MEDICAL GASES

COMPARISON OF EUROPEAN, US & JAPANESE PHARMACOPOEIA MONOGRAPHS FOR MEDICINAL GASES

Doc 152/18

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Prepared by WG-7 Medical and Breathing Gases

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Note: Technical changes from the previous edition are underlined

1 Introduction

There are three prime regional Pharmacopoeia organisations that are responsible for the preparation and publication of Pharmacopoeia monographs, covering the commonly used substances involved in the manufacture and supply of medicinal products.

The three organisations are:

- European Directorate for the Quality of Medicines (EDQM), who are responsible for the European Pharmacopeia (Ph. Eur.) monographs
- United States Pharmacopeia Convention, who are responsible for the US Pharmacopoeia (USP)
- Ministry of Health and Welfare, who are responsible for the Japanese Pharmacopoeia (JP)

The three Pharmacopoeias have monographs for a number of medical / medicinal gases. These gases can be used either as active ingredients in medicinal products or excipients, used in the manufacture of medical gas mixtures, administered to patients. Alternatively, they can be used as pharmaceutical gases, used in the manufacture, storage or distribution of all medicinal products.

The purpose of these monographs is to specify for each gas:

- Minimum assay / purity for the product that is suitable for medicinal use;
- Maximum level of defined impurities, that could have an adverse effect on the patient; and
- Appropriate test methods for determining quality of the product.

This publication provides a comparison between the specifications and the test methods defined in each of the regional pharmacopoeia compendiums.

2 Scope and purpose

2.1 Scope

This publication covers the pharmacopoeia monographs for medicinal and pharmaceutical gases published by the:

- European Pharmacopoeia;
- United States Pharmacopeia; and
- Japanese Pharmacopoeia.

It includes the monographs for gases used in the manufacture and supply of medicinal products including:

- Medicinal gases, that are used as active ingredients in medical gases and gas mixtures supplied for patient use;
- Excipient gases, that are added to gas mixtures but have no pharmacological effects; and
- Pharmaceutical gases, that are specified in the manufacture, storage and distribution of medicinal products.

The comparison tables provide a comparison between the European and the United States Pharmacopoeia monographs for all of the specified gases.

A separate table is included to detail the monographs published by the Japanese Pharmacopoeia, where the monographs do not specify acceptance limits and only provide test criteria for compliance.

2.2 Purpose

To provide a cross reference between the three sets of published monographs to enable a comparison of the requirements for each method. This is intended to demonstrate compliance between monographs but should not be used as a detailed method of carrying out the relevant tests.

Where the testing to a specific monograph is required, the user should refer to the original document (and all supporting documents within the relevant pharmacopoeia) to ensure that the tests are carried out correctly.

3 Specifications and test methods

The most commonly used medicinal gases have been included in the Pharmacopoeia for many years but recently a number of new medical gases have been added.

The following table gives a reference for the different gases that have been covered by published monographs in the three Pharmacopoeias:

Gases	Monograph reference		
	European Pharmacopoeia	**US Pharmacopeia**	**Japanese Pharmacopoeia**
Medical oxygen	0417	No reference no.	No reference no.
Oxygen 93%	2455	No reference no.	NS
Nitrous oxide	0416	No reference no.	No reference no.
Nitrogen	1247	No reference no.+	No reference no.
Nitrogen 97%	NS	No reference no.	NS
Low oxygen nitrogen	1685	No reference no.	NS
Carbon dioxide	0375	No reference no.	No reference no.
Medicinal air	1238	No reference no.	NS
Synthetic medicinal air	1684	See medicinal air	NS
Helium	2155	NS	NS
Nitric oxide	1550	NS	NS
Argon	2407	NS	NS
Carbon monoxide	2408	NS	NS
Carbon monoxide intermix (5 per cent) in nitrogen	2904	NS	NS
Methane	2413	NS	NS
Methane intermix (2 per cent) in nitrogen	2905	NS	NS
Acetylene	IP	NS	NS
Acetylene intermix (1 per cent) in nitrogen	2903	NS	NS

+ Nitrogen is covered in the National Formulary

NS: Not specified

IP: In preparation

Each monograph defines the specification of the medicinal gas, including the:

- Assay of the product;
- Maximum allowable impurity levels for those contaminants specified in the product;
- Approved analytical method for identifying the gas;

- Approved analytical method for determining the assay, and
- Approved analytical test method for determining each contaminant specified within the monograph.

The validated analytical methods described in the monographs are the official test methods upon which the specifications in the relevant Pharmacopoeia are based.

3.1 European Pharmacopoeia test requirements

For the European Pharmacopoeia, the test methods are verified against the protocols set out in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, (ICH) guidelines for accuracy and precision, linearity and range and specificity. The results also need to conform to the requirements of repeatability and peak symmetry.

