for the production, control, storage and distribution of oxygen and other medicinal gases to guarantee that gases for medicinal use are of assured quality when they reach the patients.

1.5. The recommendations in this guideline are harmonized with the principles from other similar and published guidelines.

1.6. WHO good manufacturing practices (GMP) guidelines are reviewed, updated regularly and available in the WHO Technical Report Series. Manufacturers and distributors of medicinal gases should comply with the relevant parts of WHO GMP guidelines as well as the content of this document. For ease of reference, a list of some applicable guidelines, such as those

reflecting the principles in GMP for Active Pharmaceutical Ingredients *(1),* main principles in GMP *(2)*, Water for pharmaceutical use *(3)*, Data integrity *(4)*, Good quality control laboratory practices *(5)*, Good storage and distribution practices *(6)* and others, are referenced below *(7-15).*

2. Scope

2.1. This guideline focuses on the production, control, storage and distribution of medicinal gases.

2.2. This document does not cover the manufacturing of medicinal gases in hospitals or at home for personal use. However, the principles contained in this document may be applied in those instances to ensure that oxygen generated at hospitals or at home are suitable for their intended use and meet the appropriate quality standards.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They have been aligned as much as possible with the terminology in related WHO guidelines and good practices (GxP) and included in the WHO Quality Assurance of Medicines Terminology Database - List of Terms and related guideline https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461cfc_5,but may have different meanings in other contexts.

Active substance gas. Any gas intended to be an active substance for a medical product or medicinal gas.

Air separation. The separation of atmospheric air into its constituent gases using fractional distillation at cryogenic temperatures.

Compressed gas. A gas which, when packaged under pressure for transport, is entirely gaseous at -50 °C; this category includes all gases with a critical temperature less than or equal to -50 °C.

Container. A container is a cryogenic vessel (tank, tanker or other type of mobile cryogenic vessel), a cylinder, a cylinder bundle or any other package that is in direct contact with the gas.

Cryogenic gas. Gas which liquefies at 1.013 bar at temperatures below –150 ° C .

Cylinder. A container, usually cylindrical suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

Cylinder bundle. An assembly of cylinders which are fastened together, interconnected by a manifold, transported and used as a unit.

Evacuate. The removal of residual gas from a container/system to a vacuum level of 0.84 bar absolute at sea level using a vacuum system.

Gas. Any substance that is completely gaseous at 1.013 bar and +20 ° C or has a vapour pressure exceeding 3 bar at +500 °C.

Home cryogenic vessel. A mobile cryogenic vessel designed to hold liquid oxygen and dispense gaseous oxygen at a patient's home.

Hydrostatic pressure test. A test performed, as required by national or international regulations, in order to ensure that pressure containers are able to withstand pressures up to the container's design pressure.

Liquefied gas. Gas which, when packaged for transport, is partially liquid (or solid) at a temperature above –50 °C.

Manifold. Equipment or an apparatus designed to enable one or more gas containers to be emptied and filled at the same time.

Maximum theoretical residual impurity. A gaseous impurity coming from a possible backflow that remains after the cylinders pre-treatment before filling. The calculation of the maximum theoretical residual impurity is only relevant for compressed gases and supposes that these gases act as perfect gases.

Medicinal gas. Any gas or mixture of gases classified as a medical product.

Minimum pressure retention valve. 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.

Mobile cryogenic vessel. A mobile thermally insulated container designed to maintain the contents in a liquid state.

Non-return valve. A valve which permits flow in one direction only.

Purge. To remove the residual gas from a container/system by first venting the residual gas from the container/system, then pressurizing the container/system to 2 bar and then venting the gas used for purging to 1.013 bar.

Tank. A static thermally insulated container designed for the storage of liquefied or cryogenic gas. They are also called "fixed cryogenic vessels".

Tanker. A thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas.

Valve. A device for opening and closing containers.

Vent. To remove the residual gas from a container/system down to 1.013 bar by opening the container/system to the atmosphere.

