MEDICAL GASES

GOOD MANUFACTURING PRACTICE GUIDE

PART II FOR MEDICAL GASES:

BASIC REQUIREMENTS FOR ACTIVE SUBSTANCES USED AS STARTING MATERIALS

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Prepared by WG-7 Medical Gases

Disclaimer

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Table of Contents

Tables

Amendments to 99/17

Section	Change
Doc	Re-affirmation without any changes

1 Introduction

According to Article 46 (f) of Directive 2001/83/EC as amended by Directive 2004/27/EC of the European Parliament on the Community code relating to medicinal products for human use and Article 50 (f) of Directive 2001/82/EC; as amended by Directive 2004/28/EC on the Community code relating to veterinary medicinal products [1 2] [1], the manufacturing authorisation holders shall use only active substances that have been manufactured in accordance with Good Manufacturing Practice (GMP) for starting materials.

2 Scope and purpose

2.1 Scope

These guidelines cover the requirements regarding the manufacturing of the active pharmaceutical ingredients, (API) in Good Manufacturing Practice condition in the field of medicinal gases manufacturing.

In this publication, manufacturing includes all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of active substances and the related controls.

2.2 Purpose

This publication is intended to provide guidance regarding Good Manufacturing Practice for the manufacture of active substances used in the manufacturing of medicinal gases and mixture.

3 Definitions

3.1 Publications terminology

3.1.1 Shall

Indicates that the procedure is mandatory. It is used wherever the criterion for conformance to specific recommendations allows no deviation.

3.1.2 Should

Indicates that a procedure is recommended.

3.1.3 May and Need not

Indicate that the procedure is optional.

3.1.4 Will

Is used only to indicate the future, not a degree of requirement.

3.1.5 Can

Indicates a possibility or ability.

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

3.2 Technical definitions

3.2.1 Active substance starting material

Raw material, intermediate, or an active substance that is used in the production of an active substance.

4 General

4.1 Identification of the active substance starting material

In the case of medicinal gases manufacturing the active substance starting material can be a product manufactured in large scale in industrial production or an intermediate mixture of gases called intermix.

An active substance starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.

Active substance starting materials normally have defined specifications.

The manufacturer should designate and document the rationale for the point at which production of the active substance begins. For synthetic processes, this is known as the point at which active substance starting materials are entered into the process.

Table 1 gives guidance on the identification of the active substance starting material for the medicinal gases and mixture that are normally produced as medicinal product.

When the API starting material enters into the chemical manufacturing process then appropriate GMP as defined in this publication should be applied to these manufacturing steps.

In the remainder of this publication the term active pharmaceutical ingredient is used repeatedly and should be considered interchangeable with the term active substance.

Table 1 Identification of the active substances starting materials (not exclusive list)

GMP Part II			GMP Part I
API starting material	**Chemical manufacturing process**	**API/drug substance**	**Manufacturing finished medicinal product**
Industrial ammonium nitrate	Thermal decomposition and purification	Bulk nitrous oxide	Nitrous oxide in cylinder/tank
Purified ambient air	Cryogenic distillation	Bulk oxygen	Oxygen in cylinder /tank
Purified ambient air	Cryogenic distillation	Bulk nitrogen	Nitrogen excipient in cylinder /tank
Oxygen	Mixing	Synthetic medical air –premixed buffer	Synthetic medical air in cylinder
Crude / tall oil from steam reforming or natural source or fermentation	Purification	Carbon dioxide	Carbon dioxide in cylinder , mixture
Pure carbon monoxide	Mixing	Intermix	Lung function mixture
Crude / tall oil from steam reforming or catalytic partial oxidation	Purification	Carbon monoxide	Lung function mixture
Sodium nitrite / sulfuric acid	Chemical reaction and purification	Nitric oxide	Nitric oxide mixture
Pure nitric oxide	Mixture	Intermix	Nitric oxide mixture
Industrial acetylene	Purification	Pure acetylene	Lung function mixture
Pure acetylene	Mixture	Intermix	Lung function mixture
Liquid helium	Gasification	Compressed Helium	Helium mixture
Compressed helium	Mixture	Intermix	Lung function mixture
Industrial methane	Purification	Pure methane	Lung function mixture
Pure methane	Mixture	Intermix	Lung function mixture

5 Guidelines

Table 2 gives indicates and provides additional explanation about the application of the specific point of GMP Part II text to the medical gases active substance manufacturing.

In the table only the specific points that need specification are reported.

The points that are not included should be applied as they are.