In addition to the specific medicinal gas monographs there are several general notices that apply to all monographs.

The following general test methods are particularly applicable to the analysis of medical gases:

Test reference	Test method
2.1.6	Gas detector tubes
2.2.24	Absorption spectrophotometry, infrared
2.2.28	Gas chromatography
2.2.46	Chromatographic separation techniques
2.5.24	Carbon dioxide in gases
2.5.25	Carbon monoxide in gases
2.5.26	Nitrogen monoxide and nitrogen dioxide in gases
2.5.27	Oxygen in gases
2.5.28	Water in gases
2.5.35	Nitrous oxide in gases

Alternative methods of analysis can be used for testing medical gases, after agreement with the competent authority, provided that the test methods have been validated in line with the ICH protocols to demonstrate that they are equivalent to the specified methods.

The European Pharmacopoeia monographs test methods specified for medical gases are divided into two main sections, production and tests.

The production methods are intended to be the methods used by the manufacturers. These methods are the basis for the release of the product at the manufacturer's site for patient use. The methods specified in the production section of the monograph normally utilise the latest analytical instruments, that should be available to the manufacturers of the gases.

The test methods are intended to be the methods used by the end user to assure themselves that the medical gases are of the appropriate quality. For example, these could be used for routine testing by the Pharmacist at the hospital of the pipeline gases at the terminal outlets in the hospital. The test methods generally utilise detector tubes for the test method as it is unlikely that the end users would have all of the appropriate analytical instruments available to them for testing.

Where the hospital is the manufacturer, for example where they are producing medicinal air on site using an air compressor, the production test methods should be applied.

The United States and Japanese Pharmacopoeia monographs only specify one method for the analysis of the medical gas.

The Japanese Pharmacopoeia monographs only detail the test methods and do not give the values of the specification limits for the impurities in percentage terms or parts per million. The approved test methods include either gas chromatography, detector tubes or wet chemistry as the approved methods.

In all cases the test methods specified in the monographs should have been validated. For the European Pharmacopoeia, this work is normally undertaken by one of the national representative on the relevant Pharmacopoeia committee.

4 Currency of information

The versions of the relevant Pharmacopoeias used to provide the information for the comparison tables are:

- European Pharmacopoeia: 9.4 (2018)
- United States Pharmacopeia: USP40, NF35 (2017)
- Japanese Pharmacopoeia: 17 (2016)

As and when there are relevant changes to any of these monographs this publication shall be updated. However, where it is important that the latest information is available, the original Pharmacopoeia document should be referenced to ensure that there have been no revisions to the individual monograph.

5 European Pharmacopoeia compared to United States Pharmacopoeia

The following tables provide a comparison between the European and US Pharmacopoeia monographs for each of the specified medicinal or pharmaceutical gas.

5.1 Medical oxygen

Oxygen			
Monograph		**Ph. Eur.**	**USP**
Name		Oxygen	Oxygen
Reference		01/2010:0417	Not specified
Chemical formula		O_2	O_2
Definition		Oxygen contains not less than 99.5% V/V of oxygen. It is produced by a purification process followed by a cryodistillation of the ambient air.	Oxygen contains not less than 99.0% V/V of oxygen Note: Oxygen produced by the air-liquefaction is exempt from the requirements of carbon monoxide and carbon dioxide testing.
Identification		Complies with the assay	Complies with the assay
Production			
Assay	Specification	≥ 99.5% V/V oxygen	≥ 99.0 % V/V oxygen
	Analytical method	Paramagnetic analyser	Paramagnetic analyser
Impurities			
CO	Limit	≤ 5 ppm V/V	≤ 0.001% V/V
	Analytical method	Infrared analyser	Detector tube
CO_2	Limit	≤ 300 ppm V/V	≤ 0.03% V/V
	Analytical method	Infrared analyser	Detector tube
H_2O	Limit	≤ 67 ppm V/V	Not specified
	Analytical method	Electrolytic hygrometer	
Tests			
CO	Limit	≤ 5 ppm V/V	No tests section specified
	Analytical method	Detector tube	
CO_2	Limit	≤ 300 ppm V/V	
	Analytical method	Detector tube	
H_2O	Limit	≤ 67 ppm V/V	
	Analytical method	Detector tube	