4. Quality management

4.1. Companies that are involved in the manufacture, control, storage and distribution of medicinal gases should document, implement and maintain a comprehensively designed and clearly defined quality management system. This is the responsibility of senior management.

4.2. Senior management should also assume responsibility for the quality of the medicinal gases manufactured, controlled, released, stored and distributed.

4.3. All parts of the quality system should be adequately resourced and maintained.

4.4. The quality system should incorporate the principles of GxP which should be applied to the life cycle stages of medicinal gases. This includes steps such as the receipt of raw materials, manufacturing, filling, testing, release, distribution and container return after use of a medicinal gas.

4.5. The quality system should ensure that:

- medicinal gases are manufactured, controlled, stored and distributed in accordance with the recommendations in this document and other associated guidelines such as good quality control laboratory practices and good storage and distribution practices, where appropriate;
- managerial roles, responsibilities and authorities are clearly specified in job descriptions;
- operations and other activities are clearly described in a written form such as standard operating procedures (SOPs) and work instructions;
- arrangements are made for the manufacture, supply and use of the correct containers and labels;
- all necessary controls are in place;
- there is a system for quality risk management;
- calibrations and validations are carried out where necessary;
- the finished product is correctly processed and checked according to the defined procedures and specifications;
- deviations, suspected product defects, out-of-specification test results and any other non-conformances or incidents are reported, investigated and recorded. An appropriate level of root cause analysis is applied during such investigations and the most likely root cause(s) is/are identified;
- proposed changes are evaluated and approved prior to implementation, considering regulatory notification and approval where required. After implementation of any change, an evaluation should be undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;
- appropriate corrective actions and preventive actions (CAPAs) are identified and taken where required processes are in place to ensure the management of any outsourced activities that may impact product quality and integrity;

- finished products are not released and supplied before the authorized person has certified that each production batch has been manufactured and controlled in accordance with product specifications, the recommendations in this document and any other regulations relevant to the production, control and release of these products;
- there is a system for handling complaints, returns and recalls from the market;
- there is a system for self-inspection; and
- satisfactory arrangements exist to ensure that medicinal gases are filled, stored, distributed and subsequently handled so that their quality is maintained.

4.6. The system for quality risk management should cover a systematic process for the assessment, control, communication and review of risks in the production, filling, control, storage and distribution of medicinal gases and, ultimately, protect the patient from receiving the wrong or contaminated product.

5. Personnel

5.1. Personnel involved in the manufacture, control, certification or release of a batch, storage and distribution of medicinal gases should possess the qualifications, scientific education and practical experience required by national legislation. They should undergo medical examinations prior to employment and at periodic intervals thereafter.

5.2. Personnel should receive the appropriate training in relevant guidelines covering GxP and company procedures.

5.3. Personnel should be aware of the risks and potential hazards to products and patients.

5.4. Personnel of outsourced service providers should be appropriately trained, especially where activities could influence the quality of medicinal gases and containers, such as the maintenance and cleaning of cylinders or valves.

6. Documentation

6.1. Specifications, SOPs and related documents, as appropriate for the manufacture, control, storage, and distribution of medicinal gases, should be established and implemented.

6.2. Documents should be designed, prepared, reviewed and distributed with care.

6.3. Documents should be authorized (approved, signed and dated) by the appropriate responsible persons. No document should be changed without prior authorization and approval.

6.4. Documents should have unambiguous content and be laid out in an orderly fashion. The title, nature and purpose should be clearly stated.

6.5. Documents should be periodically reviewed and kept up-to-date.

6.6. Superseded documents should not be used.

6.7. Where documents require the entry of data, these entries should be clear, legible and indelible, in compliance with good documentation practices and data integrity requirements.

6.8. Records should be made or completed when any action is taken and in such a way that all significant activities are traceable. Records should be retained for a period of time as defined by internal procedures or national legislation, as appropriate.

