GOOD MANUFACTURING PRACTICE GUIDE FOR MEDICINAL GASES

AIGA 023/17

(Revision of AIGA 023/05)

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Acknowledgement

This document is adopted from the European Industrial Gases Association, Doc 99/15: 'Good Manufacturing Practice Guide Part 1 for Medicinal Gases'. Acknowledgement and thanks are hereby given to EIGA for permission granted for the use of their document

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Amendments to AIGA 023/05

Section	Change
	Rewrite to reflect current GMP and change in AIGA office address

1 Introduction

Directive 2001/83/EC of the European Parliament and of the council of 6 November 2001 on the community code relating to medicinal products for human use [1][1] and as amended by Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 [2] defines a medicinal product as any substance or combination of substances:

- presented for treating or preventing disease in human beings; and
- which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings.

This Directive requires that the manufacture of all medicinal products shall be controlled following the principles of Good Manufacturing Practice (GMP), detailed in the EC Good Manufacturing Practice Guide and defined in Commission Directive 2003/94 of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use [3].

The EC GMP Guide details the principles of the quality management system (QMS) that should be established by every manufacturer or importer of medicinal products and is laid out in nine chapters, dealing with each aspect of the QMS. The purpose of the EC GMP Guide is to ensure that the manufacturing process is controlled so that the medicinal products are produced to the quality level specified in the appropriate marketing authorisation, where required, or the product specification.

The EC GMP Guide recognises the differences between the manufacture of traditional pharmaceutical products and medicinal gases and prescribes in Annex 6 of the Guide the specific elements of the QMS to be used to control the manufacture of medicinal gases. The requirements of Annex 6 have to be followed in addition to those of the main EC GMP Guide.

To assist the Medical Gas Industry in the interpretation of the overall requirements of the EC legislation with respect to GMP, this EIGA GMP Guide has been prepared. It has been structured so that it integrates the specific requirements of the Annex 6 of the EC GMP Guide into the parts of the main text that are relevant to medicinal gas manufacture. Where the requirements of the EC Guide have no relevance to the manufacture of medicinal gases, these requirements have been omitted from the AIGA GMP Guide.

Hence, this AIGA GMP Guide may be used by all medicinal gas manufacturers to assist them in the preparation of a quality management system to ensure that all medicinal gases are manufactured to a defined product specification.

This AIGA GMP Guide mainly addresses the quality requirements for the manufacture, storage and distribution of medicinal gases. These activities shall also comply with all of the other appropriate operational, safety and environmental requirements detailed within AIGA documents and any relevant national / international legislation and regulations.

This version of the AIGA GMP guide covers the:

- EU Guidance on GMP Part I: Basic Requirements for Medicinal Products of 2003
- -Annex 6 Manufacturing of Medicinal Gases of July 2010

It does not specifically cover any International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. (ICH)

[1] References are shown by bracketed numbers and are listed in order of appearance in the reference section.

2 Scope and purpose

2.1 Scope

This AIGA GMP guide is intended for use by all manufacturers of medicinal gases and fillers of medicinal gas cylinders. It covers the:

- manufacture and storage of all medicinal gases on licensed gas company premises;
- filling of medicinal gas cylinders; and
- distribution of bulk medicinal gases and medicinal gas cylinders.

It specifies the requirements necessary to meet the specifications set in the relevant Pharmacopoeia standards and, where required by the national authorities, in the relevant marketing authorisations.

Where medicinal gases are covered by a marketing authorisation, issued by a national authority, the requirements detailed in this guide may be replaced with specific requirements detailed in those marketing authorisation.

This guide does not cover manufacturing and handling of medicinal gases in hospitals, which will be subject to national legislation. However relevant parts of this guide may be used as a basis for such activities.

The contents of this AIGA guide covers only the requirements set out in the chapters 1 to 9 of Part I of the EC GMP guide and in Annex 6, covering the manufacture of medicinal gases.

It currently does not cover the specific requirements detailed in:

- Annex 15, Qualification and validation;
- Annex 16, Certification by a qualified person and batch release;
- Annex 17, Parametric release;
- GMP Part II, Basic requirements for active substances used as starting material; and
- GMP Part III, Site master file.

Certain aspects of the above requirements are covered in the AIGA GMP guide where they have been referred to in the text of the main EC GMP guide.

This guide provides the minimum standards that are required to meet the requirements of the EC Directive 2001/83 [1]. Although the terminology of the AIGA Guide refers to activities that 'shall' be carried out, it may be appropriate to utilise alternative procedures provided that:

- It can be demonstrated by risk assessment that the alternative method provides at least the same level of protection to ensure that the quality of the final product is maintained.
- Any risk assessment is formally documented.
- Appropriate approval is obtained from the national authorities to deviate from the requirements of the EC GMP guide.

Certain national authorities define some of the medical gases that do not fall strictly under the definition of a medicinal product, as medical device gases. These gases, normally used in conjunction with medical devices, do not strictly fall under the control of the EC GMP guide, but for the purposes of this publication can be considered in the same way as for other medicinal gases. Within the text,

any reference to the manufacture, filling, storage or distribution of medicinal gases shall apply equally to any medical device gases.

2.2 Purpose

The purpose of this publication is to provide manufacturers and importers of medicinal gases and fillers of medicinal gas cylinders with a comprehensive guide for the development of a quality management system (QMS) to control their relevant manufacturing processes to meet the GMP requirements. Other requirements for management systems, such as ISO 9001, and may also be used as a guide during pharmaceutical inspections by the national authorities.

3 Definitions

There following terms have the specific meanings detailed below when used in the context of the AIGA GMP guide.

Shall / must	Indicates a requirement that is mandatory that is either prescribed by the legislation or is considered to be the best operating practice by the medicinal gas industry.
Should / may	Indicates a requirement which is preferred method of achieving a requirement but may be substituted by an alternative method provided that this method achieves the same requirement to at least the same standard.
Good Manufacturing Practice	Is that part of quality assurance which ensures that medicinal gases are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specification.
Medicinal gas	Gas used for treating or preventing disease in human beings or administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions through pharmacological effect.
Medical device gas	Gas classified as a Medical Device according to Directive 93/42/CE as a substance used alone or in combination intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of :
•	diagnosis, prevention, monitoring, treatment or alleviation of disease,
•	diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
•	investigation, replacement or modification of the anatomy or of a physiological process,
•	control of conception.
Marketing authorisation	An authorisation issued by the national authority to permit a medicinal gas to be marketed within their territory, as described by Article 6 of EC Directive 2001/83EC [1]. The marketing authorisation details include the specification of the medicinal gas, the method and sites of manufacture, the method of supply, including specification of the cylinder or container and the valve closure, clinical indication and contra-indications and precautions for use. Currently, not all national authorities require a marketing

	authorisation for all medicinal gases to allow them to be marketed within their territory.
Manufacturing authorisation	An authorisation issued by the national authority to permit the manufacture of specified medicinal gases on specific sites as described by Article 40 of EC Directive 2001/83EC [1]. The manufacturing authorisation specifies the medicinal gases that may be manufactured and filled into cylinders on specific sites, the names of the responsible persons on each site and the name of the Qualified Person, where required by the national authority.
Qualified person	Nominated person responsible for the final certification of all medicinal gases prior to supply to the patient, as described by Article 48 of EC Directive 2001/83EC [1]. The qualifications required by the qualified person are described in Article 49 of EC Directive 2001/83EC [1].
Test	Unless otherwise stated, the term test refers to either the sampling and analysis of the medicinal gas at various stages in the process of manufacture or cylinder filling or to the process of validating that the specification of the finished conforms to the requirements of the marketing authorisation or product specification.
Pharmacopoeia monograph	Refers to the specification and test methods for specific medicinal gases prepared and issued by the European Pharmacopoeia.
Manufacturing site	Refers to any site, covered by a manufacturing authorisation, where medicinal gas cylinders are filled.
Bulk medicinal gas	Gas supplied directly to the end user or to a medicinal gas cylinder filling site, where it has to be further processed before it can be used by the patient.

4 Quality Management (EC GMP Chapter 1)

4.1 Principle

Any manufacturer of medicinal gases or filler of medicinal gas cylinders, holding an appropriate Manufacturing Authorisation, shall ensure that the medicinal gases they produce are:

- fit for their intended use by the patient;
- compliant with the requirements of their marketing authorisation, where required; and
- safe, of an appropriate defined quality and efficacious so that they do not place patients at risk.

The attainment of this quality objective is the responsibility of the senior management and requires the participation and commitment of staff in many different departments, at all levels within the company, and by the company's suppliers and distributors.

To achieve the quality objective reliably there shall be a comprehensively designed and correctly implemented quality assurance system, incorporating the principles of Good Manufacturing Practice and quality control. (Note: the ICH Q10 refers to Pharmaceutical Quality System [4]). The quality assurance system shall be fully documented and have its effectiveness monitored on a regular basis.

All parts of the quality assurance system shall be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. In addition, where required by the

national authority, all medicinal gases shall be formally released for patient use by the Qualified Person.

EC Directive 2001/83 [1] specifies the specific legal responsibilities for both the holder of the Manufacturing Authorisation and the qualified person.

The basic concepts of quality assurance, Good Manufacturing Practice and quality control are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of the manufacture of medicinal gases and the filling of medicinal gas cylinders.

4.2 Quality assurance (QA)

Quality assurance is a wide ranging concept which covers all matters which individually or collectively influences the quality of the medicinal gas. It is the total of the organised arrangements made with the object of ensuring that medicinal gases are of the quality required for their intended use. Quality assurance therefore incorporates the principles of Good Manufacturing Practice as well as other factors outside the scope of this AIGA GMP Guide.

The system of quality assurance appropriate for the production of medicinal gases and the filling of medicinal gas cylinders shall ensure that:

- The equipment and procedures used for the production of medicinal gases and the filling of medicinal gas cylinders are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice.
- Production and quality control operations are clearly specified and the principles of Good Manufacturing Practice and Good Laboratory Practice adopted.
- Managerial responsibilities are clearly specified.
- All necessary controls on starting and packaging materials, intermediate products, and any other in-process controls and validations are carried out.
- The bulk medicinal gases and the filled medicinal gas cylinders are correctly processed and checked, according to the defined standard operating procedures and individual work instructions.
- Where the national regulations specify, medicinal gases are not sold or supplied before a qualified person has certified that each production batch has been produced and controlled in accordance with the specifications of the marketing authorisation and any other regulations relevant to the production, quality control and release of medicinal gases.
- Satisfactory arrangements exist to ensure, as far as possible, that the medicinal gases are stored, distributed and subsequently handled so that safety and quality of the gas and the condition of the containers are maintained throughout their shelf life.
- There is a procedure for self-inspection and quality audit which regularly appraises the effectiveness and applicability of the quality assurance systems

4.3 Good Manufacturing Practice (GMP) for medicinal gases

Good Manufacturing Practice is that part of quality assurance which ensures that medicinal gases are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specification.

Good Manufacturing Practice is concerned with the quality control of the production, filling and distribution of medicinal gases.