5.2 93% Oxygen

Oxygen 93			
Monograph		**Ph. Eur.**	**USP**
Name		Oxygen (93 per cent)	Oxygen 93 Percent
Reference		04/2011:2455	Not Specified
Chemical formula		O_2	O_2
Definition		Oxygen 93% contains between 90.0%V/V and 96% V/V of oxygen. Remainder mainly consists of argon and nitrogen. Monograph applies to oxygen 93% produced in single-stage concentrators by absorption purification of ambient air using zeolites. It does not apply to gas produced using individual concentrators for domiciliary use.	Oxygen 93 is oxygen produced from air by molecular sieve process. Contains not less than 90.0 % V/V and not more than 96 % oxygen V/V, the remainder consists of mostly argon and nitrogen
Identification		Complies with the assay	Complies with the assay
Production			
Assay	Specification	90.0% ≤ O_2 ≤ 96.0% V/V oxygen	90.0% ≤ O_2 ≤ 96.0% V/V oxygen
	Analytical method	Paramagnetic analyser	Paramagnetic analyser
Impurities			
CO	Limit	≤ 5 ppm V/V	≤ 0.001 % V/V
	Analytical method	Infrared analyser	Detector tube
CO_2	Limit	≤ 300 ppm V/V	≤ 0.03 % V/V
	Analytical method	Infrared analyser	Detector tube
H_2O	Limit	≤ 67 ppm V/V	Not specified
	Analytical method	Electrolytic hygrometer	
Odour	Limit		No odour
	Analytical method		Organoleptic
NO/ NO_2	Limit	≤ 2 ppm V/V in total	Not specified
	Analytical method	Chemiluminescence analyser	
SO_2	Limit	≤ 1 ppm V/V	
	Analytical method	UV Fluorescence analyser	
Oil	Limit	≤ 0.1 mg/m^3	
	Analytical method	Detector tube	
Tests			
CO	Limit	≤ 5 ppm V/V	No specific tests section
	Analytical method	Detector tube	
CO_2	Limit	≤ 300 ppm V/V	
	Analytical method	Detector tube	
H_2O	Limit	≤ 67 ppm V/V	
	Analytical method	Detector tube	
NO/ NO_2	Limit	≤ 2 ppm V/V	
	Analytical method	Detector tube	
SO_2	Limit	≤ 1 ppm V/V	
	Analytical method	Detector tube	
Oil	Limit	≤ 0.1 mg/m3	
	Analytical Method	Detector tube	

5.3 Nitrous oxide

Nitrous oxide			
Monograph		**Ph. Eur.**	**USP**
Name		Nitrous oxide	Nitrous oxide
Reference		01/2008:0416	Not specified
Chemical Formula		N_2O	N_2O
Definition		Contains not less than 98.0% V/V of nitrous oxide in the gaseous phase, when sampled at 15°C. Nitrous oxide is produced from ammonium nitrate by thermic decomposition.	Nitrous Oxide contains not less than 99.0% V/V of nitrous oxide
Identification		Complies with the assay. ***or*** - Place a glowing splinter of wood in the substance to be examined. The splinter bursts into flame. ***or*** - Introduce the substance to be examined into alkaline pyrogallol solution R. A brown colour does not develop.	Comparison of pressure between nitrous oxide container and certified standard. Distinction from carbon dioxide detector tube. Distinction from oxygen (alkaline pyrogallol solution)
Production			
Assay	Assay	≥ 98.0% V/V nitrous oxide Measured in gas phase at 15°C	≤ 1.0% air indicating ≥ 99.0% V/V of nitrous oxide
	Analytical method	Infrared analyser	Gas chromatography
Impurities			
CO	Limit	≤ 5 ppm V/V	≤ 0.001% V/V
	Analytical method	Gas chromatography	Detector tube
CO_2	Limit	≤ 300 ppm V/V	≤ 0.03% V/V
	Analytical method	Gas chromatography	Detector tube
NO/ NO_2	Limit	≤ 2 ppm V/V in total in the gaseous and liquid phases	Nitric oxide ≤ 1ppm, nitrogen dioxide≤ 1ppm
	Analytical method	Chemiluminescence analyser	Detector tube
H_2O	Limit	≤ 67 ppm V/V	≤ 150 mg/m³
	Analytical method	Electrolytic hygrometer	Detector tube
NH_3	Limit	Not specified	≤ 0.0025 % V/V
	Analytical method		Detector tube
Halo-gens	Limit	Not specified	≤ 1ppm
	Analytical method		Detector tube
Tests			
CO	Limit	≤ 5 ppm V/V	No specific tests section
	Analytical method	Detector tube	
CO_2	Limit	≤ 300 ppm V/V	
	Analytical method	Detector tube	
NO/ NO_2	Limit	≤ 2 ppm V/V	
	Analytical method	Detector tube	
H_2O	Limit	≤ 67 ppm V/V	
	Analytical method	Detector tube	