6.9. Labels should be clear, unambiguous and in compliance with national or regional legislation as appropriate *(16,17).*

6.10. Labels on the cylinders of medicinal gases should contain at least the information as recommended in the pharmacopoeia, where applicable, as well as the following information:

a) the name of the medicinal gas;

b) the batch number assigned by the manufacturer;

c) the expiry or use-before date, if applicable;

d) any special storage conditions or handling precautions that may be necessary;

e) directions for use;
f) warnings and precautions;
g) the name and address of the manufacturer; and
h) test date (month and year).

6.11. Authorized specifications and testing procedures should be available.

6.12. Records should be maintained for each batch of gas manufactured.

Standard operating procedures and records

6.13. SOPs and associated records should be available for at least, but not limited to:
a) equipment;
b) analytical apparatus and instruments;
c) maintenance and calibration;
d) cleaning and sanitization;
e) personnel matters such as training, clothing and hygiene;
f) qualification and validation;
g) self-inspection
h) complaints;
i) recalls; and
j) returns.

6.14. The SOPs for sampling should specify the person(s) authorized to take samples and the sampling instructions.

6.15. The SOPs describing the details of the batch (lot) numbering system should ensure that each batch of medicinal gas is identified with a specific batch number.

6.16. Records of analysis should be maintained.

6.17. Written release and rejection procedures should be available, in particular for the release of the finished product for sale.

6.18. Records should be maintained of the distribution of each batch of medicinal gas.

6.19. Records should be kept for major and critical equipment, as appropriate, of any qualifications, calibrations, maintenance, cleaning or repair operations, including the dates and the identities of the people who carried out these operations.

7. Complaints

7.1. There should be a written procedure describing the handling of complaints.

7.2. Any complaint concerning a defect of a medicinal gas should be recorded in detail and thoroughly investigated.

7.3. Where necessary, the appropriate follow-up action should be taken after the investigation and evaluation of a complaint. Where necessary, a recall of the batch or batches should be considered.

7.4. All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

7.5. The competent authorities should be informed if a manufacturer is considering action following the identification of serious quality problems with a medicinal gas that may be impacting patients.

8. Recalls

8.1. There should be a written, authorized procedure describing the managing of a recall of medicinal gases.

8.2. The competent authority of the countries in which a product is recalled or withdrawn from the market should be notified.

8.3. The recall of a medicinal gas should be documented. Records should be kept.

9. Returns

9.1. There should be a written, authorized procedure describing the managing of returns of medicinal gases.

9.2. Once distributed, medicinal gases may only be returned under agreed conditions as defined by the manufacturer.

9.3. Returned medicinal gases should be stored in a controlled manner, in a dedicated area. Returned goods should be clearly identified and kept until a decision is made as to what should be done with the returned goods.

9.4. Inventory records of returned medicinal gases should be kept.

10. Self-inspection, quality audits and supplier's audits and approvals

10.1. Self-inspections should be carried out according to a written, authorized procedure. The objective should be to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions.

10.2. Self-inspections should be performed routinely and may be, in addition, performed on special occasions.

10.3. Self-inspections should be done by a team of personnel with knowledge of the manufacture and control of medicinal gases and who are qualified to evaluate compliance with GxP.

10.4. Self-inspections should cover, for example:

a) personnel;

b) premises;
c) maintenance;
d) equipment;
e) production;
f) quality control;
g) documentation including label control;
h) sanitation and hygiene;
i) validation and qualification;
j) calibration;
k) batch release;
l) recall procedures;
m) complaints management; and
n) results of previous self-inspections and any corrective steps taken.

10.5. A report should be made at the completion of a self-inspection.

10.6. Appropriate recommendations for corrective action should be implemented and an effective follow-up programme should be implemented. The effectiveness of corrective actions taken should be verified.

10.7. Self-inspections may be supplemented by quality audits and conducted by outside or independent specialists. The qualifications of external auditors should be documented.

