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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON MEDICINAL GASES: PHARMACEUTICAL DOCUMENTATION (INCLUDING RECOMMENDATION ON NON-CLINICAL SAFETY REQUIREMENTS FOR WELL ESTABLISHED MEDICINAL GASES)

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Note:
The subject of the revision of the guideline started in 2007 (rev 1) was the addition, as annex 1, of the recommendation on non-clinical safety requirements for well established medicinal gases. No other changes have been introduced with this revision.

Because no changes have been introduced to the existing part of the guideline with rev. 1, the current template for guidelines has not been used, and the previous format has been retained, in order to avoid confusion.

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1. INTRODUCTION

Gases are packaged as compressed gas under pressure, liquefied gas at high pressure *(saturating vapour pressure)* or liquefied gas at low pressure at low temperature *(cryogenic gas)*.

The aim of the present guideline is to specify the elements relating to the quality of medicinal gases in the context of compiling the pharmaceutical documentation for Module III (Quality) of the dossier.

The MA covers the gas and its primary packing (container including the valve), but not the equipment attached later to the container at the time of use, which falls into the medical device domain *(e.g. pressure regulator and pipe network)*. A valve/built-in pressure regulator assembly that cannot be separated from the cylinder is part of the MA, but a CE mark certificate, which should be included in the dossier, is sufficient.

Gases produced *in situ* in hospitals i.e. manufacturing processes undertaken in or by the hospitals and home care containers of gases are not in the scope of this guideline.

Reference:
Medicinal gases should be classified as medicinal products according to Article 1.2 of Council Directive 65/65/EC.

Registration dossier data for medicinal gases should comply with the general requirements described in the Directive 75/318/EC, Notice to applicants and with the relevant monographs of the European Pharmacopoeia where they exist. Annex 6 to GMP should also be taken into account.

This guideline deals with the specific aspects in relation to medicinal gases.

2. S – ACTIVE SUBSTANCE

For part S current European Pharmacopoeia monographs and guidelines should be taken into account.

3. S 7 STABILITY

The stability of the active substance is demonstrated by stability studies. In particular, degradation products are described. If the finished product is a mixture of gases, the reciprocal chemical reactivity of these gases is documented.

In the case of highly stable gases with a long history of utilisation, bibliographic data is sufficient *(e.g. for oxygen)*.

P DRUG PRODUCT

P1 – DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Medicinal gases consist of active substances or of a mixture of active substances and gaseous excipients.

Mixtures can consist of one or more active substances or one active substance diluted in a gaseous excipient. The percentage formula (v/v) and the deliverable volume are provided, together with the tolerated deviations. The density or the compressibility factor for each gas and for the mixture under standard conditions *($15^{o}C$, 1 atm)* are provided as scientific data. These data make it possible to establish the relationship between concentration values expressed as pressure *($15^{o}C$), volume ($15^{o}C$, 1 atm)* and weight, which nevertheless, are quoted.

For each gas, the MA should include details of the physical state, the pressure of compressed gases *(15°C)*, the type of container and, in case of mixtures, the concentration(s) of the active substance(s). Containers that have different types of valves can be included in the same MA.

The names comply with the European Pharmacopoeia monograph and are completed with the following information:

- name of the gas followed by ***medicinal*** or invented name
- physical form of the product
- name of manufacturer,
- pressure and/or concentration,
- gas for inhalation, etc.
- in a cylinder, in a cylinder bundle in a mobile evaporator, for a fixed evaporator, in a mobile cryogenic container, for a fixed cryogenic container,

and that may correspond to separate MAs.

Cylinder/cylinder bundle are included in the same MA. Mobile evaporator/mobile cryogenic container are included in the same MA. Fixed evaporator/fixed cryogenic containers are included in the same MA.

CONTAINER

The brief description of the containers should specify the capacity, type of material used for the container and the reference code for the manufacturer and the supplier(s) of the containers.

In addition, in the case of cylinders, the type of valve and its reference code, the suppliers and the type of valve outlet connection are stated.