5.4 Nitrogen

Nitrogen			
Monograph		**Ph. Eur.**	**USP**
Name		Nitrogen	Nitrogen
Reference		01/2008:1247	7727-37-9
Chemical formula		N_2	N_2
Definition		Nitrogen contains not less than 99.5% V/V of nitrogen.	Nitrogen contains not less than 99.0%, by volume of nitrogen
Identification		Retention time of peak with gas chromatography ***or*** - Place a glowing splinter of wood in the substance to be examined. The splinter is extinguished. ***or*** **-** Test with magnesium turnings	Extinguishing of burning wood splinter in a nitrogen test tube.
Production			
Assay	Assay	≥ 99.5% V/V nitrogen	≤ 1.0% oxygen indicates ≥ 99.0% V/V of nitrogen
	Analytical method	Gas chromatography	Gas chromatography
Impurities			
CO	Limit	≤ 5 ppm V/V	≤ 0.001 % V/V
	Analytical method	Infrared analyser	Detector tube
CO_2	Limit	≤ 300 ppm V/V	Not specified
	Analytical method	Infrared analyser	
O_2	Limit	≤ 50 ppm V/V	≤ 1.0 %
	Analytical method	Oxygen analyser with electrochemical cell	Determined in assay
H_2O	Limit	≤ 67 ppm V/V	Not specified
	Analytical method	Electrolytic hygrometer	
Odour	Limit	Not specified	No odour
	Analytical method		Organoleptic
Tests			
CO	Limit	≤ 5 ppm V/V	No specific tests section
	Analytical method	Detector tube	
CO_2	Limit	≤ 300 ppm V/V	
	Analytical method	Detector tube	
H_2O	Limit	≤ 67 ppm V/V	
	Analytical method	Detector tube	

5.5 97% Nitrogen

Nitrogen 97%			
Monograph		**Ph. Eur.** No equivalent European Pharmacopoeia monograph	**USP**
Name			Nitrogen 97 Percent
Reference			Not Specified
Chemical formula			N_2
Definition			Nitrogen 97 % is nitrogen produced from air by physical separation. Contains not less than 97.0% nitrogen V/V
Identification			Extinguishing of burning wood splinter in a nitrogen test tube.
Production			
Assay	Assay		≤ 3.0% oxygen indicates ≥ 97.0% V/V of nitrogen
	Analytical method		Gas chromatography
Impurities			
CO	Limit		≤ 0.001 % V/V
	Analytical method		Detector tube
CO_2	Limit		≤ 0.03 % V/V
	Analytical method		Detector tube
SO_2	Limit		≤ 5 ppm V/V
	Analytical method		Detector tube
NO/ NO_2	Limit		≤ 2.5 ppm V/V
	Analytical method		Detector tube
O_2	Limit		≤ 3.0 % V/V
	Analytical method		Gas chromatography (determined in the assay)
Odour	Limit		No odour
	Analytical method		Organoleptic
Tests			
	Limit		No specific tests section
	Analytical method		

5.6 Low oxygen nitrogen

Low oxygen nitrogen			
Monograph		Ph. Eur.	USP No equivalent US Pharmacopoeia monograph
Name		Nitrogen low oxygen	
Reference		01/2008:1685	
Chemical formula		N_2	
Definition		This monograph applies to nitrogen which is used for inerting finished medicinal products which are particularly sensitive to degradation by oxygen. Does not necessarily apply to nitrogen used in earlier production steps of pharmaceutical manufacturing.	
Identification		Examine the chromatograms obtained in the test for impurities. or - Flame of burning wood splinter in a nitrogen test tube/ test with magnesium turnings.	
Production			
Assay	Assay	≥ 99.5% V/V nitrogen	
	Analytical method	Gas chromatography	
Impurities			
O_2	Limit	≤ 5 ppm V/V	
	Analytical method	Oxygen analyser with electrochemical cell	
Total impurities	Limit	≤ 0.5% V/V	
	Analytical method	Gas chromatography	
Tests			
	Limit	No test section specified	