10.8. Suppliers and contractors should be evaluated before they are approved and included in the approved list. The evaluation should consider a supplier's or contractor's history and the nature of the materials to be supplied or services to be contracted. If an audit is required, it should determine the supplier's or contractor's ability to conform with GMP or the applicable standards.

11. Premises

11.1. The premises where medicinal gases are manufactured should be located, designed, constructed and maintained to suit the operations to be carried out.

11.2. 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 products.

11.3. The premises should provide sufficient space for manufacturing, quality control testing and storage operations.

11.4. There should be:

a) separate marked areas for different gases; and

b) clear identification and segregation of cylinders/mobile cryogenic vessels at various stages of processing (e.g. “filled cylinders/mobile cryogenic vessels”, “waiting checking”, "awaiting filling", "quarantine", "certified", “rejected“, “prepared deliveries”, “empty cylinders/home cryogenic vessels”).

Note: 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 could be used.

The segregation of the products may be achieved electronically using a validated electronic system as long as the standards for the cylinders and the vessels intended for medicinal gases are maintained.

11.5. Empty cylinders/home cryogenic vessels (after sorting or maintenance), as well as filled cylinders, should be stored under cover and be protected from adverse weather conditions.

11.6. Filled cylinders/mobile cryogenic vessels should be stored in a manner that ensures that they will be delivered in a clean state, compatible with the environment in which they will be used. Specific storage conditions should be provided as required (e.g. for gas mixtures where phase separation occurs upon freezing).

12. Equipment and utilities

12.1. Equipment and utilities should be selected, located, constructed and maintained to suit the

operations to be carried out.

12.2. The layout, design, installation and use of equipment and utilities should aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

12.3. Equipment should be designed to ensure that the correct gas is filled into the correct container. There should normally be no cross connections between pipelines carrying different gases. If cross connections are needed (e.g. filling equipment of mixtures), qualification and controls should ensure that there is no risk of cross-contamination between the different gases. In addition, the manifolds should be equipped with specific connections. These connections may be subject to international or national standards. The use of connections meeting different standards at the same filling site should be carefully controlled, as well as the use of adaptors needed in some situations to bypass the specific fill connection systems.

12.4. Tanks and tankers should be dedicated to a single and defined quality of gas. Where non-dedicated tanks and tankers are used, risks of contamination should be assessed and controlled. This may include applying the same good practices in the production and having the same quality specification for industrial and medicinal gas.

12.5. A common system supplying gas to medicinal and industrial gas manifolds is only acceptable if there is a validated method to prevent backflow from the industrial gas line to the medicinal gas line.

12.6. Filling manifolds should be dedicated to a single medicinal gas or to a given mixture of medicinal gases. In exceptional cases, filling gases used for other medical purposes on manifolds dedicated to medicinal gases may be acceptable if justified and performed under control. In these cases, the quality of the industrial gas should be at least equal to the required quality of the medicinal gas and GMP standards should be maintained. Filling should then be carried out by campaigns.

12.7. Repairs, maintenance, cleaning and purging operations of equipment should not adversely affect the quality of the medicinal gases. Procedures should describe the measures to be taken after repair and maintenance operations involving breaches of the system's integrity. It should be demonstrated that the equipment is free from any contamination that may adversely affect the quality of the finished product before releasing it for use. Records should be maintained.

12.8. A procedure should describe the measures to be taken when a tanker is taken back into medicinal gas service, for example, after transporting industrial gas or after a maintenance operation. This should include, for example, a change in service documentation and analytical testing. The methods should be validated.

13. Qualification and validation

13.1. The scope and extent of qualification and validation should be determined based on risk management principles.

13.2. Risk assessment should be done and cover, for example, the premises, equipment, processing, filling, storage and distribution of medicinal gases.

13.3. Authorized procedures, protocols and records should be maintained.

14. Production

14.1. The manufacturing of medicinal gases should generally be carried out in closed equipment.

Note: Active substance gases can be prepared by chemical synthesis or be obtained from natural sources followed by purification steps, if necessary (e.g. in an air separation plant). Where air separation is used to manufacture active substance gases, the manufacturer should ensure that the ambient air is appropriate for the established process. Changes in ambient air quality should be documented and evaluated.