In the case of cylinder bundles, the material and dimensions e.g. internal diameter used for the loop are provided. The outlet valves and the suppliers are provided.

This information can be provided as a table.

CLINICAL TRIAL FORMULA(E)

For new medicinal gas products as well as for new indications for well-established medicinal gases this documentation is required.

P2 PHARMACEUTICAL DEVELOPMENT

Physical properties of gases

The physical properties of the gases concerned are stated, together with the relevant laws that govern them (e.g. law on perfect gases).

On this basis, the principle of the manufacturing method chosen by the manufacturer is explained and justified.

The manufacturer should take into account the physical properties of the gases and the container compatibilities.

Single Gases

Due to the long use of medicinal gases, this part may be presented as bibliographical data. Thus, this heading is limited to a brief overview of the historic development of gas pressure equipment.

In addressing the compatibilities of gas with packaging materials the following issues are to be

considered:

- the compatibility of the packaging/container material with gas of recent utilisation or limited stability. This information will also serve to formulate recommendations concerning equipment for administration.
- the choice of new packaging components, especially the valves, the most fragile part of the cylinder, especially in terms of air-tightness (*e.g. residual pressure valves*).
- the use of new materials and their gas compatibility *(alloys for container shells, plastic materials for valves, etc.).*
- container filling at a pressure not previously used in the medicinal field for this type of container.
- the suitability of the container capacity or the concentration of active ingredient for the posology for gases of limited stability. It should be remembered that the posology of a gas is not expressed as a weight, but as the concentration of gas mixture inhaled which is related to gas administration output.
- the suitability of large capacity cylinders (> 20 L), given the difficulty in handling them, the risks to the safety of personnel and the patient and the difficulty in eliminating traces of water if the valve remains open during the storage.
- the diversity of cylinders used, if they have very different capacities and dimensions and are of different materials.

Mixtures

In some cases, only one gas may be considered as the active substance and the other as excipient. The choice of the excipient gas is justified particularly if this is a new gas or a new combination.

The compatibility between the gases is documented, taking into account their different physical properties and their chemical reactivities. In the case of liquefied gases, the composition and homogeneity of the different superimposed layers of the mixture are described along with their controls, especially at the level of the outlet of the dispensing system.

Thus, the following points should be addressed:

- stability of the gases during the different stages of the manufacturing process as a function of their conditions of storage, transport and handling,
- chemical and physical compatibility between the gases,
- physical stability and homogeneity of the gas mixture under different conditions of storage and utilisation (pressure and output). In the case of gas mixtures that are not very stable, especially mixtures of liquefied gas and permanent gas that can separate at low temperatures, the measures proposed are described and validated *(conditions of storage and transport, rehomogenisation procedure),*
- homogeneity of the gas mixture delivered by the dispensing system, taking into account the varied conditions and duration of storage,
- compatibility and suitability of the packaging,
- justification of the choice of manufacturing procedure, taking the preceding factors into account,
- highlighting of the critical points of the manufacturing procedure that should be taken into account for its validation.

P3 MANUFACTURE

The name of the gas, followed by ***medicinal*** must be systematically used from the time that reference is made to the product being the responsibility of the pharmaceutical establishment so as to clearly delimit the gas to the medicinal field.

Manufacture consists of the operations of division or distribution and filling into dedicated pharmaceutical and medicinal packaging. Packaging is often automated and may include prior modification of the physical state of the gas *(vaporisation by heating of liquefied gas and compression).* It may also include one or several successive mixing operations *(by weight or manometrically, with or without homogenisation).*

A detailed diagram of the manufacturing process is presented, together with the controls carried out at the different stages.

The production station that supplies each filling area is indicated.

The automated packaging system or mixing systems and the specification of the equipment *(pumps, balances, etc)* are described and validated.

P 3.5 PROCESS VALIDATION AND/OR EVALUATION

General case: cylinders of single gases

Validation of the cylinder filling process is performed by a weighing *(or double weighing)* control, including the calculation of the mean, standard deviation and coefficients of variation, or by pressure if justified.