5.7 Carbon dioxide

Carbon dioxide			
Monograph		**Ph. Eur.**	**USP**
Name		Carbon dioxide	Carbon dioxide
Reference		01/2008:0375	Not specified
Chemical Formula		CO_2	CO_2
Definition		Carbon dioxide contains not less than 99.5% V/V carbon dioxide in gaseous phase.	Carbon dioxide contains not less than 99.0%, by volume of carbon dioxide
Identification		Infrared absorption spectrophotometry *or* - glowing wood splinter extinguished *or* - test with magnesium turnings	Carbon dioxide detector tube
Production			
Assay	Assay	≥ 99.5% V/V carbon dioxide	≥ 99.0% V/V of carbon dioxide
	Analytical method	Infrared analyser	Determined with volumetric gas absorption apparatus
Impurities			
CO	Limit	≤ 5 ppm V/V	≤ 0.001% V/V
	Analytical method	Gas chromatography	Detector tube
NO/ NO_2	Limit	≤ 2 ppm V/V in total (in gas phase)	NO ≤ 2.5 ppm (in gas phase) NO_2 ≤ 2.5 ppm (in liquid phase)
	Analytical method	Chemiluminescence analyser	Detector tube
Total Sulfur	Limit	≤ 1 ppm V/V	Not specified
	Analytical method	UV fluorescence analyser	
H_2O	Limit	≤ 67 ppm V/V	≤ 150 mg/m3
	Analytical method	Electrolytic hygrometer	Detector tube
NH_3	Limit	Not specified	≤ 0.0025 % V/V
	Analytical method		Detector tube
H_2S	Limit	Not specified	≤ 1 ppm
	Analytical method		Detector tube
SO_2	Limit	Not specified	≤ 5 ppm
	Analytical method		Detector tube
Tests			
CO	Limit	≤ 5 ppm V/V	No specific tests section
	Analytical method	Detector tube	
SO_2	Limit	≤ 2 ppm V/V	
	Analytical method	Detector tube	
H_2S	Limit	≤ 1 ppm V/V	
	Analytical method	Detector tube	
NO/ NO_2	Limit	≤ 2 ppm V/V	
	Analytical method	Detector tube	
H_2O	Limit	≤ 67 ppm V/V	
	Analytical method	Detector tube	

5.8 Medicinal air

Medicinal air			
Monograph		**Ph. Eur.**	**USP**
Name		Air, Medicinal	Medical air
Reference		01/2009:1238	Not specified
Chemical formula		N/A	N/A
Definition		Compressed ambient air containing not less than 20.4 %V/V and not more than 21.4 % V/V of oxygen.	Natural or synthetic mixture consisting largely of nitrogen and oxygen, containing not less than 19.5% and not more than 23.5% V/V of oxygen.
Identification		Complies with the assay ***or -*** glowing wood splinter not extinguished ***or -*** tested by passing sample through potassium hydroxide /sodium dithionite solution.	Meets the assay acceptance criteria
Production			
Assay	Assay	20.4%V/V ≤ oxygen ≤ 21.4 % V/V	19.5% V/V ≤ oxygen ≤ 23.5% V/V
	Analytical method	Paramagnetic analyser	Paramagnetic analyser*
Impurities			
CO	Limit	≤ 5 ppm V/V	≤ 0.001% V/V*
	Analytical method	Infrared analyser	Detector tube
CO_2	Limit	≤ 500 ppm V/V	≤ 0.05% V/V*
	Analytical method	Infrared analyser	Detector tube
SO_2	Limit	≤ 1 ppm V/V	≤ 5 ppm V/V*
	Analytical method	UV fluorescence analyser	Detector tube
NO/ NO_2	Limit	≤ 2 ppm V/V in total	≤ 2.5 ppm V/V*
	Analytical method	Chemiluminescence analyser	Detector tube
Oil	Limit	≤ 0.1 mg/m^3	No condensate on mirror
	Analytical method	Detector tube when oil lubricated compressor is used	Pass gas slowly over stainless steel mirror*
H_2O	Limit	≤ 67 ppm V/V	No condensate on mirror
	Analytical method	Electrolytic hygrometer	Pass gas slowly over stainless steel mirror*
Tests			
CO	Limit	≤ 5 ppm V/V	No specific tests section
	Analytical method	Detector tube	
CO_2	Limit	≤ 500 ppm V/V	
	Analytical method	Detector tube	
SO_2	Limit	≤ 1 ppm V/V	
	Analytical Method	Detector Tube	
NO/ NO_2	Limit	≤ 2 ppm V/V	
	Analytical Method	Detector Tube	
Oil	Limit	≤ 0.1 mg/m^3	
	Analytical Method	Detector Tube	
H_2O	Limit	≤ 67 ppm V/V	
	Analytical Method	Detector Tube	

* Not required for synthetic air if so labelled

5.9 Synthetic medicinal air

Synthetic medicinal air			
Monograph		**Ph. Eur.**	**USP** No equivalent US Pharmacopoeia monograph specified, but covered by medical air
Name		Air, Synthetic Medicinal	
Reference		01/2008:1684	
Chemical formula		N/A	
Definition		Gas mixture of nitrogen (Ph. Eur) and oxygen (Ph.Eur) containing between 95.0 % to 105.0 % of the nominal value which is between 21.0 % V/V to 22.5 % V/V of oxygen.	
Identification		Complies with the assay ***or*** **-**glowing wood splinter not extinguished ***or -*** oxygen content tested by passing sample through potassium hydroxide/sodium dithionite solution.	
Production			
Assay	Assay	Containing between 95.0% to 105.0% of the nominal value which is between 21.0 % V/V to 22.5 % V/V of oxygen.	
	Analytical method	Paramagnetic analyser	
Impurities			
H_2O	Limit	≤ 67 ppm V/V	
	Analytical method	Electrolytic hygrometer	
Tests			
H_2O	Limit	≤ 67 ppm V/V	
	Analytical method	Detector tube	