14.2. Controls should be identified and implemented to exclude the risks of contamination, for example, from personnel and the environment.

14.3. Manufacturing data and information should be included in the records for each batch of cylinders/mobile cryogenic vessels produced.

14.4. Records should be maintained for each batch of gas manufactured. These records should, as appropriate, include relevant information such as the following:

a) name of the product;
b) batch number;
c) identification of the person(s) carrying out each significant step;
d) equipment used (e.g. filling manifold);
e) quantity of cylinders/mobile cryogenic vessels before filling, including individual identification references and water capacity(ies);
f) pre-filling operations performed;
g) key parameters that are needed to ensure correct fill at standard conditions;
h) results of appropriate checks to ensure the containers have been filled;
i) specification of the finished product and the results of quality control tests (including reference to the calibration status of the test equipment);
j) quantity of rejected cylinders/mobile cryogenic vessels with individual identification references and reasons for rejections;
k) details of any problems or unusual events and signed authorisation for any deviation from instructions;
l) batch label; and
m) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment) by the responsible person, date and signature.

14.5. Each filled cylinder should be traceable to significant aspects of the production and filling operations.

14.6. Cylinders and mobile cryogenic vessels should be checked, prepared, filled and stored in a manner that will prevent mix-ups. Controls should be appropriate and may include labelling,

colour coding, signage or separate areas to facilitate segregation between industrial and medicinal cylinders and vessels.

14.7. There should be no exchange of cylinders/mobile cryogenic vessels used for medicinal and industrial gases in or from these areas, unless all comply with the specifications of medicinal gases and the manufacturing operations are performed according to GMP standards.

14.8. The production through a continuous process such as air separation should be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation.

14.9. The transfers and deliveries of active substance gases in bulk should comply with the same requirements as those for the medicinal gases.

14.10. The filling of active substance gases into cylinders or into mobile cryogenic vessels should comply with the same requirements as those for the medicinal gases.

14.11. Requirements applying to cylinders should also apply to cylinders bundles (except storage and transportation under cover).

14.12. Records should be maintained for each batch of gas transferred to tankers. These records should include, as appropriate, relevant information such as the following:

a) name of the product;
b) batch number;
c) identification reference for the tank (tanker) in which the batch is certified;
d) date and time of the filling operation;
e) identification of the person(s) carrying out the filling of the tank (tanker);
f) identification of the person(s) carrying out each significant step (e.g. line clearance, receipt, preparation before filling, filling, etc.);
g) reference to the supplying tanker (tank), reference to the source gas as applicable;
h) relevant details concerning the filling operation;
i) equipment used (e.g. filling manifold);
j) pre-filling operations performed;

k) key parameters that are needed to ensure correct fill at standard conditions;

l) a sample of the batch label;

m) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);

n) details of any problems or unusual events, and signed authorisation for any deviation from filling instructions; and

o) certification statement by the authorized responsible person, date and signature.

Transfers and deliveries of cryogenic and liquefied gas

14.13. The transfers of cryogenic or liquefied gases from primary storage, including controls before transfers, should be in accordance with validated procedures designed to avoid any contamination. Transfer lines should be equipped with non-return valves or suitable alternatives. Flexible connections and coupling hoses and connectors should be flushed with the relevant gas before use.

14.14. The transfer hoses used to fill tanks and tankers should be equipped with product-specific connections. The use of adaptors allowing the connection of tanks and tankers not dedicated to the same gases should be adequately controlled.

14.15. Deliveries of gas may be added to tanks containing the same quality of gas provided that a sample is tested to ensure that the quality of the delivered gas is acceptable. This sample may be taken from the gas to be delivered or from the receiving tank after delivery.

Filling and labelling of cylinders and mobile cryogenic vessels

14.16. Before filling cylinders and mobile cryogenic vessels, a batch (batches) of gas(es) should be determined, controlled according to specifications and approved for filling.