The basic requirements of Good Manufacturing Practice are that:

- All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing or filling medicinal gases to the required quality so that they comply with their specifications.
- Critical steps of the manufacturing processes and any significant changes to the process are validated
- All necessary facilities for Good Manufacturing Practice are provided including:
    - appropriately qualified and trained personnel;
    - adequate premises and space to carry out all operations;
    - suitable equipment and services;
    - correct materials, containers and labels;
    - approved standard operating procedures and work instructions; and
- Suitable finished product storage and methods of distribution.
- Work instructions and standard operating procedures are written in an instructional form in clear and unambiguous language, applicable to the facilities provided.
- Operators are trained to carry out procedures correctly and their competency assessed against a documented programme.
- Records are made, manually or electronically during manufacture of the medicinal gases and the filling of medicinal gas cylinders. These records shall demonstrate that all the required steps, defined by the standard operating procedures and work instructions, have been taken and that the quantity and quality of the medicinal gas is as defined. Any significant deviations from these requirements are fully recorded and investigated.
- Records of the manufacture and distribution of the medicinal gases provide the complete history of the batch and are retained in a comprehensible and accessible form. These records shall be comprehensive enough to allow the batch to be traced in the event of a product recall.
- The method of storage and distribution of the medicinal gases minimises any risk to their quality.
- A system is available to recall any batch of product, from sale or supply.
- Complaints about marketed products are examined, causes of quality defects investigated and appropriate measures taken in respect of the defective products to prevent reoccurrence.

4.4 Quality control (QC)

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

The basic requirements of quality control are that:

- Adequate facilities, trained personnel and approved procedures are available for the sampling, inspecting and testing of starting materials, packaging materials, bulk medicinal gases and filled medicinal gas cylinders for Good Manufacturing Practice purposes.

- Samples of starting and packaging materials, bulk products and filled cylinders are taken by personnel and the test methods approved by the quality controller.

- Test methods are validated.

- Records are made, manually or electronically by recording instruments, to demonstrate that all the required sampling, inspecting and testing procedures are carried out. Any deviations are fully recorded and investigated.

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

- Records are made of the results of inspection and testing of starting materials, bulk medicinal gases and filled medicinal gas cylinders. These records shall be formally assessed against the specification by the relevant quality controller. Product assessment shall include a review of the relevant medicinal gas production and filling documentation and a review of any significant deviations from the specified procedures.

- Each batch of bulk medicinal gas or medicinal gas cylinders is released for patient use and certified by the qualified person, where required by the national authorities, prior to supply, confirming that it is in accordance with the requirements of the marketing authorisation and the product specification.

4.5 Product quality review

Regular periodic or rolling quality reviews of the authorised medicinal products, including export only products are to be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.

4.6 Quality risk management

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

5 Personnel (EC GMP Chapter 2)

5.1 Principle

The establishment and maintenance of a satisfactory system of quality assurance for the correct production of medicinal gases and filling of medicinal gas cylinders relies upon people. For this reason there shall be sufficient qualified and trained personnel to carry out all the tasks involved in the production of medicinal gases and the filling of medicinal gas cylinders.

Records shall be maintained to demonstrate that individuals clearly understand their specific responsibilities.

All personnel involved in the manufacture and assembly of medicinal gases shall receive initial and continuing training relevant to their needs and responsibilities. Specifically they shall be trained and assessed in their awareness of Good Manufacturing Practice and be made aware of the critically important aspects of their roles and the potential hazards for patients from the medicinal gases should they not follow the specified procedures.

5.2 General

5.2.1 Personnel requirements

The manufacturer of medicinal gases and the filler of medicinal gas cylinders shall have an adequate number of personnel with the necessary qualifications and practical experience available to carry out all operations. The responsibilities placed on any one individual shall not be so extensive as to present any risk to quality of the gas supplied for patient use.

5.2.2 Organisation chart

Manufacturers of medicinal gases and fillers of medicinal gas cylinders shall have an organisation chart detailing the reporting structures throughout the organisation. All personnel in responsible positions shall have their specific duties recorded in their written job descriptions and adequate authority to carry out their responsibilities. These duties may be delegated to designated deputies of a satisfactory qualification level.

There shall be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application and control of GMP.

5.3 Key personnel

5.3.1 Responsibilities

The holder of a manufacturing authorisation shall have available on every manufacturing site a nominate person:

- responsible for production; and
- responsible for quality control.

Normally these key posts should be occupied by full time personnel. If these persons are not resident on the site they shall still retain the overall responsibilities for production and/or quality control.

The heads of production and quality control shall be independent from each other. In large organisations, it could be necessary for the nominated head of production or quality control to delegate some of their responsibilities to another suitably qualified person.

The manufacturing authorisation holder shall have permanently and continuously at their disposal a qualified person, who shall be responsible for the final release of all bulk medicinal gases or filled medicinal cylinders prior to the supply to the patient. The duties of the qualified person are fully described in EC Directive 2001/83 EC [1].

5.3.2 Independence

The level of independence of quality control to production is considered fundamental to the satisfactory operation of quality control. The quality controller shall have the authority to prevent any finished medicinal gases that do not meet the specification from being supplied for patient use.

5.3.3 Person responsible for production

The person responsible for production is generally responsible for:

- ensuring that the manufacture of medicinal gases and the filling of medicinal gas cylinders follows the authorised procedures detailed on the marketing authorisation, where required, in order to obtain the specified quality;
- checking that the maintenance of the equipment and premises under his control are carried out correctly;

- ensuring that the appropriate process validations are completed;
- ensuring that the required initial and continuing training of his department personnel is carried out and adapted according to the identified need; and
- ensuring that any agreed self-inspection programme is completed and that the appropriate actions are taken to correct any identified non-compliances.

5.3.4 Person responsible for quality control

The head of the quality control department is generally responsible for:

- approving or rejecting, as they see fit, starting materials, packaging materials, and intermediate bulk and finished product;
- evaluating batch records;
- ensuring that all necessary testing is carried out.
- approving specifications, sampling instructions, test methods and other QC procedures;
- approving and monitoring any contract analysis.
- checking the maintenance of their department, premises and equipment;
- ensuring that the appropriate quality control validations are completed; and
- ensuring that the required initial and continuing training of their department personnel is carried out and adapted according to need.

5.3.5 Joint responsibilities

The persons responsible for production and quality control generally have some shared or jointly exercised responsibilities relating to the quality of the medicinal gases.

These responsibilities can include:

- authorisation of written procedures and other documents, including amendments;
- validation of procedures;
- training;
- designation and monitoring of storage and distribution conditions for materials and products;
- retention of records;
- monitoring of compliance with the requirements of GMP; and
- control of any changes to procedures or equipment, including any relevant validations.

5.3.6 The qualified person

Where required by the national authorities, the qualified person's responsibilities shall include:

- Ensuring that each batch of bulk medicinal gas or filled medicinal gas cylinders has been produced and tested /checked in accordance with the relevant directives and the appropriate marketing authorisation.
- Certifying in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of the EC Directive 2001/83 EC [1].
- Approving specifications, sampling instructions, test methods and any other quality control procedures
- Verifying that the appropriate validations are completed.
- Verifying that the required initial and continuing training of their department personnel is carried out and adapted according to the identified need.
- Approving and monitoring of suppliers and materials.
- Approving and monitoring of contract manufacturers.
- Making the decision to recall potentially defective finished product and to assist, as necessary, in the investigation procedure and any follow-up actions when informed of any product non-conformance

The person responsible for the qualified person duties shall meet the qualification requirements laid down in EC Directive 2001/83 EC [1] and shall be permanently and continuously at the disposal of the holder of the manufacturing authorisation to carry out these responsibilities.

The qualified person's responsibilities may be delegated to another qualified person with the appropriate experience.

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

5.4 Training

Manufacturers of medicinal gases and fillers of medicinal gas cylinders shall provide training for all the personnel whose duties take them into production areas or laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

Besides the basic training on the theory and practice of GMP relevant to the manufacture of medicinal gases, newly recruited personnel shall receive training appropriate to the duties assigned to them.

Continuing training shall also be given, and its practical effectiveness shall be periodically assessed.

Training programmes for all personnel and consultants shall be available, approved by either the head of production or the head of quality control, as appropriate. Training records shall be retained.

5.4.1 Hazard areas

Personnel working in areas where contamination is a hazard or areas where toxic materials are handled shall be given specific training.

5.4.2 Visitors

Visitors or untrained personnel should not be taken into the production and quality control areas.

If this is unavoidable, they should be closely supervised and given the appropriate information in advance, particularly about personal hygiene and the prescribed protective clothing.

5.4.3 Quality assurance training

The concept of quality assurance and all the measures capable of improving its understanding and implementation shall be fully discussed as part of the overall training programme during training sessions.

5.5 Protective clothing

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

Personnel shall be instructed to use gloves when handling medicinal gas cylinder valves.

5.6 Personal hygiene

Separate facilities shall be provided for personnel for eating, drinking or smoking remote from any production and quality control areas. These facilities should include storage for food and drink or any smoking materials. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected shall be forbidden.

6 Premises and equipment (EC GMP Guide Chapter 3)

6.1 Principle

Premises and equipment for manufacture of medicinal gases and the filling of medicinal cylinders shall be located, designed, constructed, adapted and maintained to suit all of the relevant operations. The layout and design of the premises shall aim to minimise the risk of errors and permit effective cleaning and maintenance of the equipment and not have any adverse effect on the quality of products.

The manufacture of medicinal gases and the filling of medicinal gas cylinders is carried out in closed pipework, containers and tanks. Consequently, environmental contamination of the product is minimal, provided that the equipment is suitably commissioned and maintained in an operational condition. However there could be a risk of cross-contamination with other gases if the pipework allows for interconnections between different gases without any suitable backflow protection and the appropriate, validated procedures are not followed correctly.

6.2 Premises

Premises shall provide sufficient space for manufacturing, filling, testing, inspection and storage of medicinal gases to avoid the risk of mix-up. Premises shall be kept clean and tidy to encourage orderly working and have adequate space to permit the storage of cylinders to be correctly laid out with adequate segregation.

6.2.1 Maintenance

Premises and equipment shall be cleaned and maintained regularly to a documented preventative maintenance programme. The repair and maintenance operations shall ensure that they do not present any hazard to the quality of the medicinal gas, and be carried out according to detailed written procedures.

6.2.2 Unauthorised entry

Steps shall be taken to prevent the entry of unauthorised people to production, cylinder filling, storage and quality control areas, which shall not be used as a right of way by personnel who do not work in them.

6.3 Manufacturing areas - Production

6.3.1 Location

Except where special precautions are taken, production equipment shall be located away from any incompatible activities such as those that generate any chemical or biological emissions

6.3.2 Storage areas

Where starting materials are stored prior to use, they shall be kept in an environment where contamination is avoided and deterioration is controlled.

6.4 Manufacturing areas - Cylinder filling

6.4.1 Layout

Premises used for the filling of medicinal gas cylinders should preferably be laid out in such a manner as to allow a flow through the area, with cylinder filling steps taking place in areas connected in a logical order corresponding to the sequence of the cylinder filling operations. Cylinder filling areas shall be of a sufficient size and have an orderly layout, providing separately marked areas for different gases and, where applicable, different cylinder sizes.