5.10 Helium

Helium			
Monograph		**Ph. Eur.**	**USP**
Name		Helium	Helium
Reference		01/2008:2155	Not specified
Chemical formula		He	He
Definition		Helium contains not less than 99.5 % V/V of helium. Applies to helium obtained by separation from natural gas supplies.	Helium contains not less than 99.0 % V/V of helium
Identification		Complies with the assay	The flame of a burning splinter of wood is extinguished. A small balloon filled with helium shows decided buoyancy
Production			
Assay	Specification	≥ 99.5 % V/V helium,	≥ 99.0 % V/V helium
	Analytical Method	Gas chromatography	Gas chromatography
Impurities			
CH_4	Limit	≤ 50 ppm V/V	Not specified
	Analytical method	Infrared analyser	
O_2	Limit	≤ 50 ppm V/V	Not specified
	Analytical method	Electrochemical cell	
H_2O	Limit	≤ 67 ppm V/V	Not specified
	Analytical method	Electrolytic hygrometer	
CO	Limit	Not specified	≤ 0.001 % V/V
	Analytical method		Detector tube
Air	Limit	Not specified	≤ 1.0 % V/V
	Analytical method		Determined in the assay
Odour	Limit	Not specified	No odour
	Analytical method		Organoleptic
Tests			
	Limit	No tests section specified	No tests section specified
	Analytical method		

5.11 Nitric oxide

Nitric oxide			
Monograph		**Ph. Eur.**	**USP** No equivalent US Pharmacopoeia monograph specified
Name		Nitric oxide	
Reference		01/2008:1550	
Chemical Formula		NO	
Definition		Nitric oxide contains not less than 99.0% V/V of nitric oxide.	
Identification		Examine by infrared spectrometry and compare with the reference spectrum	
Production			
Assay	Specification	≥ 99.0 % V/V nitric oxide	
	Analytical method	Determine content of nitric oxide by difference using the mass balance equation after determining the sum of the impurities described under production.	
Impurities			
CO_2	Limit	≤ 3000 ppm V/V	
	Analytical Method	Gas chromatography	
N_2	Limit	≤ 3000 ppm V/V	
	Analytical method	Gas chromatography	
NO_2	Limit	≤ 400 ppm V/V	
	Analytical method	UV spectrophotometry analyser	
N_2O	Limit	≤ 3000 ppm V/V	
	Analytical method	Gas chromatography	
H_2O	Limit	≤ 100 ppm V/V	
	Analytical method	Electrolytic hygrometer	
Tests			
	Limit	No tests section specified	
	Analytical Method		

5.12 Argon

Argon			
Monograph		**Ph. Eur.**	**USP** No equivalent US Pharmacopoeia monograph specified
Name		Argon	
Reference		07/2010:2407	
Chemical Formula		Ar	
Definition		Gas obtained by cryogenic fractional distillation of ambient air. Argon contains not less than 99.995% v/v of argon calculated by deduction of the sum of impurities found when performing the test for impurities and water content.	
Identification		Gas chromatography; and Verify that the gas is not oxygen using a paramagnetic analyser.	
Production			
Assay	Specification	≥ 99.995 % V/V argon	
	Analytical method	Gas chromatography	
Impurities			
O_2	Limit	≤ 5 ppm V/V	
	Analytical method	Gas chromatography	
H_2O	Limit	≤ 10 ppm V/V	
	Analytical method	Electrolytic hygrometer	
Tests			
	Limit	No tests section specified	
	Analytical method		

5.13 Carbon monoxide

Carbon monoxide			
Monograph		**Ph. Eur.**	**USP** No equivalent US Pharmacopoeia monograph specified
Name		Carbon monoxide	
Reference		01/2011:2408 corrected 7.2	
Chemical Formula		CO	
Definition		Gas obtained by steam reforming (catalytic oxidation) of hydrocarbons. Carbon monoxide contains not less than 99.5% V/V of carbon monoxide.	
Identification		Infrared absorption spectrophotometry or it complies with the limits of the assay.	
Production			
Assay	Specification	≥ 99.5 % V/V carbon monoxide	
	Analytical method	Infrared analyser	
Impurities			
CO_2	Limit	≤ 300 ppm V/V	
	Analytical method	Gas chromatography	
CH_4	Limit	≤ 100 ppm V/V	
	Analytical method	Gas chromatography	
H_2	Limit	≤ 300 ppm V/V	
	Analytical method	Gas chromatography	
Nickel tetracarbonyl / Iron pentacarbonyl	Limit	Not detectable	
	Analytical method	Detector tube	
H_2O	Limit	≤ 10 ppm V/V	
	Analytical Method	Electrolytic Hygrometer	
Tests			
	Limit	No tests section specified	
	Analytical method		