14.17. In the case of continuous processes, adequate in-process controls should be performed to ensure that the gas complies with specifications.

14.18. Cylinders, mobile cryogenic vessels and valves should conform to appropriate technical specifications and any relevant requirements by the applicable regulatory authorities. They should be dedicated to a single medicinal gas or to a given mixture of medicinal gases.

14.19. Cylinders should be colour-coded according to relevant standards. They should preferably be fitted with minimum pressure retention valves unless other controls are in place to ensure the quality and integrity of the medicinal gas.

14.20. Cylinders, mobile cryogenic vessels and valves should be checked before first use in production and should be properly maintained.

14.21. Checks and maintenance operations should not affect the quality and the safety of the medicinal gas. The water used for the hydrostatic pressure testing carried out on cylinders should be at least of drinking quality.

14.22. As part of the checks and maintenance operations, cylinders should be subject to an internal visual inspection before fitting the valve to make sure they are not contaminated with water or other contaminants.

14.23. Internal visual inspection should be done:

a) when they are new and initially put into medicinal gas service;

b) following any hydrostatic statutory pressure test or equivalent test where the valve is removed; and

b) whenever the valve is replaced.

Note: After fitting, the valve should be kept closed to prevent any contamination from entering the cylinder.

14.24. 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. Subcontractors should be audited to ensure that appropriate standards are maintained.

14.25. Where possible, a system should be implemented to ensure traceability of cylinders and mobile cryogenic vessels.

14.26. Checks to be performed before filling should be done in accordance with an authorized procedure. The following checks should be observed:

a) in the case of cylinders fitted with a minimum pressure retention valve, for a positive residual pressure in each cylinder;

b) in the case of cylinders that are not fitted with a minimum pressure retention valve, to make sure it is not contaminated with water or other contaminants;

c) ensuring that all previous batch labels have been removed;

d) the removal and replacement of damaged product labels;

e) a visual external inspection of each cylinder, mobile cryogenic vessel and valve for dents, arc burns, debris, other damage and contamination with oil or grease; cleaning should be done if necessary;

f) on each cylinder or mobile cryogenic vessel outlet connection to determine that it is the proper type for the particular gas involved;

g) for the date of the next test to be performed on the valve (in the case of valves that need to be periodically tested);

h) on cylinders or mobile cryogenic vessels to ensure that any tests required by national or international regulations (e.g. hydrostatic pressure test or equivalent for cylinders) have been conducted and are still valid; and

i) that each cylinder is labelled as required.

14.27. A batch should be defined for filling operations.

14.28. Cylinders and mobile cryogenic vessels, which have been returned for refilling, should be prepared with care in order to minimise risks for contamination. These procedures, which should include evacuation and/or purging operations, should be validated.

14.29. There should be appropriate checks to ensure that each cylinder/mobile cryogenic vessel has been properly filled.

14.30. Each filled cylinder should be tested for leaks using an appropriate method prior to fitting the tamper resistant seal or device. The test method should not introduce any contaminant into the valve outlet and, if applicable, should be performed after any quality sample is taken.

14.31. After filling, cylinder valves should be fitted with covers to protect the outlets from contamination. Cryogenic vessels should be fitted with tamper resistant devices.

14.32. Each cylinder or mobile cryogenic vessel should be labelled. Patient Information Leaflets can be made available electronically.

14.33. In the case of medicinal gases produced by mixing two or more different gases (in-line before filling or directly into the cylinders), the mixing process should be validated to ensure that the gases are properly mixed in every cylinder and that the mixture is homogeneous.

15. Quality control

15.1. Each batch of medicinal gas (cylinders, mobile cryogenic vessels, tanks) should be tested in accordance with the Marketing Authorization, authorized specification and/or pharmacopoeia.

Sampling

15.2. There should be an authorized sampling procedure with a sampling plan for testing medicinal gases.

15.3. In the case of a single medicinal gas:

a) 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; and

b) 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.