A typical plant layout is shown in Figure 1,

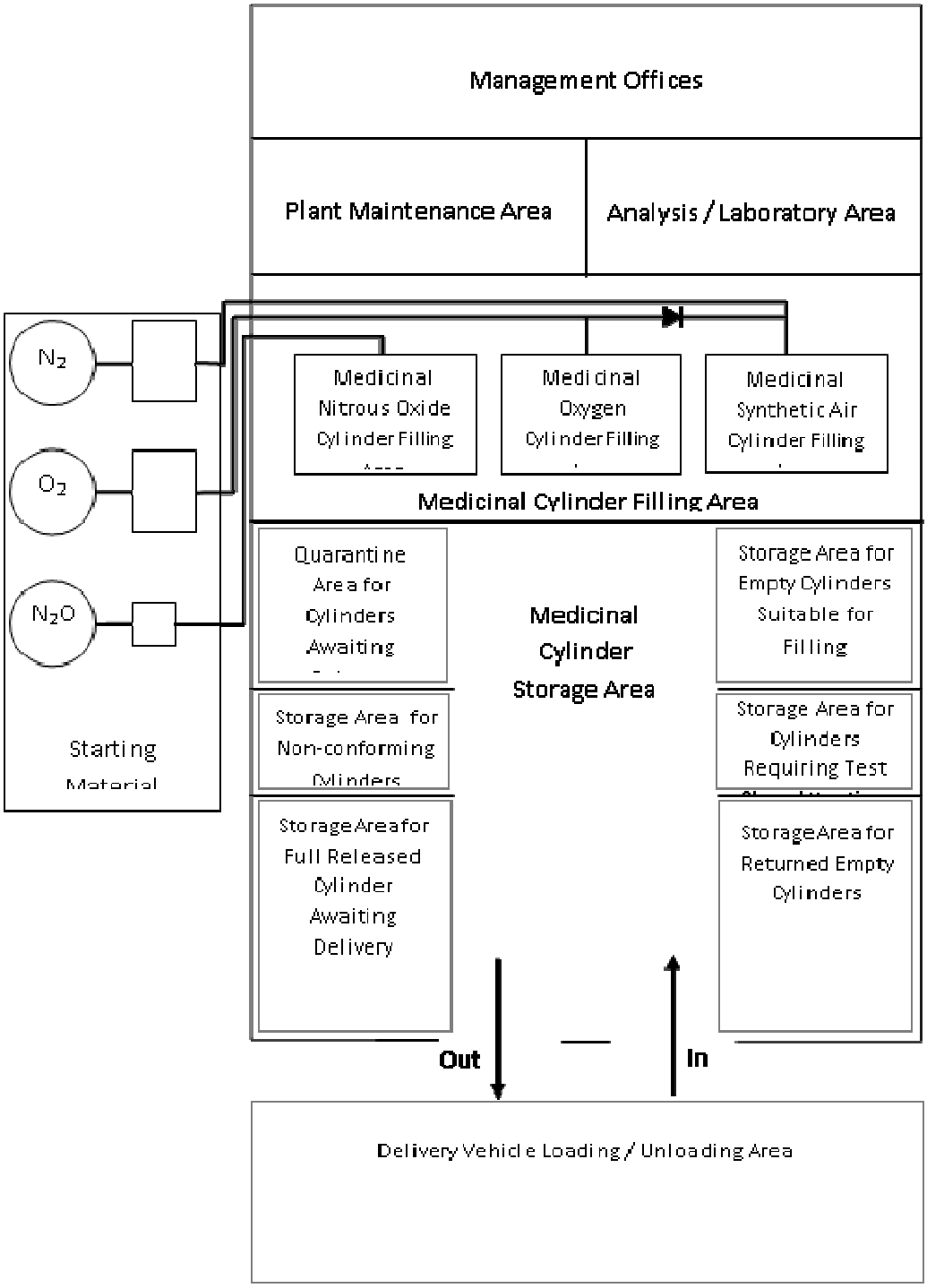

Fig 1 Layout of a Typical Medicinal Cylinder Filling Plant

6.4.2 Segregated areas

Medicinal gases should preferably be filled in a separate area from non-medicinal gases and there should be no exchange of cylinders 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 to ensure that there is no confusion between medicinal and non-medicinal gas cylinders.

6.4.3 Inspection and testing areas

Facilities for the inspection, testing and maintenance of medicinal gases cylinders shall be specifically designed and laid out so as to avoid mix-ups or contamination of the cylinders.

6.4.4 Lighting

Cylinder filling areas shall be well lit, particularly where cylinders are inspected to ensure they are suitable for filling and where visual, on-line controls are used.

6.4.5 In-process controls

In-process controls may be carried out within the production and filling areas provided they do not present any risks to the production of medicinal gases and the filling of medicinal gas cylinders.

6.4.6 Storage areas - Cylinder filling

Storage areas for medicinal gas cylinders shall be of a sufficient size and capacity to allow for orderly storage and to permit clearly identifiable segregation areas of the different gases filled on site and to differentiate the status of the stored cylinders.

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

6.4.7 Layout

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

- empty cylinder storage area where cylinders returned from customers can be stored prior to cylinder sorting;
- empty cylinder sorting area where cylinders can be segregated into those suitable for refilling and those requiring either statutory testing or rectification prior to refilling;
- empty cylinder storage area for cylinders suitable for refilling;
- quarantine area for filled cylinders awaiting quality control and formal release;
- full cylinder storage area for released cylinders; and
- rejected non-conforming cylinders.

6.4.8 Storage area protection

Sorted empty cylinders and full cylinders shall be stored in nominated storage areas, preferably under cover and not subjected to extremes of weather conditions and ambient temperature.

Storage areas shall be kept clean, dry, well ventilated and free of combustible materials to ensure that cylinders remain in an appropriate condition compatible with the environment in which they will be used, up to the time of supply.

6.4.9 Stock rotation

In order to permit batch segregation, medicinal gas cylinder shall be stored in an orderly fashion with adequate segregation of different gases and of full/empty cylinders.

The storage arrangements shall permit suitable rotation of stock to ensure that cylinders are used for supply to customers on a first in / first out basis.

6.4.10 Reject cylinder storage

Segregated labelled areas shall be provided for the storage of complaint and reject cylinders.

6.4.11 Label storage

Cylinder labels and package inserts (patient information leaflets) are considered critical to the conformity of the medicinal gas product and special attention shall be paid to the safe and secure storage of these materials.

6.4.12 Storage protection

Full gas cylinders shall be suitably protected from adverse weather conditions during storage. and transportation. For gas mixtures where phase separation can occur, the storage and transportation arrangements shall be as defined in the marketing authorisation

6.5 Quality control areas

The layout of the medicinal gas quality control areas shall have sufficient space for cylinder storage to avoid mix-ups or cross-contamination of sample cylinders. There shall be adequate suitable storage space for all medicinal gas sample cylinders and for the associated records.

6.5.1 Environmentally controlled areas

Laboratories for the testing of medicinal gases are only required where the analytical equipment needs to be maintained in a controlled environment.

6.5.2 Area segregation

Finished product analysis areas should preferably be separated from production areas, unless the analysis equipment is installed adjacent to the medicinal cylinder filling point.

6.6 Ancillary areas

6.6.1 Rest areas

Rest and refreshment rooms shall be separate from production, cylinder filling, quality control and storage areas.

6.6.2 Toilet areas

Washing and toilet areas, as well as facilities for changing clothes shall be easily accessible and designed for the appropriate number of users. These toilet facilities shall not have direct access with production, cylinder filling, quality control or storage areas.

6.6.3 Maintenance areas

As far as practicably possible, maintenance workshops should be separate from production and cylinder filling areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

6.7 Equipment

All equipment for the manufacture, cylinder filling and analysis of medicinal gases shall be designed, qualified, calibrated and maintained to suit its intended purpose.

6.7.1 Maintenance and cleaning

Repair and maintenance operations shall not adversely affect the quality of medicinal gases produced or filled into cylinders.

The design of manufacturing and cylinder filling equipment should be designed to permit easy and effective cleaning and evacuation to remove any internal contamination.

Where the pipework or equipment requires specific cleaning, the system shall be designed so that any residual cleaning material can be easily removed prior to use. Detailed written procedures shall be available to cover the appropriate methods of purging and cleaning all equipment and putting the system back into operation.

The manufacturing and cylinder filling equipment systems shall be designed so as to minimise the release any particulate matter into the finished product.

6.7.2 Material selection

Manufacturing and cylinder filling equipment shall not present any hazard to the finished products.

The parts of the equipment that come into contact with the product shall not be reactive, additive or absorptive to such an extent that it will affect the quality of the medicinal products and thus present a hazard.

This specifically includes the use of halogenated materials for oxygen at high pressure that could produce toxic gases if they should ignite, such as under adiabatic compression conditions.

6.7.3 Calibration

Critical instruments used for measuring, weighing, recording and controlling equipment shall have specific calibration periods using appropriate validated methods. All critical instruments shall be calibrated and checked at the prescribed intervals. Detailed records of all of the calibration tests, including the 'as found' and the 'post calibration' values shall be maintained.

6.7.5 Defective equipment

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

6.8 Equipment - Bulk production

6.8.1 Plant segregation

It is acceptable to manufacture non-medicinal gases and medicinal gases concurrently, such as in an air separation unit (ASU), provided that the quality of the non-medicinal gas is at least equal to the quality of the medicinal gas.

6.8.2 Air filtration

In an ASU, where atmospheric air is used as a raw material, it shall be filtered at the inlet point to restrict the intake of particulate matter into the plant.

6.9 Equipment - Medicinal cylinder filling

6.9.1 Cylinder filling manifolds

The medicinal gas cylinder filling manifolds shall be dedicated to the filling of either a single medicinal gas or to a given mixture of medicinal gases to different concentrations.

It is necessary to ensure that the correct gas is put into the correct container.

The manifolds shall be equipped with filling hose connectors that correspond only to the valve outlet for that particular gas or mixture of gases so that only the correct containers can be attached to the manifold without the use of an adapter.

The use of specific cylinder and container valve connections could be subject to international or national standards.

Where the same medicinal gas cylinder valve outlet is used for more than one medicinal gas, additional precautions shall be taken to ensure that the correct gas is filled into the correct cylinder.

The name of the gas or gas mixture being filled shall be displayed on each medicinal gas cylinder filling manifold. An exception to this rule is described in 6.9.3.

6.9.2 Medicinal cylinders

Cylinders in medicinal gas service shall be dedicated to that service and have the appropriate technical characteristics, according to international or national regulations. Cylinders shall be labelled and painted correctly, according to the national standards and to comply with the relevant marketing authorisation, where applicable

6.9.3 Shared filling systems

Filling of medicinal gas cylinders shall be avoided in non-medicinal gas cylinders filling areas .and not filled with equipment used for filling non medicinal gas cylinders.

