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Annex 6

Manufacture of Medicinal Gases

Document History	
The Annex was revised as a consequence of the restructuring of the GMP Guide and the need to modify the requirements of Part II of the Guide for applicability to medicinal gases. There was a need to define more clearly what should be considered as a starting material as opposed to a bulk pharmaceutical product. The opportunity was also been taken to update the annex in general.	February 2007
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PRINCIPLE

Gases which fulfil the definition of medicinal product of Directive 2001/83/EC or Directive 2001/82/EC (hereinafter, medicinal gases) are subject to the requirements laid down in these Directives, including the requirements on manufacturing. In this regard, this Annex deals with the manufacture of active substance gases and with the manufacture of medicinal gases.

The delineation between the manufacture of the active substance and the manufacture of the medicinal product should be clearly defined in each Marketing Authorisation dossier. Normally, the production and purification steps of the gas belong to the field of manufacture of active substances. Gases enter the pharmaceutical field from the first storage of gas intended for such use.

Manufacture of active substance gases should comply with the Basic Requirements of this guide (Part II), with the relevant part of this Annex, and with the other Annexes of the guide if relevant.

Manufacture of medicinal gases should comply with the Basic Requirements of this guide (Part I), with the relevant part of this Annex, and with the other Annexes of the guide if relevant.

In the exceptional cases of continuous processes where no intermediate storage of gas between the manufacture of the active substance and the manufacture of the medicinal product is possible, the whole process (from starting materials of active substance to medicinal finished product) should be considered as belonging to the pharmaceutical field. This should be clearly stated in the Marketing Authorisation dossier.

The Annex does not cover the manufacture and handling of medicinal gases in hospitals unless this is considered industrial preparation or manufacturing. However, relevant parts of this Annex may be used as a basis for such activities.

MANUFACTURE OF ACTIVE SUBSTANCE GASES

Active substance gases can be prepared by chemical synthesis or be obtained from natural sources followed by purification steps, if necessary (as for example in an air separation plant).

1. The processes corresponding to these two methods of manufacturing active substance gases should comply with Part II of the Basic Requirements. However:

(a) the requirements regarding starting materials for active substances (Part II Chapter 7) do not apply to the production of active substance gases by air separation (however, the manufacturer should ensure that the quality of ambient air is suitable for the established process and any changes in the quality of ambient air do not affect the quality of the active substance gas);

(b) the requirements regarding on-going stability studies (Part II chapter 11.5), which are used to confirm storage conditions and expiry/retest dates (Part II chapter 11.6), do not apply in case initial stability studies have been replaced by bibliographic data (see Note for Guidance CPMP/QWP/1719/00); and

(c) the requirements regarding reserve/retention samples (Part II chapter 11.7) do not apply to active substance gases, unless otherwise specified.

2. The production of active substance gases through a continuous process (e.g. air separation) should be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation.

3. In addition:

(a) transfers and deliveries of active substance gases in bulk should comply with the same requirements as those mentioned below for the medicinal gases (sections 19 to 21 of this Annex);

(b) filling of active substance gases into cylinders or into mobile cryogenic vessels should comply with the same requirements as those mentioned below for the medicinal gases (sections 22 to 37 of this Annex) as well as Part II Chapter 9.

MANUFACTURE OF MEDICINAL GASES

Manufacture of medicinal gases is generally carried out in closed equipment. Consequently, environmental contamination of the product is minimal. However, risks of contamination (or cross contamination with other gases) may arise, in particular because of the reuse of containers.

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

Personnel

5. All personnel involved in manufacture and distribution of medicinal gases should receive an appropriate GMP training specifically applying to this type of products. They should be aware of the critically important aspects and potential hazards for patients from these products. The training programs should include the tanker lorries drivers.

6. Personnel of subcontractors that could influence the quality of medicinal gases (such as personnel in charge of maintenance of cylinders or valves) should be appropriately trained.

Premises and equipment

Premises

7. Cylinders and mobile cryogenic vessels should be checked, prepared, filled and stored in separate areas from non-medicinal gases, and there should be no exchange of cylinders / mobile cryogenic vessels between these areas. However, it could be accepted to check, prepare, fill and store other gases in the same areas, provided they comply with the specifications of medicinal gases and that the manufacturing operations are performed according to GMP standards.