This validation should ideally be presented for all types of cylinder, but at least for critical types of containers. A bracketing approach may be used as a function of the capacity, material used for construction and whether fitted with a built-in pressure regulator or a residual pressure valve. If needs be, for each type of alloy used, a single validation can be performed on one cylinder of this alloy, on the condition that this is justified.

Validation can be performed by determining the amount of gas contained in a cylinder compared with a reference cylinder filled with the charge of gas to avoid the problems of fluctuations in pressure as a function of temperature.

The reproducibility of filling is also verified whatever the composition of the finished product batch *(homogenous or heterogeneous).*

For compressed gases, the temperature and pressure stabilisation time after filling which depends upon various capacities, nature of material, thermal exchange, ambient temperature (and any variation in it during the stabilisation time), rate of filling of the cylinder, airflow over the cylinder and its proximity to any adjacent filled cylinders is specified, unless otherwise justified.

Cylinders, which have been returned for filling, are prepared in accordance with Annex 6 of the GMP.

The integrity of the filling system to indicate leak tightness to prevent possible contamination of the system under vacuum or an estimate of the yield accounted for losses as an annual average is provided.

The tolerated limits of temperature and pressure are provided *(specifying especially the hydrostatic pressure test and the bursting pressure of the cylinder).* On the safety level, any problems of possible overload of compressed or liquefied gas are addressed.

Other containers for single gases

In the case of cylinder bundles and mobile evaporators, validation of the filling procedure is also performed by weighing or by pressure if justified.

In the case of fixed evaporators, validation can consist of the absence of impurity enrichment due to the formation of degradation products with time, to trapping because of the temperature and to transfers from one container to another during the manufacturing process or during sampling. It is specified whether the impurities remain at the same proportions between the gaseous and liquid phases as the container is emptied. The minimal threshold for filling the fixed evaporator is specified to avoid any risk of impurity enrichment.

Thus, scientific data are provided for:

- a theoretical evaluation of the level of impurity enrichment during blowing down/filling cycles for a cryogenic container,
- an analysis of liquid phase samples (performed on the dedicated tank in the filling area or on the dedicated tank in the production station annex) and of gaseous and liquid phase samples (performed on fixed hospital evaporators), supported by a comprehensive list of potential impurities.

Gas Mixtures

In the case of mixtures, validation is concerned with the manufacturing operation for the mixture considered. It should take into account all the critical parameters of the manufacturing process and especially discuss reproducibility in the case of manual cylinder-by-cylinder filling, the role of the nature of the phase and of the temperature of each gas when introduced into the cylinder and the homogenisation conditions. The successive physical states of each gas and of the gas mixture during filling are indicated. A phase diagram is provided.

Validation can also be concerned with other types of mixtures.

In the case of the manufacture of an intermediate product, its validation is carried out under the same conditions and using the same methodology.

P5 CONTROL OF DRUG PRODUCT

P5.1 . SPECIFICATION

In the case of a single gas, the specifications of the finished product are at least the same as those of the starting material.

In the case of mixtures, the specifications chosen for the starting materials, any intermediate products and the finished product are consistent *(taking into account, for example, dilution factors for the active substances).*

The control of the finished product consists of the control according to the monograph in force or using validated methods if shown to be equivalent *(identity, assay and purity)*, the appearance of the cylinders, the labelling and the pressure *(for cylinders and cylinder bundles).* All the constituents of the mixture are identified including excipients. The different constituents of the mixture are assayed, unless otherwise justified.

The control of the filling charge can be performed during packaging and the control of air-tightness after filling.

P5.2. ANALYTICAL PROCEDURES

In the case of liquefied gases, the nature of the phase *(liquid or gaseous)* is indicated, as is the method of sampling for the control. In the case of impurities that are preferentially present in the gaseous phase and eliminated to a large extent during the first drawing off *(e.g. nitric oxide in medical nitrous oxide),* the order of analyses is specified.