In exceptional circumstances, where it is impracticable to have a dedicated medicinal gas cylinder filling facility, and where the national regulations permit, the principle of campaign filling may be used to allow medicinal gas cylinders to be filled on non-medicinal gas cylinder filling equipment. In these circumstances, the area shall be dedicated to medicinal gas cylinder filling during the campaign and appropriate tests and procedures carried out to ensure that the product is not contaminated with non-medicinal gas and the cylinders filled comply with the relevant specifications. GMP standards shall be maintained during the campaign filling process.

Ideally, filling lines used to supply medicinal gas filling areas should be dedicated to that service. However, where it is necessary to have a shared facility serving both products, there shall be a validated method of backflow prevention in any line supplying the filling area for non-medicinal gases to prevent contamination of the medicinal gas from the possible impurities that may be returned in the non-medicinal gas cylinders.

6.9.4 Pipeline interconnections

Except for validated automated filling processes there shall be no direct interconnections between pipelines carrying different gases other than for medical gas mixture filling systems.

6.9.5 Non-automated filling systems

Where an automated filling process is not available for the filling of medicinal gas mixtures, there shall be a documented procedure to demonstrate that the mixtures have been filled correctly and consistently and that there has been no backflow from any other cylinder filling process.

6.10 Equipment - Bulk storage and transport

6.10.1 Storage tanks

Storage tanks and mobile delivery tankers shall be dedicated to one gas. The quality of the gas stored in the storage tank or mobile delivery tanker shall be well defined and shall be at least equal to the medicinal gas quality standard. The storage tank and delivery tanker shall have product specific

couplings for the transfer of product to another storage tank or tanker to prevent the wrong gas from being transferred into the tank.

6.10.2 Common storage tanks

Bulk medicinal gases from the manufacturing plant may be stored in the same batch or bulk storage tank as non-medicinal gases, provided that, if permitted by local regulations, the quality of the non-medicinal gas is at least equal to the quality of the medicinal gases.

6.10.3 Common delivery vehicles

If permitted by local regulations, cryogenic liquefied medicinal gases may be transported in the same tankers as non-medicinal gases. This may only be permitted provided that the quality of the non-medicinal gas is at least equal to the quality of the medicinal gas. There shall also be a validated backflow protection device fitted to prevent back feeding of non-medicinal product from the customer's storage tank into the tanker when product is being transferred.

Where tankers are used for delivering medicinal liquefiable gases also to non-medical customers, where a two hose filling system is used to balance the pressure between the tanker and the storage tank, then either:

The deliveries of medicinal gases shall be made before any non-medicinal deliveries are made, to ensure that there is no cross contamination between medicinal and non-medicinal customer storage tanks

The assay of the gas being delivered to a medicinal customer is monitored prior to the tanker off loading any product. The testing procedure needs to consider the likely contaminants that could be present to confirm that there has been no degradation of the product.

With this type of delivery system, there shall be a procedure in place to assess the likely contaminants from the non-medicinal customers and procedures put in place to ensure that the tanker has not been contaminated with any likely contaminants prior to the tanker being refilled for medical deliveries.

7 Documentation (EC GMP Chapter 4)

7.1 Principles

Good documentation is an essential part of any quality assurance system used for the production of bulk medicinal gases and the filling of medicinal gas cylinders. Clearly written documentation prevents errors and permits the tracing of batch history. Specifications, standard operating procedures, work instructions, and records shall be controlled and available to all of the relevant personnel either in written or electronic format.

All written documents shall be legible and free from errors.

7.2 General

7.2.1 Starting materials

All starting materials involved in both the production of bulk medicinal gases and the filling of medicinal gas cylinders shall be specified to the appropriate standards, as detailed in the relevant marketing authorisation or any other relevant legislation. As well as any bulk starting materials, the specifications shall include, as required, the details of cylinders, cryogenic containers, valves, labels and leaflets used in the supply of the medicinal gases.

These specifications shall serve as the basis for all quality evaluations in the quality control system used to control any starting materials.

7.2.2 Document Control

All documentation shall be designed, prepared, reviewed, dated and distributed and controlled to comply with the specific requirements of the manufacturer's licence, marketing authorisations and any other relevant legislation.

All standard operating procedures, work instructions and specifications shall be controlled to ensure that only the current version is readily available for reference.

The document control procedure shall ensure that only the current version of any document is available and all superseded documents are destroyed or archived.

Photocopied documents shall be clear and legible. The copying of any working document from a master document shall not allow any error to be introduced through the reproduction process.

7.2.3 Document approval

All documents involved in the production of medicinal gases and the filling of medicinal gas cylinders shall be approved, signed and dated.

7.2.4 Data entry

Where documents require the manual entry of data, these entries shall be made in clear, legible, indelible handwriting. Under no circumstances shall data be entered using a pencil.

Sufficient space shall be provided for all data entries.

All records shall be completed at the time that each quality control check or action is taken and in such a way that all product significant activities relating to the production and transfer of medicinal gases and the filling of medicinal gas cylinders are traceable for each batch.

7.2.5 Alterations

Any alteration made to an entry on a controlled document or data record shall be signed and dated. The alteration shall permit the original information to be read and, where appropriate, the reason for the alteration shall be recorded.

7.2.6 Record retention

Batch records shall be retained for at least one year after the expiry date of the finished product.

Any quality control documentation relating to the batch record shall be retained for one year after the expiry date or at least five years after the certification of the batch by the qualified person, whichever is the longer. This documentation shall also include any other relevant original data such as production records.

7.2.7 Electronic records

Where data is recorded electronically, detailed procedures relating to the validation of the system shall be available. If data is recorded electronically, only authorised persons shall be able to enter or modify data in the computer and changes or deletions shall be recorded. Access to the system shall be restricted by passwords or other means and the results of entry of any data critical to the correct performance of the plant shall be independently checked by appropriate authorised person to ensure that the plant is in control.

Electronically stored batch records shall be protected by a reliable back-up system. It is particularly important that all data is readily available throughout the period that batch records need to be retained.

7.2.8 Continuous processes

For continuous processes, a definition of a batch shall be defined and related to the frequency of analysis of the bulk gas.

7.3 Specifications

7.3.1 General

There shall be appropriately authorised and dated specifications for all starting materials, including bulk products, packaging materials and finished medicinal gases.

7.3.2 Starting and packaging materials

Specifications for starting materials and packaging materials used for the production of medicinal gases or the filling of medicinal gas cylinders shall include, as appropriate:

- description of all of the starting and packaging materials;
- chemical formula of the starting material;
- designated name or reference code of the starting material;
- relevant pharmacopoeia monograph of the starting material, where specified;
- original producer and the approved suppliers of the materials;
- specimen of the product label;
- detailed methods for the sampling and testing of the starting materials, including any specified analytical procedures and equipment;
- qualitative and quantitative testing requirements of the starting materials with the acceptance limits; and
- storage conditions and precautions.

7.3.3 Bulk medicinal gases

Specifications for bulk medicinal gases shall be available where they are:

- purchased for the production of finished products;
- dispatched for supply to the customers; and
- referred to for the evaluation of the finished product.

The specifications for the bulk medicinal gases shall include, as appropriate:

- chemical formula;
- designated name or reference code;
- description of the pharmaceutical form of the bulk medicinal gas;
- detailed methods of sampling and testing the bulk medicinal gas, including the specified analytical procedures and equipment;

- qualitative and quantitative testing requirements for the bulk medicinal gas, with acceptance limits;
- storage conditions and any handling precautions; and
- the maximum period of storage before re-examination.

7.3.4 Finished medicinal gas

Specifications for finished medicinal gas shall include:

- designated name of the product;
- relevant pharmacopoeia monograph, where specified ;
- chemical formula and the concentration of each component, where appropriate;
- description of the pharmaceutical form of the finished product;
- any relevant details of the gas cylinder, cryogenic container and the outlet valve ;
- detailed methods for the sampling and testing of the finished product, including the specified analytical procedures and equipment;
- qualitative and quantitative requirements for the finished product, including the acceptance limits;
- specimen of the product label and patient information leaflet where appropriate;
- any storage conditions and any handling precautions; and
- shelf life of the finished product (where detailed in the relevant marketing authorisation).

7.3.5 Medicinal gas cylinders

Specifications for medicinal gas cylinders used for storage and distribution of compressed or liquefied gases or refrigerated liquefied gases shall include:

- water capacity of the cylinder and the volumetric content for the appropriate medicinal gas;
- design code, design pressure and maximum working pressure of the cylinder;
- material of construction of the cylinder;
- colour coding for its intended gas service;
- physical dimensions of the cylinder, where required;
- any internal cleanliness requirements, including the method of cleaning and the acceptance limits for both new and re-tested cylinders;
- statutory periodic inspection requirements; and
- approved suppliers and retesting facilities.

7.3.6 Medicinal gas cylinder valves

Specifications for cylinder valves fitted to medicinal gas cylinders for storage and distribution of compressed, liquefied or refrigerated liquefied medicinal gases shall include:

- materials of construction - of the cylinder valve, with specific reference to the compatibility of materials used in its manufacture with the medicinal gas for its intended service;
- design pressure and maximum working pressure of the cylinder valve;
- testing criteria and any maintenance requirements for approving the valve for use;
- inlet and outlet connections (as appropriate) with reference to the appropriate valve outlet standards (where specified by national or international standards);
- approved method of operation; and
- approved suppliers and retesting facilities, where appropriate.

7.3.7 Medicinal gas cylinder labels and patient information leaflets

Specification for printed cylinder labels and patient information leaflets shall include:

- label and leaflet material including details of the inks, adhesives and any protective coatings, where appropriate;
- printed text details (including the version control reference). A specimen of the current version of the printed materials shall be retained with the specification; and
- approved suppliers.

7.3.8 Medicinal gas storage tanks

Specification for the medicinal gas storage tanks for storage and distribution of refrigerated liquefied gases shall include:

- volumetric capacity / water capacity of the storage tank appropriate for the medicinal gas;
- design code, design pressure and the maximum working pressure of the storage tank;
- materials of construction;
- physical dimensions; and
- any internal cleanliness requirements, the acceptance limits for both new and re-tested storage tanks statutory periodic inspection requirements.

7.4 Procedures and work instructions

7.4.1 General

Formally authorised production methods, standard operating procedures and work instructions shall exist for the production of each medicinal gas and the filling of each medicinal gas cylinders. The production methods, standard operating procedures and work instructions shall be compliant with the requirements of the relevant marketing authorisation (where required) and be part of the documentation for each medicinal gas.

7.4.2 Bulk medicinal gases production procedures

The documented method of production and the detailed standard operating procedures shall be available for each bulk medicinal gas.

These procedures shall include:

- product name, with reference to its specification and pharmaceutical form;
- a list of all starting materials and their relevant specifications;
- a list of the principle equipment to be used;
- a statement of expected yield from the plant, where appropriate; and
- the analytical limits of acceptance for the product quality.

7.4.3 Bulk medicinal gases production work instructions

There shall be formally authorised stepwise Work instructions for the manufacture and processing of each bulk medicinal gas.

