OXYGEN

OXYGENIUM

Draft proposal for revision in The International Pharmacopoeia

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidt@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by 26 February 2021.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/current-projects) for comments under the “Working documents in public consultation” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

[Note from the Secretariat. It is proposed to revise the monograph on Oxygen. The draft proposed is based on a review of current pharmacopoeial requirements for oxygen. Comments are in particular sought:

- on the proposal to combine quality requirements of oxygen produced by cryogenic distillation and by pressure/vacuum swing adsorption (PSA/VSA) oxygen generating plants in one monograph;
- on the suitability of the proposed test methods; and
- on the need to specify further impurities.

In case additional impurities would need to be added to the monograph, please also kindly provide the rational for the inclusion and suggest the test methods and limits which could be used.

Changes to the current chapter are indicated in the text by insert or delete.]


OXYGEN

OXYGENIUM

O₂

Relative molecular mass. 32.00


Description. A colourless gas.

Category. Gas for inhalation.

Storage. Oxygen, if stored in appropriate containers, should comply with the safety regulations of the national authority. Valves or taps should not be lubricated with oil or grease, unless they are oxygen-compatible.

Additional information. Oxygen is mentioned in the current WHO Model list of essential medicines (EML) and in the EML for Children.

This monograph does not apply to gas produced using concentrators for home care or bedside use.¹⁰

Requirements
Oxygen contains not less than 90.0 % v/v of O₂.

Production. Oxygen is produced of ambient air by cryogenic distillation or by pressure/vacuum swing adsorption (PSA/VSA) oxygen generating plants.¹¹

Identity test. Carry out the test as described under “Assay”. The sample gas complies with the limit. The paramagnetic signal exhibited confirms the presence of oxygen.


Oxygen labelled as having been produced by cryogenic distillation may be exempted from the requirements of the tests for carbon monoxide and carbon dioxide.

**Carbon monoxide.** Determine the content using a carbon monoxide detector tube according to the manufacturer’s instruction. Pass the required volume of the test gas through the tube and read the value corresponding to the length of the coloured layer or the intensity of the colour on the graduated scale; not more than 10 μl/L.

**Carbon dioxide.** Determine the content using a carbon dioxide detector tube according to the manufacturer’s instruction. Pass the required volume of the test gas through the tube and read the value corresponding to the length of the coloured layer or the intensity of the colour on the graduated scale; not more than 300 μl/L.

**Assay.** Determine the percentage content of Oxygen (O₂) using a paramagnetic analyser which measures electronically the molecule’s interaction with magnetic fields.

**Impurities**
A. CO₂, carbon dioxide;
B. CO, carbon monoxide.
O$_2$

**Relative molecular mass.** 32.00

**Chemical name.** Oxygen; CAS Reg. No. 7782-44-7.

**Description.** A colourless gas; odourless.

**Solubility.** One volume dissolves in about 32 volumes of water and in about 7 volumes of ethanol (~750 g/l) TS, both at a pressure of 101.3 kPa and 20°C.

**Category.** Gas for inhalation.

**Storage.** Oxygen should be kept as compressed gas or liquid at cryogenic temperature, in appropriate containers complying with the safety regulations of the national authority. Valves or taps should not be lubricated with oil or grease.

**Labelling.** An ISO standard$^1$ requires that cylinders containing oxygen intended for medical use should bear the name of the contents in legible and permanent characters and, preferably, also the molecular formula O$_2$.


**Additional information.** In the analysis of medicinal gases certain tests are not intended for hospital pharmacists. They are solely applicable by laboratories equipped with the specialized apparatus.

**Requirements**

Oxygen contains not less than 99.5% v/v of O$_2$.

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**Identity tests**

A. Place a glowing splinter of wood into the test gas; the splinter bursts into flame.

B. Shake with alkaline pyrogallol TS; the test gas is absorbed and the solution becomes dark brown (distinction from Dinitrogen oxide).
Figure 7. Apparatus for the determination of carbon monoxide in medicinal gases
- Measurements in mm.