Note: An example of an uninterrupted filling cycle is one shift's production using the same personnel, equipment and batch of gas to be filled.

15.4. In the case of a medicinal 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.

15.5. 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 case of validated automated filling system.

15.6. Premixed gases should follow the same principles as single gases when continuous in-line testing of the mixture to be filled is performed. Premixed gases should follow the same principle as medicinal gases produced by mixing gases in the cylinders when there is no continuous inline testing of the mixture to be filled.

15.7. The testing for water content should be performed, where required. (Note the requirements in the pharmacopoeia and as specified by the national regulatory authority.)

15.8. Other sampling and testing procedures that provide at least an equivalent level of quality assurance may be justified.

15.9. Final testing on mobile cryogenic vessels should include a test for assay and identity on each vessel unless otherwise authorized by the medicines regulatory authority. 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.

Note: Where mobile cryogenic vessels are warm or returned from the market with residual product, the gas generated when filling the vessel is sufficient to purge the vessel adequately without any additional purging steps to remove any atmospheric contamination.

15.10. 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.

15.11. Records of manual analysis should include at least the following:

a) name of the medicinal gas;
b) batch number;
c) references to the relevant specifications and testing procedures as approved in the Marketing Authorization;
d) test results and reference to any specifications (limits);
e) date(s) and reference number(s) of testing;
f) initials of the persons who performed the testing;
g) date and initials of the persons who verified the testing and the calculations, where appropriate; and
h) a clear statement of release or rejection (or other status decision) and the date and signature of the designated responsible person.

15.12. Records of automatic analysis should include at least the following:

a) name of the medicinal gas and time and date and the identity of the person initiating the test. Where access to the sampling and analysis system is controlled, the initials of the person initiating the test may be automatically recorded. The person initiating the test is not required to be part of the Quality Control department;
b) batch number;
c) test results, reference to the specification limits and a statement of passed or rejected; and
d) a clear statement of the change of status of the product being tested.

Note: For automated systems, the person initiating the testing may be the same person responsible for filling the cylinders. Formal approval of the test results may be performed by the responsible person remotely to indicate approval or rejection.

15.13. For bulk medicinal liquid oxygen tankers used for the filling of cryogenic vessels at the customers premises, certification and release of batches by the responsible person may be performed retrospectively within a defined timeframe provided the medicinal gas manufacturer can demonstrate that the product being supplied is suitable for patient use.

15.14. Reference and retention samples are not required, unless otherwise specified.

16. Product life cycle and continuous improvement

16.1. Manufacturers of medicinal gases should consider adopting a life cycle approach and continuous improvement. These principles should be applied in the relevant areas of the facility, equipment, instrument, utility, product and processes.

16.2. A means should be identified for continuous improvement to enable optimizing production and control whilst meeting current demands for supply and satisfying quality requirements of medicinal gases.

17. Storage and distribution

17.1. Precautions should be taken to prevent unauthorized persons from entering storage areas.

17.2. Storage areas should be under cover with sufficient capacity to allow the orderly storage of the different medicinal gases. In exceptional cases where this is not possible, such as bundles of cylinders and large size cylinders, the gas outlet should be protected from environmental contamination.

17.3. Storage areas should be appropriately designed, constructed and maintained. They should be kept clean and dry and there should be sufficient space and ventilation.

17.4. Where special storage conditions are required, these should be provided, controlled, monitored and recorded.

17.5. Empty cylinders should be stored separately.

17.6. A written cleaning programme should be available indicating the frequency of cleaning and the methods to be used to clean the storage areas.

17.7. There should be a written programme for pest control.

17.8. Broken or damaged cylinders that can no longer be used should be withdrawn from usable stock and stored separately.

17.9. Periodic stock reconciliation should be performed at defined intervals by comparing the actual and recorded stocks. Discrepancies should be identified and investigated. The appropriate corrective action should be taken.