These Work Instructions shall normally include:

- reference to the production methods to be used for preparation of the manufacturing equipment, including any cleaning or calibrating requirements
- detailed stepwise processing instructions, including checks on starting materials, process temperatures, pressures and flowrates and pipework configurations
- in-process analytical controls or tests, with their appropriate acceptance limits
- any requirements for the bulk storage of the products.

7.4.4 Medicinal cylinders filling procedures

The documented method of production and the detailed procedures shall be available for the filling of cylinders for each medicinal gas.

These procedures shall include:

- the details of the specific cylinder filling equipment for each medicinal gas;
- checks on the bulk medicinal gases used as starting material in the cylinder filling process;
- any pre-treatment requirements for the medicinal gas cylinders;
- the pre-filling inspection requirements for the medicinal gas cylinders;
- the in-process quality control requirements, where applicable;
- the definition of the filling batch;
- the labelling requirements for the filled medicinal gas cylinders, including any batch labelling requirements for the traceability of the product;
- the finished product analytical testing methods with the acceptance limits; and

- storage requirements for the handling and storage of the filled medicinal gas cylinders.

7.4.5 Medicinal cylinders filling work instructions

There shall be approved work instructions for the filling cylinders of each:

- medicinal gas;
- cylinder type; and
- cylinder size.

These work instructions shall normally include:

- name of the medicinal gas;
- composition of the medicinal gas mixture, where applicable;
- size of the cylinder to be filled, expressed either as a reference code or as the volumetric or weight content of the filled cylinder;
- number of cylinders that constitutes a batch;
- an example of the cylinder label and the batch and shelf life label, indicating where the labels should be applied;
- precautions to be observed, including initial purging of the cylinder filling line to ensure that the gas used for cylinder filling will meet the filled cylinder specification;
- any in-process quality control checks, with the appropriate acceptance limits;
- any post-filling quality control tests, with the appropriate acceptance limits; and
- a description of the final packaging operations, including fitting of tamper evident seals.

7.4.6 Bulk medicinal gas supply procedures

Documented method and detailed procedures shall be available for the supply of each bulk medicinal gas.

These procedures for each medicinal gas shall include:

- product name, with reference to its specification, pharmacopoeia monograph and pharmaceutical form;
- specification of the approved bulk medicinal gas;
- statement of the approved bulk medicinal gas loading location and details of the equipment to be used; and
- finished product analytical testing methods with their acceptance limits.

7.4.7 Bulk medicinal gas supply work instructions

There shall be approved work instructions for the supply of each bulk medicinal gas.

These work instructions shall normally include:

- the name of the bulk medicinal gas;
- the size of the tankers used for distribution of bulk medicinal gas, expressed as a volumetric or weight content;
- the precautions to be observed when loading and discharging the tanker, including the initial purging of the tanker and tanker filling line for tanker loading and the delivery hose purging for tanker off loading, in order to ensure that the bulk medicinal gas meets the finished product specification when supplied as a starting material into the storage tank at the cylinder filling site or into the customer's storage tank;
- details of any in-process quality control checks, with the appropriate acceptance limits; and
- details of any post-fill quality control tests, with the appropriate acceptance limits.

7.5 Batch records

Batch records shall provide a history of each batch of bulk medicinal gas produced or batch of medicinal gas cylinders filled. These batch records should include all details pertinent to the quality of the final product.

Batch records shall be designed such that all significant recordable activities involved in either the manufacture of medicinal gases or the filling of medicinal gas cylinders permit the traceability of each defined batch. All batch records shall be dated and signed by the quality controller or his nominated deputy.

This documentation shall also include any other relevant original data such as laboratory notebooks or production records

7.5.1 Bulk manufacture batch definition

Bulk medicinal gases are usually produced continuously and their quality continuously monitored. This does not comply with the normal batch philosophy used for the manufacture of pharmaceutical products.

A batch of bulk medicinal gas may be defined as:

- product produced into a bulk storage tank, where the product is defined as being a homogeneous batch;
- product transferred from a bulk storage tank into a bulk gas tanker, where the contents of the tanker is defined as being a homogeneous batch; and
- a continuous production defined within a defined time period or a time period.

7.5.2 Continuous production batch records

For continuous production the batch record shall only reference the in-process quality control checks made. Where the bulk product is produced in defined batches, a batch record shall be kept for each batch processed.

The batch record shall be based on the relevant parts of the currently approved manufacturing procedure and processing instructions. The method of preparation of such records shall be designed to avoid transcription errors. The batch identity number shall be recorded on the batch record.

7.5.3 Production batch data

During the manufacture of bulk medicinal gases, the relevant manufacturing information and quality control results shall be recorded on the batch record. The information shall be recorded by hand or electronically at the time each test or action is taken. The batch record shall be dated and signed once the manufacture of the batch is complete to indicate agreement by the person responsible for the processing operations that the product meets the specification.

The batch record for the manufacture of the bulk medicinal gas shall include as appropriate:

- name of the manufacturing site;
- name of the gas;
- the time of commencement of the manufacture of the bulk gas and the completion of the batch production. Where the bulk medicinal gas is produced by a continuous process and / or an automated system, this requirement may not be relevant;
- initials of the operator / person responsible for checking each stage of the production of the bulk gas;
- batch number;
- a record of the results of any in-process quality control checks, with the initials of the person(s) responsible for carrying them out;
- details of any specific problems encountered during the manufacturing process, with signed authorisation for any deviation from the manufacturing formula and processing instructions.

7.5.4 Cylinder filling bulk gas supply

When the bulk medicinal gas is added to the storage tank, used for medicinal gas cylinder filling, the identity of the batch is broken as the residual product from the previous batch in the storage tank will still be present. Once the transfer is complete the content of the storage tank shall be re-defined as a batch.

The filling of medicinal gas cylinders permits the identity of the filling batch to be defined for the purposes of batch release.

7.5.5 Cylinder filling batch record

The cylinder filling batch record shall be prepared for each batch of cylinders filled.

During the cylinder filling process, the relevant batch information shall be recorded at the time each product significant action or test is taken, either by hand or electronically.

Data included in the records for each batch of cylinders filled shall ensure that each filled cylinder is traceable to significant steps of the relevant filling operations.

As appropriate, the following shall be entered on the batch record:

- name of the product;
- date and the time of the filling operations;
- 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;
- the quantity and size of cylinders before and after filling;
- name of the person carrying out the filling operation;
- 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; and
- records of any non-conformances and the appropriate corrective action taken.

After the cylinder batch is completed, the batch record shall be dated and signed by the person responsible for filling the cylinders.

7.5.6 Bulk Medicinal Gas Batch Records

A batch record for each supply of bulk medicinal gas shall be kept, based on the relevant parts of the current approved bulk medicinal gas production and bulk medicinal gas tanker filling procedures and work instructions.

The bulk medicinal gas batch records shall be designed to avoid transcription errors.

Data included in the records for each batch of bulk medicinal gas shall ensure that each batch is traceable to significant aspects of the relevant filling operations.

During the filling of the bulk gas tanker, the following information shall be recorded, by hand or electronically, at the time each action is taken and shall include:

- filling site;
- loading manifold and storage tank used for filling the cryogenic gas tanker;
- name of the bulk gas being loaded;
- initials of the operator / person responsible for the bulk gas tanker loading operation;
- batch number and / or the analytical control number of the bulk medicinal gas being loaded;
- results of any in-process quality control measurements and the initials of the person(s) carrying them out;

- quantity filled into the bulk gas tanker, expressed as a volumetric or weight content;
- records of any non-conformity and details of the appropriate corrective actions taken.

After completion, the record shall be dated and signed by the person responsible for the bulk gas tanker filling operation.

7.6 Other records

7.6.1 Trend analysis

It is recommended for some data, such as in-process analytical tests results, plant yields and finished product tests that these records shall be kept in a manner that will permit trend evaluation.

7.6.2 Sampling procedures

There shall be a validated written procedure for the sampling of all starting materials, intermediate products and finished products.

The procedures shall include:

- person(s) authorised to take the samples;
- methods and equipment to be used for taking the sample;
- amount of samples to be taken;
- any precautions to be observed to avoid contamination of the sample material or any deterioration in its quality.

7.6.3 In-process controls

There shall be validated written procedures for any product quality significant in-process control tests, which describe the test methods and the equipment to be used.

These shall be recorded on the batch record.

7.6.4 Release and rejection procedures

Written release and rejection procedures shall be available for starting materials, intermediate products and, where required by national regulations, for the release for sale of the finished product by the qualified person(s).

7.6.5 Batch distribution records

Records shall be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

There shall be a system in place ensuring traceability of cylinders and valves as well as for the bulk medicinal gases and the filled medicinal gas cylinders.

7.7 Records

There shall be written procedures and the associated records of actions taken or conclusions reached for:

- validation of the manufacturing and filling equipment;
- equipment maintenance, cleaning and calibration;

- operator training;
- personal protective equipment requirements;
- complaints;
- product recalls; and
- product returns.

8 Production (EC GMP Chapter 5)

8.1 Principles

The operations for the production of medicinal gases and the filling of medicinal gas cylinders shall follow defined procedures which shall comply with the principles of Good Manufacturing Practice. This is necessary in order to produce medicinal gases in bulk and in filled cylinders of the requisite quality and in accordance with the relevant manufacturing licence and marketing authorisations, as required by the national authorities.

For the purposes of medicinal gases, a batch (or lot) is defined as a well determined quantity of starting material or finished product subjected to a process or series of processes, the quality of which is identified as being uniform.

For bulk medicinal gas production a batch will normally relate to a quantity of finished product. This can either be a defined quantity of gas transferred to a bulk medical gas storage tank or a defined quantity loaded into the bulk medicinal gas tanker for delivery to customers. For medicinal gas cylinders a batch is normally defined as a number of cylinders filled together on a manifold at the same time or, for cylinders filled individually, cylinders filled within a defined period where there have been no changes to operators, filling equipment or starting materials.

8.2 General

Production of medicinal gases can refer to either the filling of medicinal gas cylinders or the production of the bulk medicinal gases, supplied either as finished product direct to the customer or as a starting material for medicinal cylinder filling.

8.2.1 Production personnel

Production of medicinal gases should be carried out and supervised by competent persons who have a thorough knowledge of the production and control of medicinal gases.

All personnel involved in the production of medicinal gases or the filling of medicinal gas cylinders shall understand the GMP requirements relevant to medicinal gases and be aware of the critically important aspects and potential hazards for patients from products in the form of medicinal gases.

8.2.2 Product identification

The receipt, quarantine, sampling, storage, and labelling of all starting materials and finished product shall be done in accordance with validated written operating instructions and, where appropriate, recorded.

8.2.3 Validated processes

The processing, packaging and distribution of medicinal gases shall be validated and follow agreed operating procedures in accordance with the relevant manufacturing or marketing authorisation, as required by the national authority.

8.2.4 Control of starting materials

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

8.2.5 Plant yield

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

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

8.2.6 Plant equipment labelling

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

8.2.7 Deviations from procedures

As far as practicably possible, any deviations from the approved work instructions or standard operating procedures shall be avoided.

If a deviation occurs, it shall be formally authorised in writing by a responsible person with the involvement of the person nominated as responsible for quality control.