The interval elapsed between manufacture and the control of the finished product is indicated according to the European Pharmacopoeia. In the case of gases of limited stability, it is specified whether a second control, performed some time after the first to detect the appearance of impurities, is necessary.

P5.4. BATCH ANALYSES

In the case of cylinders, the batch analysis certificate will state**:**

- the batch number,
- the batch composition and size *(the batches are often heterogeneous)*,
- the source of the starting materials,
- the number of the cylinder controlled,
- the capacity of the cylinder controlled,
- the value for the charge of the cylinder controlled compared to its theoretical charge so as to indicate if the analysis was performed at the start, middle or end of cylinder utilisation, expressed as pressure *(compressed gas)* or weight *(liquefied gas)*,
- the phase analysed,
- the specifications,
- the date of analysis,
- the date of manufacture,
- the signature of the relevant person,
- place of manufacture

P7 – CONTAINER CLOSURE SYSTEM

Medicinal gases are often packaged in a wide range of containers:

– compressed gas cylinders,

– liquefied gas cylinders, with or without a dip tube,

– cylinder bundle,

– mobile evaporator,

– fixed evaporator,

– mobile cryogenic container,

– fixed cryogenic container.

A variety of reference codes exist, dependant on the supplier, capacity and material, particularly in the case of cylinders.

For each reference and each capacity, the water capacity of the container *(in L)*, the amount of gaseous product released at 1atm and 15^{o}C *(in m^{3})*, and the weight of product stored *(in g for compressed gases or in kg for liquefied gases)* are provided, together with the accepted deviations.

This information is necessary for compressed gas cylinders, given the variable operating pressures *(200 bar, 150 bar, etc at 15^{o}C).* For liquefied gas cylinders, the pressure remains constant then falls suddenly at the end of use. Therefore, only the weight monitors the state of filling.

The filling pressure *(at 15^{o}C)* is justified in comparison with the weight formula.

In the case of liquefied gases, the filling ratio in accordance to national and international standards and legislation is provided so as not to exceed a maximal pressure with the risk of explosion, which can occur in the event of a change from the liquid to the gaseous or supercritical state after a temperature increase above the critical temperature.

The type of safety device *(valves or rupture disks)* relating to excess pressure is specified and located *(valves or containers with pressure calibration).*

In the case of valves and outlets, a diagram summarising the nature of the different constituents is provided. The method of opening the tap *(quarter turn, half-turn, progressive wheel, etc.)* the type of standardised outlet connection and the type of gasket and valve used are specified

In the case of cylinders with a built-in pressure regulator, the number and the valve positions of the flow-meter and the corresponding accuracies are documented. The specific tests for these cylinders consists in particular of gas compatibility, adiabatic compression if needs be *(oxygen)* internal and external air-tightness, endurance test, cap shock resistance, fire-resistance, valve safety, shock vibration, output precision, etc.

The containers comply with the specifications of existing national, European *(CEN)* or international *(ISO)* standards concerning equipment intended to contain and deliver gases. The certificate of compliance with the standards in force are provided and the important points of these standards are quoted. All the standards for the various elements of the container are quoted as an appendix.

In particular, the standards provide for the existence of connections **(**cylinder valve outlet connection) and for the painting of the cylinder shoulder.

There are also rules *(national or international)* concerning gas pressure devices and the transport of dangerous materials, which are quoted.

The labelling, marking, engraving and painting that results from these different prescriptive and regulatory sources *(including drug regulations)* are described in a detailed manner, together with a diagram of the container *(packaging plan).*

In particular, the labelling makes it possible, to clearly distinguish between cylinders for medicinal use and other cylinders *(laboratory gas, welding gas, etc.),* as both types of cylinder are found together in a hospital environment.

Thus, the labelling states ***reserved for medicinal use.***

The choice criteria for each type of container are indicated so as to have a material designed, constructed and controlled for each type of gas *(general characteristics, hydraulic tests, size controls, hardness control, chemical analysis of the alloy, compatibility of the materials with the gas and with the possible impurities, etc.).*

The monitoring of manufacture performed by controlling one container in each delivery is described.