Table 2 Indication and explanation of application of GMP Part II

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
2	**Quality Management**	
2.1	**Principles**	
2.13	There should be a quality unit(s) that is independent of production and that fulfils both quality assurance *(QA)* and quality control *(QC)* responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organisation. (Annex 6 GMP) 2. The production of active substance gases through a continuous process (e.g. air separation) should be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation.	In gases manufacturing the production operator may fulfil the role of QC having received instruction from central independent quality unit (QU). Nevertheless, the operator could not cover the role of QC and production for the same batch. Within the medicinal gases environment, the QU responsibilities can be assigned to a suitable qualified and experienced person responsible for both QA and QC requirements. Where the nominated person is not resident on site the responsibilities may be delegated to a suitable qualified and nominated deputy. Where the plants used for the manufacturing of medicinal gases API is operating remotely, using automatic procedures, the Quality Unit may utilise the output of validated automatic process.
2.14	The persons authorised to release intermediates and APIs should be specified.	The release of the active pharmaceutical ingredients (APIs) is the responsibility of the quality unit and the responsible persons authorised for this release should be nominated.
2.2	**Quality Risk Management**	
2.20	Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the active substance. It can be applied both proactively and retrospectively.	Quality risk management may be part of the manufacturing process risk management.
2.6	**Product Quality Review**	
2.60	Regular quality reviews of APIs should be conducted with the objective of verifying the	If the API is the same as the finished medicinal product, for example liquid oxygen or bulk

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
	consistency of the process. Such reviews should normally be conducted and documented annually and should include at least: - A review of critical in-process control and critical API test results; - A review of all batches that failed to meet established specification(s); - A review of all critical deviations or non-conformances and related investigations - A review of any changes carried out to the processes or analytical methods; - A review of results of the stability monitoring program; - A review of all quality-related returns, complaints and recalls; and - A review of adequacy of corrective actions.	nitrous oxide manufacturing, the API product quality review could be done in the product quality review for the finished medicinal product.
3.2	**Personnel Hygiene**	
3.22	Personnel should avoid direct contact with intermediates or APIs.	Manufacturing of API gases is performed in closed pipework
3.24	Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.	Manufacturing of API gases is performed in closed pipework
4	**Buildings and Facilities**	
4.1	**Design and Construction**	
4.10	Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture.	Manufacture of intermediates and APIs for medicinal gases is carried out in closed equipment. Consequently, environmental and microbiological contamination of the product is negligible.

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
	Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.	
4.12	Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.	As the API cylinders and other containers provide adequate protection of the product, they can be stored outdoors.
4.14	There should be defined areas or other control systems for the following activities: - Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection; - Quarantine before release or rejection of intermediates and APIs; - Sampling of intermediates and APIs; - Holding rejected materials before further disposition (e.g., return, reprocessing or destruction) - Storage of released materials; - Production operations; - Packaging and labelling operations; and - Laboratory operations. -	There should be defined areas or other control systems for the different activities that should be carried out in separate marked areas for different gases. The method used to achieve these various levels of segregation will depend on the nature, extent and complexity of the overall operation. Marked-out floor areas, partitions, barriers, signs, labels or other appropriate means could be used.
4.2	**Utilities**	
4. 20	All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.	For certain API gases water is used as a utility in contact with the starting material and with the API and appropriately specified.
4.21	Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimise risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and	Manufacturing of API gases is performed in closed and pressurised systems, including pipework and related equipment.

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
	temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.	
4.22	If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.	Manufacturing of API gases is performed in closed pipework
4.3	**Water**	
4.32	If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.	For medicinal gases API drinking water is sufficient.
4.33	Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.	Typical examples of water used in intermediates and API manufacturing process for gases include: • Ammonia nitrate solutions in nitrous oxide manufacturing process; • washing towers in processes of purifying the nitrous oxide or carbon dioxide gas streams in their corresponding manufacturing processes; • Cooling by direct contact of air stream after compression in air separation units.
4.34	Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.	NA
4.4	**Containment**	
4.40	Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly	NA

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
	sensitizing materials, such as penicillin or cephalosporin.	
4.41	Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.	NA
4.42	Appropriate measures should be established and implemented to prevent cross contamination from personnel, materials, etc. moving from one dedicated area to another.	Manufacturing of API gases is performed in closed pipework
4.43	Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.	The same measures have to be taken with toxic pharmaceutical products used in the manufacturing of the intermediates or API such as: • Nitric oxide or carbon monoxide for manufacturing of intermediates or premixes; and • Ammonia for manufacturing process of nitrous oxide or carbon dioxide
5	**Process Equipment**	
5.1	**Design and Construction**	
5.14	Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.	Any substances such as lubricants, heating fluids or coolants, used in filtering operations and lubricated compressor should not come into contact with intermediates or APIs. Where this cannot be avoided it should be evaluated to ensure that it has no impact on the final product quality.
5.15	Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.	Where it is necessary to use an open system, precautions shall be taken to minimize the risk of atmospheric contamination once the equipment is open. The air intake of air separation units shall be provided with an air inlet filter The performance of the filter shall be monitored in order to ensure that it is working with is