Distribution

17.10. Filled gas cylinders and home cryogenic vessels should be handled in a manner to ensure that they are delivered to customers in a clean and safe state.

17.11. Medicinal gases should be transported in accordance with the conditions stated on the labels.

17.12. Product, batch and container identity should be maintained at all times. All labels should remain legible.

17.13. Distribution records should be sufficiently detailed to allow for a recall when required.

17.14. Appropriately equipped vehicles should be suitable for the transport of medicinal gases, with sufficient space.

17.15. Vehicles should be kept clean and maintained.

17.16. Defective vehicles and equipment should not be used. These should either be labelled as such or removed from service.

17.17. There should be procedures in place for the operation and maintenance of all vehicles and equipment.

17.18. There should be written procedures, programmes and records for the cleaning of tankers and vehicles. Agents used should not have any adverse effect on product quality or be a source of contamination.

17.19. There should be documented, detailed procedures for the dispatch of medicinal gases. Records for the dispatch should include relevant information to allow for traceability. Such records should facilitate the recall of a batch of a medicinal gas when necessary.

17.20. Tankers and cylinders should be secured to prevent unauthorized access.

17.21. Procedures for transport should ensure that:

a) the identity of the medicinal gas is not lost;

b) there is no risk of contamination of the medicinal gas;

c) precautions are taken against damage and theft; and

d) environmental conditions are maintained, if required.

17.22. The appropriate signs and warnings, where required, should be visible on tankers and vehicles.

References

Note: Some parts of the text may have been adapted from other WHO GMP guidelines, as well as those published by the European Union and Pharmaceutical Inspection Co-operation Scheme. The intention is to establish a document which reflects current requirements and is harmonized with these texts. For further details on some of the topics, further reading of original guidelines is recommended.

1. WHO good manufacturing practices for active pharmaceutical ingredients. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957).
2. WHO good manufacturing practices for pharmaceutical products: main principles. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eight report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986).
3. WHO good manufacturing practices: water for pharmaceutical use. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. Geneva: World Health Organization; 2021: Annex 3 (WHO Technical Report Series, No.1033).
4. WHO guideline on data integrity. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. Geneva: World Health Organization; 2021: Annex 4 (WHO Technical Report Series, No. 1033.

5. WHO good practices for pharmaceutical quality control laboratories. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957).

6. WHO good storage and distribution practices for medical products. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 7 (WHO Technical Report Series, No. 1025).

7. WHO guidelines for sampling of pharmaceutical products and related materials. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. Geneva: World Health Organization; 2005: Annex 4 (WHO Technical Report Series, No. 929).

8. WHO guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 8 (WHO Technical Report Series, No. 1010).

9. WHO good manufacturing practices: guidelines on validation. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva, World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019).

10. WHO good practices for pharmaceutical microbiology laboratories. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva, World Health Organization; 2011: Annex 2 (WHO Technical Report Series, No. 961).

11. WHO guidelines on quality risk management. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva, World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981).

12. WHO technical supplements to model guidance for storage and transport of time- and temperature-sensitive pharmaceutical products. In. WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva, World Health Organization; 2015: Annex 5 (WHO Technical Report Series, No. 992).

13. Inspection on medicinal gases – Aide-Memoire PI 025-2. Geneva, Pharmaceutical Inspection Co-Operation Scheme 2007.

14. Manufacture of Medicinal Gases. In. EudraLex – The rules governing medicinal products in the European Union, Volume 4, Good Manufacturing Practice. Brussels, European Commission Enterprise and Industry Directorate-General; 2010: Annex 6.

15. *The International Pharmacopoeia* 10th Edition. Geneva, World Health Organization; 2020.

16. ISO 32:1977(en). Gas cylinders for medical use — Marking for identification of content International Standard ISO 32. Geneva: International Organization for Standardization, 1977.

17. ISO 7225:2005(en). Gas cylinders — Precautionary labels International Standard ISO 7225. Geneva: International Organization for Standardization, 2005.

***