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

8.2.8 Retained samples

Retained samples are not required, unless otherwise specified by the national authorities.

8.2.9 Cross contamination

The manufacture and filling of medicinal gases is carried out in closed equipment and consequently the risk of environmental contamination of the product is minimal.

However, where there is any potential for the wrong medicinal gas cylinder or bulk gas tanker to be connected to a system, there is a risk of cross-contamination with other gases unless there is a comprehensive system to prevent any back-flow into the system.

8.3 Validation

8.3.1 General

All critical steps in bulk production and distribution and cylinder filling processes, i.e. those steps with a significant affect on the product safety and quality shall be subject to validation.

8.3.2 Process validation

Separation and purification steps shall be validated for effectiveness and monitored according to the results of the validation. Where necessary in-process controls should be used to continuously analyse the quality of the medicinal gas being produced to monitor the effectiveness of the production process.

Maintenance and replacement frequencies of expendable equipment components, such as purification filters, shall be based on the results of monitoring and validation.

8.3.3 Computer validation

Computer systems used in controlling or monitoring production processes shall be validated.

8.3.4 Change control

Significant amendments to the manufacturing process, including any change in process equipment or materials, which affect product quality or reproducibility of the process shall be validated.

8.3.5 Validation review

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

8.4 Starting materials

8.4.1 General

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

8.4.2 Suppliers

Starting materials shall only be purchased from suppliers who have been approved by a competent person and, where possible, they should be purchased directly from the producer.

The specification of starting materials shall be agreed with the manufacturer or supplier to ensure that it meets the requirements of the manufacturing process as defined in the marketing authorisation.

8.4.3 Bulk gas deliveries

Deliveries of bulk medicinal gases may be added to bulk storage tanks containing the same gas from previous deliveries.

The result of a sample shall show that the quality of the delivered gas is acceptable and the sample could be taken from either:

- the delivered gas before the delivery is added
- from the bulk tank after adding and mixing the new delivery.

8.4.4 Starting material release

Only starting material which has been released by the quality control function shall be used for medicinal gas cylinder filling.

Bulk gases intended for medicinal use shall be:

- defined as a batch
- controlled in accordance with relevant Pharmacopoeia monographs
- released for filling medicinal gas cylinders.

8.5 Production - Bulk medicinal gases

8.5.1 Bulk medicinal gases classification

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

8.5.2 Process flow charts

Process flow charts for each different process or part of the process shall be available to the operator for reference.

Additional information shall also be available to the operator, specifying the purity of the gas and other components and the possible impurities that could be present in the source gas and at specified purification steps, as applicable.

8.5.3 Plant design

All separation and purification steps shall be designed to operate at optimal effectiveness. For example, impurities that could adversely affect a purification step shall be removed before this step is reached such as carbon dioxide and moisture in the ambient air stream into the air separation unit.

8.5.4 In-process control

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

8.5.5 Transfer operations

All the transfer operations, including controls before transfers, of liquefied gases from primary storage shall be in accordance with written procedures designed to avoid any contamination. The transfer line shall be equipped with a validated back-flow prevention device. Particular attention shall be paid to purging the flexible connections and to coupling hoses and connectors.

8.5.6 Batch control

Bulk gases intended for medicinal use shall be defined as a batch, controlled in accordance with relevant Pharmacopoeia monographs and released for filling. For continuous processes, a definition of a batch shall be documented and related to the frequency of analysis of the bulk medicinal gas.

8.5.7 Traceability

There shall be a system in place to ensure batch traceability of the bulk gases, either used for supply to customer's storage or the supply as a starting material for medicinal gas cylinder filling.

8.6 Production - Medicinal gas cylinder filling

8.6.1 Medicinal gas filling manifolds

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

8.6.2 Traceability

As well as the traceability of the medicinal gas cylinders within a batch, there shall also be a system in place ensuring traceability of cylinders and valves used for medicinal gas supply. Where the national

standards permit the use of common medicinal cylinder valves outlets in more than one product, on cylinder filling manifolds where these connections are used, there shall be additional checks carried out on the filled medicinal gas cylinders to ensure that the correct gas has been filled into the cylinders.

8.6.3 Batch control

For filling of medicinal gas cylinders, the filling batch shall be defined and documented and shall be related to the analysis of the gas sample from the batch.

8.6.4 Medicinal cylinder valves

Containers for medicinal gases shall conform to appropriate national or international technical specifications.

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

8.6.5 Cylinder testing

Cylinders shall be cleaned, tested and maintained in an appropriate manner.

New cylinders and cylinders that have undergone statutory testing shall be subject to an internal inspection to ensure that the cylinder is dry and free from contamination, prior to the cylinder valve being fitted.

8.6.6 Pre-fill checks

All medicinal gas cylinders in a filling batch shall be inspected prior to filling to ensure that they are in a suitable condition for filling.

The pre-filling inspection checklist shall form part of the medicinal cylinder filling procedures and shall include the following checks for all medicinal gas containers in the batch:

- Cylinders are within their required periodic inspection period. The check is to confirm that the containers have undergone a relevant hydrostatic pressure test or equivalent test and that the test is still valid, as required by international or national regulation.

- External surface do not show signs of damage. Each container shall be externally inspected for external cleanliness, damage or contamination, including dents or gouges and other damage. Specific care is needed to ensure that the shell and valve has no traces of oil or grease.

- Cylinder have a residual pressure (ideally greater than 3 bar(g)). It is important that each container has not been completely emptied to prevent atmospheric contamination of the cylinder.
  Where minimum retention valve (MPR) type valves are used there shall be a check to ensure that the residual pressure device is functioning correctly and that the cylinder has been returned with a positive pressure. Cylinders with no residual pressure shall be put aside for additional measures to make sure they are not contaminated with water or other contaminants. These measures could include cleaning with validated methods or visual inspection as justified to ensure that the container is appropriately prepared for re-filling.

- All old batch labels have been removed. Any other labels fitted by the customer shall also be removed before refilling the container.

- That all product identification labels are in good condition and legible. If product labels are damaged they shall be replaced before refilling the container.

- There is the correct cylinder or cryogenic container valve connection for the particular medicinal gas involved

- Where required, cylinders are painted to the correct colour code and that the paintwork is of an appropriate standard. Containers where the paintwork condition is considered unsuitable shall be withdrawn for repainting.

Any cylinder failing the pre-filling check shall be suitably labelled and sent for rectification prior to being filled.

8.6.7 Cylinder preparation

Cylinders which have been returned for refilling shall be prepared in order to minimise the risk for contamination is kept to a minimum. 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).

Cylinders shall be prepared for refilling in line with the procedures defined in the marketing authorisation.

Cylinders equipped with MPR valves may not require the same level of preparation dependant on the functionality of the container valve.

If the MPR valve fitted has a non-return function, it could be appropriate to only vent the contents to atmosphere without carrying out any other purging steps. Changes to the above options shall be validated to demonstrate their effectiveness and shall be documented in the marketing Authorisation.

As an alternative, a full analysis of the remaining gas may be carried out of each individual container to demonstrate that the returned gas is of a suitable quality for it to be retained.

8.6.8 Gas mixing

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

Gas mixing can be achieved by rolling the cylinder or by adding the component gases of the mixture in the correct order, filling with the lowest density gas first. The method of gas mixing shall be validated to demonstrate that the method is effective.

8.6.9 Post-fill checks

Post-fill checks shall include checks to ensure all containers in the batch

- Have been filled. An indication that a permanent gas cylinder has been filled is that the exterior of the cylinder is warm to the touching immediately after filling.

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

- Are fitted with an appropriate product label. The product label fitted shall be as specified in the marketing authorisation (where appropriate) and shall be the correct version / revision

- Has been fitted with a batch label. The batch label shall specify the unique batch number and the expiry date, dependant on the shelf life detailed in the marketing authorisation (where specified)

- Have been fitted with a tamper-evident seal.

8.6.10 In-process controls

Any in-process controls shall be recorded with the batch records.

8.7 Equipment cleaning

8.7.1 Pipework cleaning

Due to the need to maintain the medicinal cylinder filling pipework and equipment clean and free from any hydrocarbon contamination for safety reasons, it could be necessary to clean any pipework or equipment with a suitable degreasing agent. However, it is essential that any traces of the degreasing agent are removed from the system prior to it being recommisioned in medicinal gas service.

Cleaning and purging of filling equipment and pipelines shall be carried out according to written procedures. This is especially important after maintenance, repair or breaches of system integrity. Checks for the absence of contaminants or cleaning materials shall be carried out before the line is released for use. Records shall be maintained of any post cleaning test results.

8.7.2 Change of service

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

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

8.8 Packaging materials - Medicinal gas cylinder filling

8.8.1 General

Packaging material for medicinal gases refers to the medicinal gas cylinder labels, batch labels and the Patient Information Leaflets (PIL). This section details the appropriate actions needed to be taken with the receipt, storage, issue, fitting and control of all printed packaging material supplied with the medicinal gas cylinder.

8.8.2 Label and leaflet supplier

Cylinder labels and patient information leaflets shall be quarantined when they are received from an approved supplier until they have been checked against either the current specification or a reference sample.

Labels shall only be issued for use by an authorised person following an approved and documented procedure.

8.8.3 Label and leaflet storage

Labels and leaflets shall be stored in adequately secure conditions so as to exclude unauthorised access. Roll-feed labels are normally preferable to cut-labels in avoiding mix-ups. Special care shall be taken when handling non roll-feed labels which shall be stored in separate closed containers to avoid mix-ups.

8.8.4 Label design

The printing on product labels shall be clear and resistant to fading when exposed to daylight for a period which is commensurate with the shelf life of the product.

The durability of the label material and the print shall be validated to ensure that it is compatible with the shelf life of the product.

8.8.5 Obsolete labels

When a revised version of a label or leaflet is approved for use, all obsolete and outdated labels and leaflets shall be removed from the filling / fitting areas and destroyed.

8.8.6 Cylinder labelling

Each cylinder shall be correctly labelled and colour-coded to conform with national or international regulations and in accordance with the marketing authorisation.

The batch number and expiry date details may be displayed on a separate label.

8.8.7 Label quality

The performance of any printing operation, including printing of separate batch labels, shall be checked for detail and legibility and the checks recorded.

8.8.8 Unused labels

Upon completion of the cylinder filling operation, any unused batch labels shall be made unusable and the number recorded on the batch record.

8.9 Finished products - Cylinders

8.9.1 General

Finished product refers to medicinal gas cylinders which have been filled, all quality control functions completed and recorded and where required by the National Authority, formally released by the Qualified Person.

8.9.2 Quarantine area

Following filling, all full cylinders shall be held in quarantine until they have been released by the Qualified Person for supply to the patient.

8.9.3 Released cylinders

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

8.10 Rejected products

8.10.1 General

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

Rejected filled cylinders shall be clearly marked or labelled and stored separately in a defined restricted area.

Any corrective actions taken shall be approved by an authorised person and recorded on the batch data.

8.10.2 Incident cylinders

Cylinders which have been involved in an incident, following an unplanned event, shall only be refilled after special inspection, investigation and approval by an authorised person. Detailed records shall be kept of these operations.

