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1. Principle

This annex deals with industrial manufacturing of medicinal gases, which is a specialised industrial process not normally undertaken by pharmaceutical companies. It does not cover manufacturing and handling of medicinal gases in hospitals, which will be subject to national legislation. However relevant parts of this annex may be used as a basis for such activities.

The manufacture of medicinal gases is generally carried out in closed equipment. Consequently, environmental contamination of the product is minimal. However, there is a risk of cross-contamination with other gases.

Manufacture of medicinal gases should comply with the basic requirements of GMP, with applicable annexes, Pharmacopoeial standards and the following detailed guidelines.

2. Personnel

2.1. The qualified person responsible for release of medicinal gases should have a thorough knowledge of the production and control of medicinal gases.

2.2. All personnel involved in the manufacture of medicinal gases should understand the GMP requirements relevant to medicinal gases and should be aware of the critically important aspects and potential hazards for patients from products in the form of medicinal gases.

3. Premises and equipment

3.1. Premises

3.1.1. Medicinal gases should be filled in a separate area from non-medicinal gases and there should be no exchange of containers between these areas. In exceptional cases, the principal of campaign filling in the same area can be accepted provided that specific precautions are taken and necessary validation is done.

3.1.2. Premises should provide sufficient space for manufacturing, testing and storage operations to avoid the risk of mix-up. Premises should be clean and tidy to encourage orderly working and adequate storage.

3.1.3. Filling areas should be of sufficient size and have an orderly layout to provide:

a. separate marked areas for different gases

b. clear identification and segregation of empty cylinders and cylinders at various stages of processing (e.g. "awaiting filling", "filled", "quarantine", "approved" “rejected “).

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

3.2. Equipment

3.2.1. All equipment for manufacture and analyses should be qualified and calibrated regularly as appropriate.

3.2.2. It is necessary to ensure that the correct gas is put into the correct container. Except for validated automated filling processes there should be no interconnections between pipelines carrying different gases. The manifolds should be equipped with fill connections that correspond only to the valve for that particular gas or particular mixture of gases so that only the correct containers can be attached to the manifold. (The use of manifold and container valve connections may be subject to international or national standards.)

3.2.3. Repair and maintenance operations should not affect the quality of the medicinal gases.

3.2.4. Filling of non-medicinal gases should be avoided in areas and with equipment destined for the production of medicinal gases. Exceptions can be acceptable if the quality of the gas used for non-medicinal purposes is at least equal to the quality of the medicinal gas and GMP-standards are maintained. There should be a validated method of backflow prevention in the line supplying the filling area for non-medicinal gases to prevent contamination of the medicinal gas.

3.2.5. Storage tanks and mobile delivery tanks should be dedicated to one gas and a well-defined quality of this gas. However liquefied medicinal gases may be stored or transported in the same tanks as the same non-medicinal gas provided that the quality of the latter is at least equal to the quality of the medicinal gas.

4. Documentation

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

- the name of the product;
- the date and the time of the filling operations;
- a reference to the filling station used;
- equipment used;
- name and reference to the specification of the gas or each gas in a mixture
- pre filling operations performed (see point 7.3.5);
- the quantity and size of cylinders before and after filling;
- the name of the person carrying out the filling operation;
- the initials of the operators for each significant step (line clearance, receipt of cylinders, emptying of cylinders etc);
- key parameters that are needed to ensure correct fill at standard conditions;
- the results of quality control tests and where test equipment is calibrated before each test, the reference gas specification and calibration check results;
- results of appropriate checks to ensure the containers have been filled
- a sample of the batch code label;
- details of any problems or unusual events, and signed authorisation for any deviation from filling instructions;
- to indicate agreement, the date and signature of the supervisor responsible for the filling operation.

5. Production

5.1. All critical steps in the different manufacturing processes should be subject to validation.

5. 2. Bulk production

5.2.1. Bulk gases intended for medicinal use could be prepared by chemical synthesis or obtained from natural resources followed by purification steps if necessary (as for example in an air separation plant). These gases could be regarded as Active Pharmaceutical Ingredients (API) or as bulk pharmaceutical products as decided by the national competent authority.

5.2.2. Documentation should be available specifying the purity, other components and possible impurities that may be present in the source gas and at purification steps, as applicable. Flow charts of each different process should be available.

5.2.3. All separation and purification steps should be designed to operate at optimal effectiveness. For example, impurities that may adversely affect a purification step should be removed before this step is reached.

5.2.4. Separation and purification steps should be validated for effectiveness and monitored according to the results of the validation. Where necessary, in-process controls should include continuous analysis to monitor the process. Maintenance and replacement of expendable equipment components, e.g. purification filters, should be based on the results of monitoring and validation.