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
		designed parameters and shows no evidences of blockage or rupture
5.2	**Equipment Maintenance and Cleaning**	
5.21	Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include: - Assignment of responsibility for cleaning of equipment; - Cleaning schedules, including, where appropriate, sanitising schedules; - A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment; - When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning; - Instructions for the removal or obliteration of previous batch identification; - Instructions for the protection of clean equipment from contamination prior to use; - Inspection of equipment for cleanliness immediately before use, if practical; and - Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.	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 API gas, and be carried out according to detailed written procedures. Repair and maintenance operations, including any outsourced activity, shall not adversely affect the quality of API gases produced or filled into cylinders. The design of manufacturing and cylinder filling equipment should be designed to permit easy and effective purging and/or evacuation to remove any internal contamination. Where the pipework or equipment requires specific internal cleaning, the system shall be designed so that any residual cleaning material can be effectively 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.
5.23	Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).	Where equipment is assigned to continuous production there is no routine requirement for cleaning operations.

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
5.24	Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.	In the manufacture of gases used as API the equipment is generally dedicate to a single product service and as such does not require cleaning between productions of different batches.
5.26	Equipment should be identified as to its contents and its cleanliness status by appropriate means.	Equipment should be identified as to its contents and its cleanliness status by appropriate means, for example, equipment cleaned for oxygen use, for use with oxidants, passivated cylinder and inert pressurized storage tank.
5.3	**Calibration**	
5.30	Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.	Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs shall be calibrated according to procedures and an established schedule.
5.31	Equipment calibrations should be performed using standards traceable to certified standards, if existing.	The requirements on calibration for equipment used in intermediates and API manufacturing are provided in the quality management system and are related to maintenance, traceability standards, records keeping, available use only on accepted status and management of deviations.
5.4	**Computerised Systems**	
5.40	GMP related computerised systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application.	The scope of this validation shall cover the control of the critical control points of the API process that are managed by the computerised systems.
6.2	**Equipment Cleaning and Use Record**	
6.20	Records of major equipment use, cleaning, sanitisation and/or sterilisation and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.	The process is carried out in closed equipment, only external cleaning is performed Sanitization and/or sterilization do not apply to medical gas API manufacturing
6.21	If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use	Equipment used in API gas manufacturing are dedicated to a single gas

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
	can be part of the batch record or maintained separately.	
6.3	**Records of Raw Materials, Intermediates, API Labelling and Packaging Materials**	
6.30	Records should be maintained including: - The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt; - The results of any test or examination performed and the conclusions derived from this; - Records tracing the use of materials; - Documentation of the examination and review of API labelling and packaging materials for conformity with established specifications; and - The final decision regarding rejected raw materials, intermediates or API labelling and packaging materials.	For raw materials and intermediates used in API gas manufacturing the certificate of analysis of the incoming material should be checked and recorded. Packaging material for raw material, intermediates and API are transport tanker, storage tank, cylinders and bundles
6.4	**Master Production Instructions (Master Production and Control Records)**	
6.40	To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).	For medicinal gases API manufacturing the master production instruction is included in the site master file and in the related site operating procedures.
6.41	Master production instructions should include: - The name of the intermediate or API being manufactured and an identifying document reference code, if applicable; - A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;	For medicinal gases API manufacturing the master production instruction is included in the site master file and in the related site operating procedures.

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry

	- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified;
	- The production location and major production equipment to be used;
	- Detailed production instructions, including the:
	  - sequences to be followed,
	  - ranges of process parameters to be used,
	  - sampling instructions and in-process controls with their acceptance criteria, where appropriate,
	  - time limits for completion of individual processing steps and/or the total process, where appropriate; and
	  - expected yield ranges at appropriate phases of processing or time;
	- Where appropriate, special notations and precautions to be followed, or cross references to these; and
	- The instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.	

6.5	**Batch Production Records (Batch Production and Control Records)**	
6.50	Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a	For liquid oxygen the manufacturing process is continuous, therefore the API batch record is made on a time point frequency of the production in the API container (main production tank) for release, between batch releases as part of the manufacturing data. Nevertheless, the liquid oxygen manufactured filled into tankers can also be classified as an extension of the original API, especially when transported into filling sites.

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
	separate part of the master document, that document should include a reference to the current master production instruction being used. (GMP Annex 6) 2. The production of active substance gases through a continuous process (e.g. air separation) should be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation	In manufacturing processes, with batches made in specific closed API containers such as nitrous oxide tanks, carbon dioxide tanks, and nitric oxide cylinders, the release is made with the closing of the batch container and with all the in-process controls and manufacturing data considered necessary for the process.
7	**Materials Management**	
7.1	**General Controls**	
7.14	Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.	In the medicinal gas API manufacturing a typical critical raw material to be considered is ammonium nitrate,
7.2	**Receipt and Quarantine**	
7.20	Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use. (Annex 6 GMP) (a) the requirements regarding starting materials for active substances (Part II Chapter 7) do not apply to the production of active substance gases by air separation (however, the manufacturer should ensure that the quality of ambient air is suitable for the established process and any changes in the quality of ambient air do not affect the quality of the active substance gas);	
7.3	**Sampling and Testing of Incoming Production Materials**	
7.32	Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of	For medicinal gas API manufacturing it applies to pure nitric oxide and carbon monoxide.