8. Premises should provide sufficient space for manufacturing, testing and storage operations in order to prevent any risk of mix-up. Premises should be designed to provide:

(a) separate marked areas for different gases;

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

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.

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

10. Specific storage conditions should be provided as required by the Marketing Authorisation (e.g. for gas mixtures where phase separation occurs on freezing).

Equipment

11. Equipment should be designed to ensure 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 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 national or international 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. Tanks and tankers should be dedicated to a single and defined quality of gas. However medicinal gases may be stored or transported in the same tanks, other containers used for intermediate storage, or tankers, as the same non-medicinal gas, provided that the quality of the latter is at least equal to the quality of the medicinal gas and that GMP standards are maintained. In such cases, quality risk management should be performed and documented.

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

14. 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 non-medicinal 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.

15. Repair and maintenance operations (including cleaning and purging) of equipment, should not adversely affect the quality of medicinal gases. In particular, procedures should describe the measures to be taken after repair and maintenance operations involving breaches of the system's integrity. Specifically 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.

16. A procedure should describe the measures to be taken when a tanker is back into medicinal gas service (after transporting non-medicinal gas in the conditions mentioned in section 12, or after a maintenance operation). This should include analytical testing.

Documentation

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

(a) name of the product;
(b) batch number;
(c) date and time of the filling operation;
(d) identification of the person(s) carrying out each significant step (e.g. line clearance, receipt, preparation before filling, filling etc.);
(e) batch(es) reference(s) for the gas(es) used for the filling operation as referred to in section 22, including status;
(f) equipment used (e.g. filling manifold);
(g) quantity of cylinders/mobile cryogenic vessels before filling, including individual identification references and water capacity(ies);
(h) pre-filling operations performed (see section 30);
(i) key parameters that are needed to ensure correct filling at standard conditions;
(j) results of appropriate checks to ensure the cylinders/mobile cryogenic vessels have been filled;
(k) a sample of the batch label;
(l) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);
(m) quantity of rejected cylinders/mobile cryogenic vessels, with individual identification references and reasons for rejections;
(n) details of any problems or unusual events, and signed authorisation for any deviation from filling instructions; and
(o) certification statement by the Qualified Person, date and signature.

18. Records should be maintained for each batch of gas intended to be delivered into hospital tanks. These records should, as appropriate, include the following (items to be recorded may vary depending on local legislation):
(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) reference to the supplying tanker (tank), reference to the source gas as applicable;
(g) relevant details concerning the filling operation;

(h) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);
(i) details of any problems or unusual events, and signed authorisation for any deviation from filling instructions; and
(j) certification statement by the Qualified Person, date and signature.

Production

Transfers and deliveries of cryogenic and liquefied gas

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

20. 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.

21. Deliveries of gas may be added to tanks containing the same defined 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.

Note: See specific arrangements in section 42 for filling of tanks retained by customers at the customer's premises.

Filling and labelling of cylinders and mobile cryogenic vessels

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

23. In the case of continuous processes as those mentioned in 'Principle', there should be adequate in-process controls to ensure that the gas complies with specifications.

24. Cylinders, mobile cryogenic vessels and valves should conform to appropriate technical specifications and any relevant requirements of the Marketing Authorisation. They should be dedicated to a single medicinal gas or to a given mixture of medicinal gases. Cylinders should be colour-coded according to relevant standards. They should preferably be fitted with minimum pressure retention valves with non-return mechanism in order to provide adequate protection against contamination.

25. Cylinders, mobile cryogenic vessels and valves should be checked before first use in production, and should be properly maintained. Where CE marked medical devices are used, the maintenance should address the medical device manufacturer's instructions.

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

27. 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. This should be done:

- when they are new and initially put into medicinal gas service;
- following any hydrostatic statutory pressure test or equivalent test where the valve is removed;
- whenever the valve is replaced.

After fitting, the valve should be kept closed to prevent any contamination from entering the cylinder. If there is any doubt about the internal condition of the cylinder, the valve should be removed and the cylinder internally inspected to ensure it has not been contaminated.

28. Maintenance and repair operations of cylinders, mobile cryogenic vessels and valves are the responsibility of the manufacturer of the medicinal 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.