The container stock should be reserved strictly for ***medicinal*** use during its whole life cycle i.e. also over the revision periods and belong to the manufacturing pharmaceutical establishment. However, the pharmaceutical establishment can package containers belonging to an operator or a wholesale distributor on condition that the data concerning these reusable containers are shown in the MA file of the manufacturer *(description of the containers, validation of the manufacturing procedure and stability data).*

P 8 STABILITY
STABILITY OF THE INTERMEDIATE PRODUCT

This is documented particularly as a function of the interval before the batch is used.

STABILITY OF THE FINISHED PRODUCT

ICH guidelines on stability are not relevant for this kind of product. Specific storage conditions are proposed by the applicant.

The stability of the finished product is documented by stability studies that are concerned with the container/contents interactions (as a function of capacity, material and supplier). There are screening tests for degradation products. A sufficient number of cylinders from the same batch is used for the study to avoid performing too many intermediate analyses on the same cylinder, since the decrease in pressure and, in the case of liquefied gases, the de-gasification, can alter the content of impurities, preferentially present in the gaseous phase.

The influence of temperature can only be studied on small cylinders placed in special ovens and under accelerated aging conditions, on condition that they are of the same composition and fitted with the same valves and gaskets.

The influence on stability of opening/closing cycles and the decrease in pressure with utilisation can also be studied.

In order to evaluate the interface between the container and the patient, stability during use is considered, i.e. when administered according to the total system intended by the applicant.

In the case of liquefied gases, the different distribution of impurities between the liquid and gaseous phases as a function of their boiling point and the stage of container utilisation are also taken into consideration.

In the case of mixtures, the stability studies include:

i) the stability of the mixture over the declared shelf life. The ingredients and appropriate impurities are assayed.

ii) if necessary, in particular in the case of mixtures of liquefied gas and permanent gas:

iii) the stability of the mixture at extreme temperatures within the safe working temperatures for cylinders,

iv) the stability during cycles of cooling or heating and returning to ambient temperature. The precise separating temperature is determined. A study of the rehomogenisation of the mixture can be presented *(e.g. by placing the cylinder horizontal, with or without rolling).*

v) the homogeneity of the mixture during cylinder utilisation.

vi) the homogeneity of the mixture in the event of abrupt opening *(study of the internal temperature of the cylinder).*

In the case of very stable gases that have been used for a long time and packaged in containers that have also been used for a long time, bibliographic data is sufficient.

In the case of evaporators of oxygen, there is, in the strict sense, no expiry date. They gradually empty during use. The length of storage can be set as the time needed for the evaporator to empty itself completely *(e.g. 3 months for a mobile evaporator and 6 months for a fixed evaporator).*

OTHER INFORMATION

A glossary of technical terms and abbreviations is provided. The terms are harmonised between the pharmaceutical establishments and between the files presented.

The safety rules and special conditions of storage, transport and utilisation are described. They are summarised in the SPC, packaging slip and labelling plans.

GLOSSARY

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

BUILT-IN PRESSURE REGULATOR
Safety system constituted of pressure regulators integrated with cylinder valves, mainly useful with oxygen because it avoids the risk of adiabatic compression.

COMPRESSED GAS
A gas which when packaged under pressure is entirely gaseous at –50°C.

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 1.103 bar at a temperature below –150^{o}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 bundles (or cylinder pack) when appropriate.

CYLINDER BUNDLE
An assembly of cylinders, which are fastened together in a frame and interconnected by a manifold, transported and used as a unit.

DEDICATED
Specific for a gas for medicinal use.

FILLING RATIO
Relationship between the weight of gas introduced into a container and the weight of water at room temperature that will fill the same container ready for use.

FIXED CRYOGENIC VESSEL
A static thermally insulated container designed to contain liquefied or cryogenic gases. The gas is removed in liquid form. It is filled on site.

FIXED EVAPORATOR
A static thermally insulated container designed to contain liquefied or cryogenic gases. The gas is removed in gaseous form. It is filled on site.