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**Note:** For the following tests deliver the test gas at a rate of 4 litres per hour.

**Carbon monoxide**

- Either test A or test B may be applied.

A. The apparatus (Fig. 7) consists of the following parts connected in series:
- a U-tube (U1) containing desiccant silica gel R impregnated with chromium trioxide R;
- a wash bottle (F1) containing 100 mL of potassium hydroxide (~400 g/l) TS;
- a U-tube (U2) containing pellets of potassium hydroxide R;
- a U-tube (U3) containing phosphorus pentoxide R dispersed on previously granulated, fused pumice;
- a U-tube (U4) containing 30 g of recrystallized iodine pentoxide R in granules, previously dried at 200 °C and kept at a temperature of 120°C (T) during the test. The iodine pentoxide is packed in the tube in 1-cm columns separated by 1-cm columns of glass wool to give an effective length of 5 cm;
- a reaction tube (F2) containing 2.0 mL of potassium iodide (160 g/l) TS and 0.15 mL of starch TS.
Flush the apparatus with 5.0 litres of argon R. If necessary, discharge the blue colour in tube F2 containing potassium iodide (160 g/l) TS by adding a sufficient volume of freshly prepared sodium thiosulfate (0.002 mol/l) VS. Continue flushing with argon R until not more than 0.045 mL of sodium thiosulfate (0.002 mol/l) VS is required after the passage of 5.0 litres of argon R. Pass 7.5 litres of the test gas from the container through the apparatus. Flush the last traces of liberated iodine into the reaction tube by passing 1.0 litre of argon R through the apparatus. Titrate the liberated iodine with sodium thiosulfate (0.002 mol/l) VS. Repeat the procedure using 7.5 litres of argon R.

B. Determine the content using a carbon monoxide detector tube. Pass the required volume of the test gas through the tube, the calibration of which is verified according to the manufacturer's instructions.

The gas supply is connected to a pressure regulator and needle valve. Connect the flexible tubing fitted with a Y-piece to the valve and adjust the flow of the test gas to purge the tubing to an appropriate flow. Fit the carbon monoxide detector tube to the metering pump following the manufacturer’s instructions. Connect the open end of the tube to the short leg of the tubing and operate the pump sufficiently to pass a suitable volume of the test gas through the tube. Read the value corresponding to the length of the coloured layer or the intensity of the colour on the graduated scale; not more than 5 μl/l.

**Note:** For the following tests—“Carbon dioxide”, “Oxidizing substances”, and “Acidity and alkalinity”—pass the test gas through the appropriate reagent contained in a hermetically closed flat-bottomed glass cylinder (with dimensions such that 50 mL of liquid reaches a height of 12-14 cm) that is fitted with (a) a delivery tube terminated by a capillary 1 mm in internal diameter and placed within 2 mm of the bottom of the cylinder; and (b) an outlet tube.

Prepare the reference solutions in identical cylinders.
Carbon dioxide

Either test A or test B may be applied.

A. Pass 1.0 litre of the test gas through 50 mL of a clear solution of barium hydroxide (0.15 mol/l) VS. Similarly prepare a reference solution by adding 1.0 mL of a 1.1 mg/mL solution of sodium hydrogen carbonate R in carbon-dioxidefree water R to 50 mL of barium hydroxide (0.15 mol/l) VS.

Any turbidity in the solution after the passage of the test gas is not more intense than that of the reference solution (300 μl/l).

B. Determine the content using a carbon dioxide detector tube. Pass the required volume of the test gas through the tube, the calibration of which is verified according to the manufacturer's instructions.

The gas supply is connected to a suitable pressure regulator and needle valve. Connect the flexible tubing fitted with a Y-piece to the valve and adjust the flow of the test gas to purge the tubing to an appropriate flow. Fit the carbon dioxide detector tube to the metering pump following the manufacturer's instructions. Connect the open end of the tube to the short leg of the tubing and operate the pump sufficiently to pass a suitable volume of the test gas through the tube. Read the value corresponding to the length of the coloured layer or the intensity of the colour on the graduated scale; not more than 300 μl/l.