5.2.5. If applicable, limits for process temperatures should be documented and in-process monitoring should include temperature measurement.

5.2.6. Computer systems used in controlling or monitoring processes should be validated.

5.2.7. For continuous processes, a definition of a batch should be documented and related to the analysis of the bulk gas.

5.2.8. Gas production should be continuously monitored for quality and impurities.

5.2.9. Water used for cooling during compression of air should be monitored for microbiological quality when in contact with the medicinal gas.

5.2.10. All the transfer operations, including controls before transfers, of liquefied gases from primary storage should be in accordance with written procedures designed to avoid any contamination. The transfer line should be equipped with a non-return valve or other suitable alternative. Particular attention should be paid to purge the flexible connections and to coupling hoses and connectors.

5.2.11. Deliveries of gas may be added to bulk storage tanks containing the same gas from previous deliveries. The results of a sample must show that the quality of the delivered gas is acceptable. Such a sample could be taken from

- the delivered gas before the delivery is added; or

- from the bulk tank after adding and mixing

5.2.12 Bulk gases intended for medicinal use should be defined as a batch, controlled in accordance with relevant Pharmacopoeial monographs and released for filling.

5.3. Filling and labelling

5.3.1. For filling of medicinal gases the batch should be defined.

5.3.2. Containers for medicinal gases should conform to appropriate technical specifications. Valve outlets should be equipped with tamper-evident seals after filling. Cylinders should preferably have minimum retention valves in order to get adequate protection against contamination.

5.3.3. The medicinal gases filling manifold as well as the cylinders should be dedicated to a single medicinal gas or to a given mixture of medicinal gases (see also 3.2.2). There should be a system in place ensuring traceability of cylinders and valves.

5.3.4. Cleaning and purging of filling equipment and pipelines should be carried out according to written procedures. This is especially important after maintenance or breaches of system integrity. Checks for the absence of contaminants should be carried out before the line is released for use. Records should be maintained.

5.3.5. Cylinders should be subject to an internal visual inspection when
- they are new
- in connection with any hydrostatic pressure test or equivalent test

After fitting of the valve, the valve should be maintained in a closed position to prevent any contamination from entering the cylinder.

5.3.6. Checks to be performed before filling should include:
- a check to determine the residual pressure (>3 to 5 bar) to ensure that the cylinder is not emptied

- Cylinders with no residual pressure should be put aside for additional measures to make sure they are not contaminated with water or other contaminants. These could include cleaning with validated methods or visual inspection as justified.

- Assuring that all batch labels and other labels if damaged have been removed

- visual external inspection of each valve and container for dents, arc burns, debris, other damage and contamination with oil or grease; Cylinders should be cleaned, tested and maintained in an appropriate manner.

- a check of each cylinder or cryogenic vessel valve connection to determine that it is the proper type for the particular medicinal gas involved;

- a check of the cylinder “test code date” to determine that the hydrostatic pressure test or equivalent test has been conducted and still is valid as required by national or international guidelines.

- a check to determine that each container is colour-coded according to the relevant standard

5.3.7. Cylinders which have been returned for refilling should be prepared with great care in order to minimise risks for contamination. For compressed gases a maximum theoretical impurity of 500 ppm v/v should be obtained for a filling pressure of 200 bar (and equivalent for other filling pressures).

Cylinders could be prepared as follows:

- any gas remaining in the cylinders should be removed by evacuating the container [at least to a remaining absolute pressure of 150 millibar]

or

- by blowing down each container, followed by purging using validated methods (partial pressurisation at least to 7 bar and then blowing down)

For cylinders equipped with residual (positive) pressure valves, one evacuation under vacuum at 150 millibar is sufficient if the pressure is positive. As an alternative, full analysis of the remaining gas should be carried out for each individual container.

5.3.8. There should be appropriate checks to ensure that containers have been filled. An indication that it is filling properly could be to ensure that the exterior of the cylinder is warm by touching it lightly during filling.

5.3.9. Each cylinder should be labelled and colour-coded. The batch number and/or filling date and expiry date may be on a separate label.

6. Quality Control

6.1. Water used for hydrostatic pressure testing should be at least of drinking water quality and monitored routinely for microbiological contamination.

6.2. Each medicinal gas should be tested and released according to its specifications. In addition, each medicinal gas should be tested to full relevant pharmacopoeial requirements at sufficient frequency to assure ongoing compliance.

6.3. The bulk gas supply should be released for filling. (see 5.2.12)

6. 6.4. In the case of a single medicinal gas filled via a multi-cylinder manifold, at least one cylinder of product from each manifold filling should be tested for identity, assay and if necessary water content each time the cylinders are changed on the manifold.