GAS
A substance or a mixture of substances that is completely gaseous at 1.013 bar (101.325 kPa) and +15°C or has a vapour pressure exceeding 3 bar (300 kPa) at +50°C.

HIGH PRESSURE LIQUEFIED GAS
A gas with a critical temperature between -50 °C and +65 °C.

HYDROSTATIC PRESSURE TEST
Test performed for safety reasons as required by national or international guidelines 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°C.

LOOP
Spiral metal tube connecting several cylinders.

LOW PRESSURE LIQUEFIED GAS
A gas with a critical temperature above +65 °C.

MEDICINAL GAS
Gases for medicinal use may be classified as medicinal products according to Article 1.2 of Council Directive 65/65/EEC.

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

MOBILE CRYOGENIC VESSEL
A mobile thermally insulated container designed to contain liquefied or cryogenic gases. The gas is removed in liquid form. It is filled in the filling area of the pharmaceutical establishment, then transported to the site of utilisation.

MOBILE EVAPORATOR
A mobile thermally insulated container designed to contain liquefied or cryogenic gases. The gas is removed in gaseous form. It is filled in the filling area of the pharmaceutical establishment, then transported to the site of utilisation.

NON RETURN VALVE
Valve, which permits flow in one direction only

PACKAGING
All the operations, including filling and labelling, that must be undergone by a bulk gas to become a finished product.

PERMANENT GAS
Gas, which has a critical temperature below –10°C.

POSOLOGY
The posology of a gas is not expressed as a weight but as the concentration of gas mixture, which is related to gas administration output.

PRESSURE REGULATOR
Medical device for pressure reduction.

REFRIGERATED LIQUEFIED GAS
A gas, which when packaged for storage or transport, is made partially liquid because of a refrigeration system.

TANK
A large-sized static thermally insulated container designed to contain liquefied or cryogenic gases, located in the production station or the filling area.

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

VALVE
Device for opening and closing containers.

VALVE OUTLET CONNECTION
Screw connector, which makes it possible to connect the rubber gas pipe or pressure regulator to the cylinder. It is standardised and ensures fool proofing.

The Glossary terms are compliant with the definitions detailed in Annex 6 of the GMP, Standards and United Nations Recommendation Book on the Transport of Dangerous Goods, when applicable.

Annex 1: Recommendation for Non-clinical Safety Requirements for Well Established Medicinal Gases

1. INTRODUCTION

The aim of this addendum is to specify the elements relating to the safety of well established medicinal gases in the context of compiling the non-clinical documentation for Module IV (Safety) of the dossier. An application for the marketing authorisation of a medicinal gas or mixture of gases should not differ significantly from that of other medicinal products.

Gases produced *in situ* in hospitals, *i.e.* manufacturing processes undertaken in or by the hospitals and home care containers of gases are not included in the scope of this guidance.

Reference:

Medicinal gases should be classified as medicinal products according to the definitions in the articles of Council Directive 2001/83/EC, as amended, on the community code relating to medicinal products for human use.

2. NON-CLINICAL REQUIREMENTS

Pharmacodynamics:

The potential for effects on lung function and gas exchange should be addressed.

Pharmacokinetics:

The possibility of metabolism, including metabolism within the lungs should be addressed.

Toxicology Studies:

In general, the principles applied under the "Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95)" should be applied. Further non-clinical investigations may be needed if safety aspects or concerns are not addressed by available non-clinical data or cannot be justified based on available literature and/or clinical data, especially when these effects are very difficult to detect clinically.
Any non-clinical toxicology studies performed should use the intended clinical route of administration, *i.e.* inhalation and should be conducted in compliance with the principles of Good Laboratory Practices (GLP) and also include toxicokinetic evaluations. Particular attention should be given to the potential for histopathological changes in the airways and lungs.

Container:

The potential for extraction and leaching of materials from valves and gaskets, *etc*, should be addressed.

In addition, any degradation of the non-metallic components, in the wetted area of the container in contact with the gas, should be addressed.