9 Quality control (EC GMP Chapter 6)

9.1 Principles

Quality control is primarily concerned with the sampling and testing of starting materials, premixes and finished products to ensure that they meet the specification detailed in the relevant marketing authorisation or product specification.

The quality controller, or his nominated deputy, shall be responsible for ensuring that the manufacturing, assembly and release procedures have been carried out correctly and any specified tests have been completed, having satisfactory results. All starting materials and pre-mixes shall not be released for use, and no finished products released for sale or supply, until their quality has been judged satisfactory.

The quality controller's responsibility includes:

- the control of in-process test;
- laboratory tests; and
- any decisions which could be concerned with the quality of the medicinal gas.

The level of independence of quality control from production is considered fundamental to the satisfactory operation of quality control, specifically having the authority to prevent the supply of finished product that is considered to be unsuitable for patient use. See also 9.2.1.

9.2 General

9.2.1 Quality control responsibilities

The responsibility for quality control shall be well defined within the organisation to ensure that the principles of Good Manufacturing Practice are fully met.

Due to the nature of the medicinal gas industry and the effective procedures and equipment used to prevent any cross contamination of the product in the manufacturing and assembly processes such as:

- cylinders are filled in fully closed equipment and pipework;
- small batches are filled throughout a working day;
- usually an automated filling processes; and
- each batch is post-filled analysed,

it may be appropriate for the quality control function to be not totally independent of the production department but in all cases the quality controller shall have the responsibility and authority to prevent any finished product that does not meet the specification from being supplied for patient use.

9.2.2 Quality control resource

Adequate resources shall be available to ensure that all the quality control procedures are carried out effectively and reliably. The quality control requirements shall only be carried out by trained operatives, under the authority of a person with appropriate qualifications and experience.

Where in-process checks are carried out by production personnel, the tests shall be performed in accordance with methods approved by the quality controller.

9.2.3 Product release

For the final release of medicinal gases for patient use, the following assessment shall include a review of:

- results of in-process tests;
- batch records to demonstrate compliance with manufacturing and testing procedures;
- final product analysis to ensure compliance with the finished product specification; and
- examination of the filled cylinder, including checking the requirements for labels, leaflets and any tamper evident seals.

Each batch of medicinal gas shall be tested and released according to its specifications. In addition, it shall also be tested to full relevant pharmacopoeial requirements at sufficient frequency to assure ongoing compliance.

9.2.4 Quality control requirements

The principal requirements of the quality control processes shall be to:

- approve and monitor any supplier(s) of starting and packaging materials, contract analysts and contract manufacturers, ensuring that there is a written contract covering the production and / or analysis arranged under contract and any connected technical arrangements;
- ensure that all analytical and measurement equipment is calibrated against a known standard and maintained in an operating condition;
- ensure that all quality control methods used for monitoring the product quality have been validated;
- ensure that a suitable training programme is established for all quality control activities and that all personnel involved in quality control measurement are adequately trained and their competency assessed;
- ensure the correct labelling of containers of starting materials and finished products; and
- participate in the investigations of complaints related to the quality of the product.

It is acceptable that some of these responsibilities can be delegated to a nominated person other than the named quality controller provided that the delegation has been formally documented and approved.

9.2.5 Quality control documentation

The documentation covering the testing of medicinal gases shall follow the general principles given in Section 7.

An important part of this documentation deals with the quality control requirements and the following details shall be readily available to the quality controller:

- specifications of the raw materials, intermediate products and the finished products;
- validated sampling procedures as specified in the marketing authorisation (where appropriate);
- validated testing methods and records (including analytical worksheets and, where appropriate, laboratory notebooks);
- analytical reports or certificates; and
- calibration procedures for any instruments used for in-process and finished product analysis and records of the calibration and maintenance of the equipment.

9.3 Sampling

9.3.1 General

All sampling methods shall be validated and approved.

Written procedures shall be available that describe the:

- method of sampling, including any purging requirements to ensure the sample is not contaminated and is representative of the product being sampled;
- sampling equipment to be used and the amount of sample to be taken;
- type, condition and identification of the sample container to be used; and
- instructions for the cleaning and storage of sampling equipment.

9.3.2 Retained samples

Retained samples are not required of medicinal gases, unless otherwise specified by the national authorities.

Where retained samples are required, they shall be retained until at least one year after the expiry date for the batch.

Reference samples should be of sufficient size to permit at least one full re-examination.

9.4 Bulk production

9.4.1 Principal requirements

The principal responsibilities for the quality controller related to the production of medicinal gases shall be to:

- verify that approve and authorise written procedures for the production of medicinal gases are used;
- verify that all production equipment is maintained in an appropriate condition and validated as suitable for use;
- approve or reject all starting material and bulk products;

- review all batch records and take appropriate corrective actions for any non-conforming products; and

- ensure that all the necessary production quality control checks are carried out using approved and validated testing methods for all documented quality control procedures, as specified in the marketing authorisation (where appropriate).

It is acceptable that some of these responsibilities can be delegated to a nominated person other than the named quality controller provided that the delegation has been formally documented and approved.

All these operations shall be carried out in accordance with the written procedures and, where necessary, recorded on the daily log or batch record.

9.4.2 Monitoring

Production of bulk gases, either as starting material, active pharmaceutical ingredients (APIs) or finished product shall be monitored for quality and impurity levels and results recorded.

9.4.3 In-process tests

All the in-process tests shall be performed to approved and validated methods and the results recorded.

9.4.4 Process water quality

Water used during compression of medicinal gases (for lubrication of the upper cylinder of the compressor) which comes in contact with the gas shall be of drinking water quality.

9.4.5 Bulk gas sampling

Where samples are taken from bulk liquefied or refrigerated liquefied gases, the sample taken shall be a liquid sample to reflect the quality of the bulk gas using a validated sampling system. Under these circumstances, where the sample has to be vaporised to test, the method used shall ensure that the results are representative of the quality of the bulk material.

9.5 Cylinder filling

9.5.1 Principal requirements

The principal responsibilities for the quality controller in the filling of medicinal gas containers shall be to:

- verify that approved and authorise written procedures for the filling of medicinal gas cylinders are used;

- verify that all cylinder filling equipment is maintained in an appropriate condition and validated as suitable for use;

- approve or reject all bulk gases, cylinder shells, valves, labels and patient information leaflets used in the filling of medicinal gas cylinders;

- review all batch records and take appropriate corrective actions for any non-conforming products; and

- ensure that all necessary quality control checks and measurements on medicinal gas cylinders are carried out, using approved and validated testing methods as specified in the marketing authorisation (where appropriate).

It is acceptable that some of these responsibilities can be delegated to a nominated person other than the named quality controller provided that the delegation has been formally documented and approved.

All of these operations shall be carried out in accordance with the written procedures and the results recorded in the quality control record.

9.5.2 Starting materials

Bulk gases supplied as starting material for the filling of medicinal gas cylinders shall be released by an authorised person for filling prior to starting the medicinal gas cylinder filling process.

Where bulk gas is added to the bulk storage tanks containing the same gas from previous deliveries, the results of a sample shall show that the quality of the delivered bulk gas is acceptable.

Samples of the bulk gas can be taken from either the:

- the delivered bulk gas before the delivery is added to the storage tank, or
- the bulk tank after adding and mixing the new delivery.

9.5.3 Manifold filled cylinders

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

If the assay is gas specific, test for identity is not necessary.

Where the gas being filled into the cylinders is continuously monitored for quality and the filling process has been validated to demonstrate that the cylinders are filled correctly, the frequency of testing of cylinders from each filling operation may be relaxed.

9.5.4 Cylinders filled singularly

In the case of a single medicinal gas filled into cylinders one at a time by individual filling operations, at least one cylinder of each uninterrupted filling cycle shall be tested for identity and assay.

If the assay is gas specific, a separate test for identity is not necessary.

An example of an uninterrupted filling operation cycle is one shift's production using the same personnel, equipment, and batch of bulk gas. This process relates specifically to medicinal gas cylinders filled individually on a weigh scale.

9.5.5 Medicinal gas mixtures

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).

Where the medicinal gas mixture is intended for breathing by the patient, every cylinder within the batch shall be tested for its oxygen content to ensure that the gas mixture is suitable for breathing. Other components within the batch may be tested at the frequency specified above.

If any of the assay tests are gas specific, a separate test for identity is not necessary.

When cylinders are filled individually, every cylinder shall 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.

Where it is possible to validate the filling system, it could be possible to reduce the level of testing, provided that it is approved by the Regulatory Authority and agreed within the marketing authorisation.

9.5.6 Correct mixing

When a medicinal gas is manufactured by mixing more than one gas in the cylinder, the filling procedure shall ensure that the component gases are correctly mixed in every cylinder and finished product is fully homogeneous before the product is tested.

9.5.7 Dynamic mixing

When gases are mixed in-line before filling, such as for nitrous oxide/oxygen gas mixtures, continuous monitoring of the gas mixture being filled into the cylinder is required.

9.6 Testing

9.6.1 Test records

All in-process and final product analytical results obtained shall be recorded in the batch records. Where multiple checks are made, the results shall be checked to make sure that they are consistent with each other.

Any calculations used in determining the result shall be critically examined.

The test result records shall include, as a minimum, the following data:

- name of the product;
- reference to the relevant specifications;
- batch number and, where appropriate, the manufacturer and supplier;
- test results, including observations and calculations, and reference to any certificates of analysis;
- test date;
- initials of the persons performing the testing;
- initials of the persons verifying the test and calculations, where appropriate; and
- a clear statement of release or rejection (or other status decision) and the dated signature of the designated quality controller or his nominee.

9.6.2 Moisture testing

The level of testing cylinders for moisture content in medicinal cylinders will be dependent on the pre-fill checks of cylinders to ensure that they are free from any potential contamination.

The testing frequency shall be validated to demonstrate compliance with the specification.

Where validated minimum pressure retention valves are used, there is no need to test for moisture, if the MPR valve has been shown to be functioning correctly prior to filling or it can be demonstrated that the cylinder has been returned for filling containing a positive pressure.

Where compressors that use water to lubricate the pistons are used, the moisture content of the filling gas shall be continuously monitored. Provided the moisture levels from the continuous monitoring are within the specification level, there is no need to carry out further moisture testing where the cylinders are fitted with a validated minimum pressure retention valve.

9.6.3 Cryogenic containers filled at the production site

In the case of medicinal gas filled into cryogenic container for delivery to either homecare users or hospitals, each container should be tested for identity and assay.

If the assay is gas specific, test for identity is not necessary.

Where it can be demonstrated that the critical attributes of the residual gas in the vessel have been maintained, testing of one vessel per batch is permissible.

9.6.4 Cryogenic container not filled at the production site

All cryogenic containers, which are retained by customers and refilled on site at the customer's premises from a mobile delivery tank need not be sampled after filling, provided the filling company has a certificate of analysis of the mobile delivery tank. It should be demonstrated that the specification of the gas in the containers is maintained over the successive refillings.