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
	Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.	
8	**Production and In-Process Controls**	
8.1	**Production Operations**	
8.10	Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.	This applies to intermixes preparation
8.17	Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.	There are no reprocessed or reworked in medical gases API manufacturing
8.2	**Time Limits**	
8.21	Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.	Intermediates are stored in tanks or cylinders/bundles
8.3	**In-Process Sampling and Controls**	
8.34	Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.	Sampling in API gas manufacturing could include daily controls, levels on storage tanks and controls on samples to analyse. (Daily controls can start from in the gas phase.
9	**Packaging and Identification Labelling of APIs and Intermediates**	
9.1	**General**	
	GMP Annex 6. 3. In addition: (a) transfers and deliveries of active substance gases in bulk should comply with the same requirements as those mentioned below for the medicinal gases (sections 19 to 21 of this Annex); (b) filling of active substance gases into cylinders or into mobile cryogenic vessels should comply with the same requirements as those mentioned below for the medicinal	

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
	gases (sections 22 to 37 of this Annex) as well as Part II Chapter 9.	
9.10	There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labelling materials.	As for finish medicinal gases products, described in GMPs Part I, there should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labelling materials for use in intermediates or API.
9.2	**Packaging Materials**	
9.22	If containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.	This is typical in cylinders of intermediates or API such as Intermix cylinders. All excess labels bearing batch numbers or other batch-related printing should be destroyed, same as for obsolete and out-dated labels.
9.4	**Packaging and Labelling Operations**	
9.42	Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or API.	If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, for example as starting material for a manufacturing process of a medicinal gas product, such as pure nitric oxide cylinders, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be attached. For intermediates or APIs with an expiry date, the expiry date should be indicated on a label and certificate of analysis (COA) or certificate of conformity (COC).
10	**Storage and Distribution**	
10.1	**Warehousing Procedures**	
10.11	Unless there is an alternative system to prevent the unintentional or unauthorised use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.	The warehousing premises should be suitable for the material stored, and should have separate areas for different stages, for example full, empty, under investigation and recall materials.
11.5	**Stability Monitoring of APIs**	
11.50	A documented, on-going testing program should be designed to monitor the stability	A documented testing program should be designed to monitor the stability characteristics

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
	characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates. Annex 6 (The on-going testing program is not necessary if the initial stability studies were replaced by bibliographic data or technical arguments, for example for LOX, a stability study is not necessary if substituted by maximum time in liquid state before vaporization).	of APIs were required, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.
11.6	**Expiry and Retest Dating**	
11.60	When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).	When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and if an expiry or retest date is assigned, supporting stability information should be available if required by the marketing authorisation.
11.7	**Reserve/Retention Samples**	
11.70	The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.	Reserve/retention samples are not required.
11.71	Appropriately identified reserve samples of each API batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch is completely distributed by the manufacturer. (GMP Annex 6) (b) the requirements regarding on-going stability studies (Part II chapter 11.5), which are used to confirm storage conditions and expiry/retest dates (Part II chapter 11.6), do not apply in case initial stability studies have been replaced by bibliographic data (see Note for Guidance CPMP/QWP/1719/00); and (c) the requirements regarding reserve/retention samples (Part II chapter 11.7) do not apply to active substance gases, unless otherwise specified.	
12	**Validation**	

GMP number	GMP Part II Text Annex 6 Medicinal gases text	Additional explanation and/or interpretation for the manufacturing of API gases coming from Annex 6 and best practices in the industry
12.2	**Validation Documentation**	
12.7	**Cleaning Validation**	
12.71	Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.	The gaseous API in the medicinal gases production is cleaned in the piping through a validated process of a number of purging and/or evacuation cycles, before a new batch of APIs is made. .
14	**Rejection and Re-Use of Materials**	
14.2	**Reprocessing**	The API used for gas manufacturing cannot be reprocessed, therefore shall be rejected for medicinal use.

6 References

Unless otherwise specified, the latest edition shall apply.

[1] Directive 2001/83/EC as amended by directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC *on the Community code relating to medicinal products for human use*. www.ec.europa.eu

[2] Directive 2001/82/EC; as amended by Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 *on the Community code relating to veterinary medicinal on the Community code relating to veterinary medicinal products* www.ec.europa.eu