5.14 Carbon monoxide intermix (5 per cent) in nitrogen

Carbon monoxide intermix (5 per cent) in nitrogen			
Monograph		**Ph. Eur.**	**USP** No equivalent US Pharmacopoeia monograph specified
Name		Carbon monoxide intermix (5% in nitrogen)	
Reference		01/2018:2904	
Chemical formula		N/A	
Definition		Mixture containing 5% carbon monoxide (2408) in Nitrogen, low-oxygen (1685)	
Identification		Carry out tests - A and C or - B and C A - Infrared absorption spectrophotometry B - Complies with limits of assay C - Gas chromatography	
Production			
Assay	Assay	95.0 per cent to 105.0 per cent of the nominal value of carbon monoxide (CO) in nitrogen (N_2). NOTE This can be considered as containing between 4.75 % and 5.25% carbon monoxide	
	Analytical method	Infrared analyser	
Impurities			
H_2O	Limit	≤ 10 ppm V/V	
	Analytical method	Electrolytic hygrometer	
Tests			
	Limit	No tests section specified	
	Analytical method		

5.15 Methane

Methane			
Monograph		**Ph. Eur.**	**USP** No equivalent US Pharmacopoeia monograph specified
Name		Methane	
Reference		01/2015:2413	
Chemical Formula		CH_4	
Definition		This monograph applies to methane obtained from natural gas and intended for medicinal use. Methane contains not less than 99.5% V/V of methane.	
Identification		Gas chromatography obtained in the assay	
Production			
Assay	Specification	≥ 99.5 % V/V methane	
	Analytical method	Gas chromatography Using molecular sieve column	
Impurities			
N_2	Limit	≤ 500 ppm V/V	
	Analytical method	Gas chromatography	
C_2-C_4 Hydrocarbons	Limit	≤ 100 ppm V/V	
	Analytical method	Gas chromatography	
H_2O	Limit	≤ 10 ppm V/V	
	Analytical Method	Electrolytic Hygrometer	
Tests			
	Limit	No tests section specified	
	Analytical method		

5.16 Methane intermix (2% per cent) in nitrogen

Methane intermix (2 per cent) in nitrogen			
Monograph		**Ph. Eur.**	**USP** No equivalent US Pharmacopoeia monograph specified
Name		Methane intermix (2%) in nitrogen	
Reference		01/2018:2905	
Chemical formula		N/A	
Definition		Mixture containing 2% methane (2413) in nitrogen, low-oxygen (1685)	
Identification		Carry out tests A or B A - Complies with limits of assay B - Gas chromatography	
Production			
Assay	Assay	95.0 per cent to 105.0 per cent of the nominal value of methane (CH_4) in nitrogen (N_2). NOTE This can be considered as containing between 1.9 % and 2.1% methane	
	Analytical method	Gas chromatography	
Impurities			
H_2O	Limit	≤ 10 ppm V/V	
	Analytical method	Electrolytic hygrometer	
Tests			
	Limit	No tests section specified	
	Analytical method		

5.17 Acetylene intermix (1 per cent) in nitrogen

Acetylene intermix (1 per cent) in nitrogen			
Monograph		**Ph. Eur.**	**USP** No equivalent US Pharmacopoeia monograph specified
Name		Acetylene intermix (1% in nitrogen)	
Reference		01/2018:2903	
Chemical formula		N/A	
Definition		Mixture containing 1% Acetylene in Nitrogen, low-oxygen (1685). The acetylene used in the manufacturing process is limited to acetylene produced by hydrolysis of calcium carbide. The method of storage of the acetylene is limited to cylinders filled with a porous mass and using acetone as a solvent. Prior to using the gas in the manufacturing process, the acetylene must be passed through an activated charcoal filter.	
Identification		Carry out tests - A or B A - Complies with limits of assay B - Gas chromatography	
Production			
Assay	Assay	95.0 per cent to 105.0 per cent of the nominal value of acetylene (C_2H_2) in nitrogen (N_2). NOTE This can be considered as containing between 0.95 and 1.05% acetylene	
	Analytical method	Gas chromatography	
Impurities			
Acetone	Limit	≤ 5 ppm V/V	
	Analytical method	Gas chromatography	
AsH_3	Limit	≤ 0.25 ppm V/V	
	Analytical method	Detector tube	
PH_3	Limit	≤ 0.2 ppm V/V	
	Analytical method	Detector tube	
H_2S	Limit	≤ 0.2 ppm V/V	
	Analytical method	Detector tube	
H_2O	Limit	≤ 10 ppm V/V	
	Analytical method	Electrolytic hygrometer	
Tests			
	Limit	No tests section specified	
	Analytical method		