29. There should be a system to ensure the traceability of cylinders, mobile cryogenic vessels and valves.

30. Checks to be performed before filling should include:

(a) in the case of cylinders, a check, carried out according to defined procedure, to ensure there is a positive residual pressure in each cylinder;

- if the cylinder is fitted with a minimum pressure retention valve, when there is no signal indicating there is a positive residual pressure, the correct functioning of the valve should be checked, and if the valve is shown not to function properly the cylinder should be sent to maintenance,

- if the cylinder is not fitted with a minimum pressure retention valve, when there is no positive residual pressure the cylinder should be put aside for additional measures, to make sure it is not contaminated with water or other contaminants; additional measures could consist of internal visual inspection followed by cleaning using a validated method;

(b) a check to ensure that all previous batch labels have been removed;

(c) a check that any damaged product labels have been removed and replaced;

(d) 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;

(e) a check of each cylinder or mobile cryogenic vessel outlet connection to determine that it is the proper type for the particular gas involved;

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

(g) a check of the 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

(h) a check to determine that each cylinder is colour-coded as specified in the Marketing Authorisation (colour-coding of the relevant national / international standards).

31. A batch should be defined for filling operations.

32. Cylinders that have been returned for refilling should be prepared with care in order to minimise the risks of contamination, in line with the procedures defined in the Marketing Authorisation. These procedures, which should include evacuation and/or purging operations, should be validated.

Note: For compressed gases, a maximum theoretical impurity of 500 ppm v/v should be obtained for a filling pressure of 200 bar at 15°C (and equivalent for other filling pressures).

33. Mobile cryogenic vessels that have been returned for refilling should be prepared with care in order to minimise the risks of contamination, in line with the procedures defined in the Marketing Authorisation. In particular, mobile vessels with no residual pressure should be prepared using a validated method.

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

35. Each filled cylinder should be tested for leaks using an appropriate method, prior to fitting the tamper evident seal (see section 36). The test method should not introduce any contaminant into the valve outlet and, if applicable, should be performed after any quality sample is taken.

36. After filling, cylinders valves should be fitted with covers to protect the outlets from contamination. Cylinders and mobile cryogenic vessels should be fitted with tamper-evident seals.

37. Each cylinder or mobile cryogenic vessel should be labelled. The batch number and the expiry date may be on a separate label.

38. 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.

Quality Control

39. Each batch of medicinal gas (cylinders, mobile cryogenic vessels, hospital tanks) should be tested in accordance with the requirements of the Marketing Authorisation and certified.

40. Unless different provisions are required in the Marketing Authorisation, 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 medicinal gas filled into cylinders 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 medicinal 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 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 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 case of 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.

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

Testing for water content should be performed unless otherwise justified

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

41. Unless different provisions are required in the Marketing Authorisation, 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.

42. 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 refillings.

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

44. On-going stability studies are not required in case initial stability studies have been replaced by bibliographic data (see Note for Guidance CPMP/QWP/1719/00).

Transportation of packaged gases

45. Filled gas cylinders and home cryogenic vessels should be protected during transportation, so that, in particular, they are delivered to customers in a clean state compatible with the environment in which they will be used.

GLOSSARY

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

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

Compressed gas
Gas which, when packaged under pressure for transport, is entirely gaseous at all temperatures above –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
A gas which liquefies at 1.013 bar at temperatures below –150°C.

Cylinder
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 that are fastened together, interconnected by a manifold and transported and used as a unit.

Evacuate
To remove the residual gas from a container / system to a pressure less than 1.013 bar, 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 +50°C.

Home cryogenic vessel
Mobile cryogenic vessel designed to hold liquid oxygen and dispense gaseous oxygen at patients' home.

Hydrostatic pressure test
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
A gas which, when packaged for transport, is partially liquid (or solid) at a temperature above $-50^{O}C$.

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

Maximum theoretical residual impurity
Gaseous impurity from a possible backflow that remains after the cylinder pre-treatment process before filling. The calculation of the maximum theoretical residual impurity is only relevant for compressed gases and assumes that the gases behave as perfect gases.

Medicinal gas
Any gas or mixture of gases classified as a medicinal product (as defined in Directives 2001/83/EC and 2001/82/EC).

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 internal contamination of the cylinder.

Mobile cryogenic vessel
Mobile thermally insulated container designed to maintain the contents in a liquid state. In the Annex, this term does not include the tankers.

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

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

Tank
Static thermally insulated container designed for the storage of liquefied or cryogenic gas. They are also called “Fixed cryogenic vessels”.

Tanker
In the context of the Annex, thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas.

Valve
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 atmosphere.