9.6.5 Leak testing

Each filled cylinder shall be tested for leaks using an appropriate method, prior to fitting the tamper evident seal. The leak test shall include the potential leak paths, based on risk management. A method of leak detection should be used such that direct application of leak detection fluid is used. Where sampling and testing of the filled cylinder is carried out, the valve outlet leak test shall be completed after testing.

9.6.6 Water quality

Water used for hydrostatic pressure testing of cylinders shall be at least of drinking water quality.

9.6.7 Calibration gases

Reference gases for calibration purposes and indicator tubes for testing should be marked with an expiry date and not used after the stated time.

10 Contract management and analysis (EC GMP Chapter 7)

10.1 Principle

Contract manufacture and analysis of medicinal gases shall be formally agreed, correctly specified and controlled by means of a contract. The contract conditions shall ensure that the contracted arrangements are carried out correctly and that there are no misunderstandings which could lead to product or work of unsatisfactory quality.

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

The contract shall clearly state, where the national arrangements require their use, the way in which the qualified person shall release each batch of product to exercise their full responsibility.

This section deals with the responsibilities of medicinal gas manufacturers towards the competent authorities of the Member States with respect to the granting of marketing authorisation and manufacturing licence. It is not intended to affect the respective liability of contract acceptors and givers to consumers, which is governed by other provisions of Community and national law.

10.2 General

10.2.1 Written contracts

There shall be a written contract between the contract giver and the contract acceptor covering the manufacture, product quality control and supply of any medicinal gases or starting materials by another supplier. The written contract shall include any specific technical arrangements or product specifications, including its container, in connection with the contracted service.

10.2.2 Compliance with marketing authorisation

All of the arrangements in connection with either the contract manufacture or analysis shall be in accordance with the details specified in the relevant marketing authorisation, where required by the national authorities. Any proposed changes to the method of manufacture or analysis shall be agreed prior to the change and be in accordance with the marketing authorisation for the product concerned.

10.3 Contract giver

The contract giver is the person who is receiving the medicinal gas or starting material covered by the contract.

10.3.1 Responsibilities

The contract giver shall be responsible for assessing the competence of the contract acceptor to carry our successfully the manufacture, product quality control and supply of any medicinal gases or starting materials by another supplier required and for ensuring, by means of the contract, that the principles and guidelines of Good Manufacturing Practice (GMP) with respect to medicinal gases are followed.

10.3.2 Product specifications

The contract giver shall provide the contract acceptor with all the information, including the specification and specified methods of manufacture or analysis, in order to comply with the marketing authorisation and any other legal requirements. The contract giver shall ensure that the contract acceptor is fully aware of any associated problems with the product manufacture or analysis which could cause a risk to their personnel, premises, equipment and other processes that could be involved.

10.3.3 Product release

The contract giver shall ensure that all manufactured medicinal gases or bulk gases for use in the manufacturing process delivered to him by the contract acceptor comply with the specification detailed in the marketing authorisation, where required by the national authorities. For finished product, the contract giver shall ensure that the medicinal gases have been formally released, using a qualified person where required.

10.4 Contract acceptor

The contract acceptor is the person who is providing the medicinal gas or starting material covered by the contract.

10.4.1 Contract acceptor qualifications

The contract acceptor shall have suitable premises and equipment to manufacture or analyse medicinal gases or starting materials to the appropriate specification. They shall also have sufficient competent personnel with adequate knowledge and experience to carry out the contracted work satisfactorily. Contract manufacture of medicinal gases shall only be undertaken by a holder of a manufacturing licence issued by the national authority, specifically covering the manufacture of the medicinal gas covered by the contract.

10.4.2 Responsibilities

The contract acceptor shall ensure that all medicinal gases or bulk gases delivered to him have been manufactured to the agreed specification and are suitable for their intended purpose.

The contract acceptor shall ensure that no other activity being undertaken when the contracted work is being carried out will adversely affect the quality of the manufactured medicinal gas or the analysis of the medicinal gas for the contract giver.

10.4.3 Sub-contract activities

The contract acceptor shall not sub-contract any of the manufacturing or analysis work, covered by the contract, without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract acceptor and any third party shall ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract acceptor. All sub-contracted work shall be in strict accordance with the arrangements detailed in both the contract giver's marketing authorisation, where required and the contract acceptor's manufacturing licence.

10.5 The contract

10.5.1 General

A contract shall be drawn up between the contract giver and the contract acceptor which specifies their respective responsibilities relating to the manufacture and control of the medicinal gas. The technical aspects of the contract shall be drawn up by a competent person, with a suitable knowledgeable of the pharmaceutical aspects of medicinal gas manufacture, analysis and the related Good Manufacturing Practice requirements.

All manufacture and analysis of medicinal gases shall be in strict accordance with the relevant marketing authorisation, where required, and agreed by both parties.

10.5.2 Release for sale

The contract shall specify the way in which the qualified person releases each batch of medicinal gas for sale to ensure that the batch has been manufactured, checked and approved for compliance with the requirements of relevant marketing authorisation, where required by the national authorities.

10.5.3 Specified responsibilities

The contract shall describe clearly who is responsible for:

- purchasing raw materials;
- testing and releasing materials for the manufacturing process;
- production of the medicinal gas;
- quality controls, including in-process controls;
- sampling and analysis of the medicinal gas;
- certification of the batch and retention of the batch records; and
- actions to be taken in the event of the product being identified as out of specification and the appropriate actions required to institute corrective actions and to recall product from the marketplace.

In the case of contract analysis, the contract shall state whether or not the contract acceptor shall take samples at the premises of the manufacturer or whether samples are sent to the analyst.

10.5.4 Records

The records for the contract manufacture, analysis and distribution of medicinal gases should be retained by, or be available to, the contract giver. Any records relevant to assessing the quality of a medicinal gas, in the event of a complaint or a suspected defect, shall be accessible to the contract giver and specified in the relevant defect/recall procedures.

10.5.5 Auditing

The contract shall permit the contract giver to audit the relevant facilities of the contract acceptor at any time. The contract should provide details of the audit programme for the contract giver to evaluate that the contract acceptor is complying with the requirements of the specification and the contract.

11 Complaint and product recall (EC GMP Chapter 8)

11.1 Principle

All complaints and other information concerning potentially defective products shall be reviewed according to written procedures. In order to provide for all contingencies, and in accordance with EC Directive 2001/83EC [1], a system shall be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

11.2 Complaints

11.2.1 Responsibilities

There shall be a designated person responsible for handling complaints concerning the supply of medicinal gases. The designated person shall be responsible for ensuring the identification of the cause of the complaint and the corrective measures to limit its impact. Sufficient resource shall be available to the designated person to carry out any investigation and implement the agreed proposed corrective actions.

Where a qualified person is required by the national authority, they shall be informed of any complaint and assist, as necessary, in the investigation procedure and any follow-up actions.

11.2.2 Written procedures

Written procedures shall be available detailing the actions to be taken in the event of receiving a complaint concerning the quality of a medicinal gas. These procedures shall include the appropriate actions to be taken if a recall is considered to be necessary.

11.2.3 Records

All medicinal gas complaints concerning product quality or adverse patient reactions shall be recorded in a complaints log. All details concerning the original complaint, subsequent investigations and any recall actions, including any analytical results and reconciliation details shall be collated and recorded in the log.

The nominated person responsible for quality control, responsible for the manufacture of the medicinal gas and the qualified person shall normally be involved in any medicinal gas complaint investigation.

11.2.4 Product review

If a product defect is discovered or suspected in a medicinal gas batch, dependant on the type of defect, consideration shall be given to checking other batches in order to determine whether they are also affected. In particular, consideration shall be given to other batches produced from the same batch of bulk gas or produced on the same filling equipment.

11.2.6 Complaints review

Complaints records shall be reviewed regularly by both the quality controller and the qualified person, where required, for any indication of specific or recurring problems requiring attention and the possible need to recall of medicinal gases.

11.2.7 Recall notification

The appropriate national authorities should be informed if a manufacturer is considering any recall action following the possible faulty manufacture, deterioration or any other serious quality problems with a medicinal gas. Where the manufacturing or testing procedures are modified, consideration shall be given to the need to vary the relevant marketing authorisation, where they are required by the national authorities.

11.3 Recalls

11.3.1 General

The recall procedure shall include the need to designate a person as responsible for the execution and co-ordination of the recall. The nominated person shall be given adequate resources to handle all the aspects of the recalls with the appropriate degree of urgency. The nominated person should normally be independent of the sales and marketing organisation.

If the nominated person is not the qualified person, he shall be made aware of any decisions to recall potentially defective finished product.

11.3.2 Procedure review

The recall procedures shall be regularly reviewed and updated when necessary, to ensure that the procedure is capable of being initiated promptly and at any time.

The documented recall system shall be routinely reviewed to evaluate its effectiveness and the system revised to reflect any shortcomings.

11.3.3 Notification

The appropriate national authorities of all countries where the potentially defective medicinal gas has been distributed shall be informed promptly if a recall is considered to be necessary.

11.3.4 Distribution records

The distribution records of the potentially defective batches of medicinal gases shall be readily available to the person nominated to control the recall. The records shall contain sufficient information concerning the customers who have received supplies of potentially defective gas including their addresses, telephone and/or fax numbers inside and outside working hours and amounts of gas delivered.

11.3.5 Identification

All recalled medicinal gases should be appropriately labelled and quarantined separately until further actions are agreed. Due to the nature of the product, it is probable that any recalled batch of bulk cryogenic medicinal gases will not be reused for medicinal purposes. An action would be to carry out

specific analytical checks on the product to determine whether there was any defect with the gas and whether the complaint was justified.

11.3.6 Reporting

The recall process shall be reviewed regularly and the interim results recorded and cross reference to the batch file. A final report shall be issued, which shall include a reconciliation between the delivered and recovered quantities of cylinders or bulk medicinal gas from the suspect batch.

12 Self-inspection (EC GMP Chapter 9)

12.1 Principle

An essential element of Good Manufacturing Practice is the routine audit of the quality assurance system, to ensure that the controls are in place to ensure that the medicinal gases supplied for patient use are of the defined quality. Self-inspection procedures shall be conducted to monitor the implementation of the approved procedures. It shall also identify any shortfall in the quality assurance system and propose necessary corrective measures to ensure compliance with the principles of Good Manufacturing Practice.

12.1.1 Self inspection programme

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

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

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

12.2 Self-inspection audits

The self-inspection audits shall be conducted by person(s), independent of the activity being audited, not connected with the day to day operation of the process being audited. It may be appropriate to use an external auditor to carry out independent audits of the system.

12.3 Self-inspection reports

The results of all self-inspection audits shall be logged. The self-inspection reports shall follow an approved format containing all the observations made during the inspections, the results of any quality control checks and, where applicable, the proposals for the agreed corrective measures. A management review shall be conducted to ensure that all identified non-conformances and the associated corrective actions have been taken and the appropriate results recorded.

13 References

[1] Directive 2001/83/EC of the European Parliament and of the council of 6 November 2001 on the community code relating to medicinal products for human use

[2] Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

[3] Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

[4] ICH Q10 Pharmaceutical Quality System International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use