7. 6.5. In the case of a single medicinal gas filled ~~put~~ into cylinders one at a time by individual filling operations, at least one cylinder of each uninterrupted filling cycle should be tested for identity and assay. An example of an uninterrupted filling operation cycle is one shift's production using the same personnel, equipment, and batch of bulk gas.

6.6. In the case of a medicinal gas produced by mixing two or more different gases in a cylinder from the same manifold, at least one cylinder from each manifold filling operation cycle should be tested for identity, assay and if necessary water content of all of the component gases and for identity of the balance gas in the mixture. When cylinders are filled individually, every cylinder should be tested for identity and assay of all of the component gases and at least one cylinder of each uninterrupted filling cycle should be tested for identity of the balance gas in the mixture.

6.7. When gases are mixed in-line before filling (e.g. nitrous oxide/oxygen mixture) continuous analysis of the mixture being filled is required.

6.8. When a cylinder is filled with more than one gas, the filling process must ensure that the gases are correctly mixed in every cylinder and are fully homogeneous.

6.9. Each filled cylinder should be tested for leaks using an appropriate method, prior to fitting the tamper evident seal. Where sampling and testing is carried out the leak test should be completed after testing.

6.10. In the case of cryogenic gas filled into cryogenic home vessels for delivery to users, each vessel should be tested for identity and assay.

6.11. Cryogenic vessels which are retained by customers and where the medicinal gas is refilled in place from dedicated mobile delivery tanks need not be sampled after filling provided the filling company delivers a certificate of analysis for a sample taken from the mobile delivery tank. Cryogenic vessels retained by customers should be periodically tested to confirm that the contents comply with Pharmacopoeial requirements.

6.12. Retained samples are not required, unless otherwise specified.

7. Storage and release

7.1. Filled cylinders should be held in quarantine until released by the qualified person.

7.2. Gas cylinders should be stored under cover and not be subjected to extremes of temperature. Storage areas should be clean, dry, well ventilated and free of combustible materials to ensure that cylinders remain clean up to the time of use.

7.3. Storage arrangements should permit segregation of different gases and of full/empty cylinders and permit rotation of stock on a first in – first out basis.

7.4. Gas cylinders should be protected from adverse weather conditions during transportation. Specific conditions for storage and transportation should be employed for gas mixtures for which phase separation occurs on freezing.

Glossary

Definition of terms relating to manufacture of medicinal gases, which are not given in the glossary of the current PIC/S Guide to GMP, but which are used in this Annex are given below.

Air separation plant
Air separation plants take atmospheric air and through processes of purification, cleaning, compression, cooling, liquefaction and distillation separates the air into the gases oxygen, nitrogen and argon

Area
Part of premises that is specific to the manufacture of medicinal gases

Blowing down
Blow the pressure down to atmospheric pressure

Bulk gas
Any gas intended for medicinal use, which has completed all processing up to but not including final packaging

Compressed gas
A gas which when packaged under pressure is entirely gaseous at –50 ^{0} C. (ISO 10286)

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

Cryogenic gas
Gas which liquefies at 1.013 bar at temperature below –150^{0} C.

Cryogenic vessel
A static or mobile thermally insulated container designed to contain liquefied or cryogenic gases. The gas is removed in gaseous or liquid form.

Cylinder
A transportable, pressure container with a water capacity not exceeding 150 litres. In this document when using the word cylinder it includes cylinder bundle (or cylinder pack) when appropriate.

Cylinder bundle
A ~~set~~ assembly of cylinders, which are fastened together in a frame and interconnected by a manifold, transported and used as a unit.

Evacuate
To remove the residual gas in a container by pulling a vacuum on it.

Gas
A substance or a mixture of substances that is completely gaseous at 1,013 bar (101,325 kPa) and +15 ^{0} C or has a vapour pressure exceeding 3 bar (300 kPa) at + 50 ^{0} C. (ISO 10286)

Hydrostatic pressure test
Test performed for safety reasons as required by national or international guideline in order to make sure that cylinders or tanks can withhold high pressures.

Liquefied gas
A gas which when packaged under pressure, is partially liquid (gas over a liquid) at –50 ^{0} C.

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

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

Medicinal gas
Any gas or mixture of gases intended to be administered to patients for therapeutic, diagnostic or prophylactic purposes using pharmacological action and classified as a medicinal product.

Minimum pressure retention valve
Valve equipped with a non-return system which maintains a definite pressure (about 3 to 5 bars over atmospheric pressure) in order to prevent contamination during use.

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

Purge
To empty and clean a cylinder
- by blowing down and evacuating or
- by blowing down, partial pressurisation with the gas in question and then blowing down.

Tank
Static container for the storage of liquefied or cryogenic gas.

Tanker
Container fixed on a vehicle for the transport of liquefied or cryogenic gas.

Valve
Device for opening and closing containers.

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