

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

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Prepared by WG-7 Medical and Breathing Gases

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Amendments from 152/18

Section	Change
3.1	Clarification relating to intended use of the sections of the monographs
4	Update of European and Japanese Pharmacopoeias
5	General update to reflect the use of the various test methods and update of the monographs to the latest version
6	Analytical method for Oxygen assay modified in Japanese Pharmacopoeia and inclusion of the type of detector for GC

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 Pharmacopoeia (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
Nitrogen, low-oxygen	1685	No reference no.	NS
Carbon dioxide	0375	No reference no.	No reference no.
Air, medicinal	1238	No reference no.	NS
Air, synthetic medicinal	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 intermix (1 per cent) in nitrogen	2903	NS	NS

+ Nitrogen is covered in the National Formulary

NS: Not specified

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.

In the medicinal gases monographs where there is a production and tests section it was originally intended that the test section can be used by the end user e.g. the hospital, whereas the production section is intended for the manufacturer. However, this structure is not present in all the medicinal gases monographs. Therefore, in this document to avoid any confusion we named the sections “Tests intended for the manufacturer” and “Tests intended for the end user”.

Where the hospital is the manufacturer, for example where they are producing medicinal gases on site (e.g. Oxygen 93 %), the “Tests intended for the manufacturer” shall 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 representatives 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: 11.0 (2023)
- United States Pharmacopoeia: USP40, NF35 (2017)
- Japanese Pharmacopoeia: 18 (2021)

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
Tests intended for the manufacturer			
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 ₂ O	Limit	≤ 67 ppm V/V	Not specified
	Analytical method	Electrolytic hygrometer	
Tests intended for the end user			
CO	Limit	≤ 5 ppm V/V	Not specified
	Analytical method	Detector tube	
CO ₂	Limit	≤ 300 ppm V/V	
	Analytical method	Detector tube	
H ₂ O	Limit	≤ 67 ppm V/V	
	Analytical method	Detector tube	