Oxidizing substances.

To two cylinders add 50 mL of freshly prepared potassium iodide/starch TS1 and about 0.2 mL of glacial acetic acid R. Protect the cylinders from light. Pass 5.0 litres of the test gas into one of the solutions and compare the colour produced.

The solutions in both cylinders remain colourless.

Water

Either test A or test B may be applied.

A. The apparatus consists either of an electrolytic hygrometer as described below, an appropriate humidity detector tube, or a capacity hygrometer.
The measuring cell consists of a thin film of phosphoric anhydride placed between two coiled platinum wires that act as electrodes. The water vapour in the test gas is absorbed by the phosphoric anhydride to form phosphoric acid, which acts as an electrical conductor. Before introducing the test gas into the device, allow the gas to stabilize at room temperature and make sure that the temperature is constant throughout the apparatus. Apply a continuous voltage across the electrodes to produce electrolysis of the water and regeneration of phosphoric anhydride. Measure the resulting electrical current, which is proportional to the water content in the test gas. (This is a self-calibrating system that obeys Faraday’s law.) Calculate the content of water; not more than 60 μg/l.

B. Determine the content using a water vapour detector tube. Pass the required volume of the test gas through the tube, the calibration of which is verified according to the manufacturer’s instructions.

The gas supply is connected to a pressure regulator and needle valve. Connect the flexible tubing fitted with a Y-piece to the valve and adjust the flow of the test gas to purge the tubing to an appropriate flow. Fit the water vapour detector tube to the metering pump following the manufacturer’s instructions. Connect the open end of the tube to the short leg of the tubing and operate the pump sufficiently to pass a suitable volume of the test gas through the tube. Read the value corresponding to the length of the coloured layer or the intensity of the colour on the graduated scale; not more than 60 μl/l.

**Acidity and alkalinity.** Pass 2.0 litres of the test gas through a mixture of 0.10 mL of hydrochloric acid (0.01 mol/l) VS and 50 mL of carbon-dioxide-free water R. For reference solution 1, use 50 mL of carbon-dioxide-free water R. For reference solution 2, use a mixture of 0.20 mL of hydrochloric acid (0.01 mol/l) VS and 50 mL of carbon-dioxide-free-water R.

To each solution add 0.1 mL of methyl red/ethanol TS; the intensity of the colour in the solution of the test gas is between those of reference solutions 1 and 2.
Assay

Either method A or method B may be applied.

A. For the determination use a 25-mL capacity gas burette (Fig. 8) in the form of a chamber with at its upper end, a tube graduated in 0.2% between 95 and 100, and isolated at each end by a tap with a conical barrel. The lower tap is joined to a tube with an olive-shaped nozzle and is used to introduce the test gas into the apparatus. A cylindrical funnel above the upper tap is used to introduce the absorbent solution. Wash the burette with water and dry. Open the two taps. Connect the nozzle to the container of the test gas and set the flow rate to 1 litre per minute. Flush the burette by passing the gas through it for 1 minute. Close the upper tap of the burette and immediately afterwards the lower tap. Rapidly disconnect the burette from the container of the test gas, and give a half turn to the upper tap to eliminate any excess pressure in the burette. Keeping the burette vertical, fill the funnel with a freshly prepared mixture of 21 mL of potassium hydroxide (~560 g/l) TS and 130 mL of sodium dithionite (200 g/l) TS. Open the upper tap slowly. The solution absorbs the oxygen and enters the burette. Allow to stand for 10 minutes without shaking.

Read the level of the liquid meniscus on the graduated part of the burette; the figure represents the content of oxygen as a percentage in v/v.

B. Oxygen in medicinal gases can also be determined using a paramagnetic analyser, which measures electronically the molecule’s interaction with magnetic fields.
Figure 8. Burette used for the assay of oxygen
- Measurements in mm.

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Carry out the method according to the instrument manufacturer's instructions.

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