6 Japanese Pharmacopoeia (16th Edition)

6.1 Oxygen

Oxygen		
Monograph		JP16
Name		Oxygen
Chemical Formula		O_2
Definition		Oxygen is oxygen produced by the air liquefaction separation method. It contains not less than 99.5 v/v% of oxygen.
Description		Oxygen is a colourless gas under atmospheric pressure, and is odourless.
Identification		The retention time of principal peak obtained from oxygen is the same as that of the peak obtained from oxygen by gas chromatography.
Purity		
N_2	Limit	The peak area of nitrogen in the oxygen is not larger than that of the control sample.
	Analytical Method	Gas chromatography
Assay		
Assay	Specification	$\geq$ 99.5% vol of O_2.
	Analytical method	Volumetric gas absorption apparatus

6.2 Nitrous oxide

Nitrous oxide		
Monograph		JP16
Name		Nitrous oxide
Chemical Formula		N_2O
Definition		Nitrous oxide contains not less than 97 vol% of nitrous oxide
Description		Nitrous oxide is a colourless gas at room temperature and at atmospheric pressure, and is odourless.
Identification		1 A glowing splinter of wood held in nitrous oxide: it bursts into flame immediately. 2. The retention time of the main peak from nitrous oxide coincides with that of nitrous oxide by gas chromatography.
Purity		
Acidity or alkalinity	Limit	Colour of the test solution is not deeper than the reference solutions
	Analytical method	Pass through acidified methyl red and bromothymol blue test solution in a Nessler tube. Compare colour against control solution
Reducing Substances	Limit	The colour is the same as the control solution
	Analytical method	Pass through potassium permanganate solution in a Nessler tube. Compare colour against control solution
Oxidising Substances	Limit	The colour is the same as the control solution
	Analytical method	Pass through potassium iodide-starch solution in a Nessler tube. Compare colour against control solution
Chloride	Limit	Turbidity produced does not exceed that produced in the control solution (can be calculated by the method)
	Analytical method	Pass through silver nitrate solution in a Nessler tube. Compare turbidity against control solution
CO_2	Limit	Turbidity produced does not exceed that produced in the control solution (can be calculated by the method)
	Analytical method	Pass through barium hydroxide in a Nessler tube. Compare turbidity against control solution of barium hydroxide containing sodium hydrogen carbonate
CO	Limit	No peak observed at the same retention time as that for carbon monoxide.
	Analytical method	Gas chromatography
Assay		
Assay	Specification	≥ 97.0 vol% of nitrous oxide
	Analytical Method	Gas chromatography

6.3 Carbon dioxide

Carbon dioxide		
Monograph		JP16
Name		Carbon dioxide
Chemical Formula		CO_2
Definition		Carbon dioxide contains not less than 99.5 vol% of carbon dioxide
Description		Carbon dioxide is a colourless gas at room temperature and under atmospheric pressure. It is odourless.
Identification		1 Put 100mL of carbon dioxide through a carbon dioxide measuring detector tube: the detector tube is changed to a stipulated colour tone by each detector tube, provided that the detector tube with an upper limit of measurement of not less than 10% is used. 2. Pass carbon dioxide into calcium hydroxide and a white precipitate is produced. Add acetic acid to the precipitate and it dissolves with effervescence.
Purity		
Acidity	Limit	The test solution is not more coloured than the control solution.
	Analytical method	Pass through water in a Nessler tube and add methyl orange detector. Compare colour against control solution.
Reducing Substances*	Limit	The turbidity is the same as the control solution.
	Analytical method	Pass through silver nitrate solution in a Nessler tube. Compare turbidity against control solution.
CO	Limit	The concentration of carbon monoxide is less than 15 ppm according to each detector tube.
	Analytical method	Carbon monoxide measuring detector tube
Assay		
Assay	Specification	≥ 99.5 vol% of carbon dioxide.
	Analytical method	Volumetric gas absorption apparatus

* Reducing substances includes test for phosphine (PH_3) hydrogen sulphide (H_2S) and reducing organic substances.

6.4 Nitrogen

Nitrogen		
Monograph		JP16
Name		Nitrogen
Chemical Formula		N_2
Definition		Nitrogen is the nitrogen produced by the air liquefaction separation method. It contains not less than 99.5 vol% of nitrogen.
Description		Nitrogen is a colourless gas at room temperature and under atmospheric pressure, and is odourless.
Identification		The principal peak obtained from nitrogen has the same retention time with the peak from nitrogen by gas chromatography.
Purity		
O_2	Limit	The peak area of oxygen obtained from nitrogen in the assay is not larger than 1/2 times that obtained from the standard gas mixture.
	Analytical method	Gas chromatography
Assay		
Assay	Specification	≥ 99.5 vol% of nitrogen.
	Analytical method	Gas chromatography