World Health Organization

MEDICINAL OXYGEN

(OXYGENIUM MEDICINALIS)

Draft proposal for revision in *The International Pharmacopoeia*

(February 2024)

DRAFT FOR COMMENTS

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For any technical questions, you may contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Ms Bezawit Kibret (kibretb@who.int, nsp@who.int).
Comments should be submitted through the online platform on or by **04 August 2024**. Please note that only comments received by this deadline will be considered for the preparation of this document.
Our working documents are sent out electronically and uploaded into PleaseReview™. The working documents are also placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation) under the "Working documents in public consultation".
If you wish to receive all our draft guidelines during the course of the year, please send your full name, organization/ affiliation, and email address to jonessi@who.int, nsp@who.intand your name will be added to our electronic mailing list and review platform.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/24.949

MEDICINAL OXYGEN

(OXYGENIUM MEDICINALIS)

Description	Date
Revision drafted by the Secretariat.	January 2024
Discussion at the Consultation on quality control and pharmacopoeial specifications for medicines	May 2024
Discussion with colleagues from WHO Access to Oxygen Initiative	June 2024
Draft revision sent out for public consultation.	June – July 2024
Presentation at the 58th meeting of the Expert Committee on Specifications for Pharmaceutical Preparations.	October 2024
Further follow-up action as required.	

[Note from the Secretariat. *It is intended to revise the monograph on Oxygen in* The International Pharmacopoeia.

Comments are particularly sought on the suitability and use of alternative oxygen analysers to determine oxygen concentrations, such as zirconia cell analysers, and on the necessity to perform a risk assessment to identify any additional impurities that may be present in oxygen produced by a two-stage adsorption plant (Oxygen 98%).

Changes to the current chapter are indicated by <u>insert</u> or ~~delete~~.]

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Note: Some parts of the monograph have been adapted from other pharmacopoeias, including the European Pharmacopoeia and the United States Pharmacopoeia. The intention is to establish a monograph that reflects current requirements and is converged and harmonized with relevant regulations on oxygen. Further details, in particular a description of analytical techniques to determine oxygen and other gases, can be found in the above pharmacopoeias and other resources.

Molecular formula. O_2

Relative molecular mass. 32.00

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

Description. A colourless gas.

Category. Gas for inhalation.

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

~~Depending on the clinical medicinal necessity, and in accordance with clinical guidelines,~~ Medicinal Oxygen is used either (1) in the undiluted form, (2) as mixtures of Oxygen 93%, Oxygen 98%, Oxygen 99.5% or other oxygen products, or (3) in the undiluted form or as mixtures in combination with ambient or compressed air of a suitable quality or other medicines.

This monograph does not apply to gas produced using portable concentrators for home care or bedside use. (Specifications for portable concentrators for home care or bedside use can be found in:

- WHO-UNICEF Technical specifications and guidance for oxygen therapy devices (WHO Medical Device Technical Series), World Health Organization and the United Nations Children's Fund (UNICEF), 2019; and in
- Priority medical devices list for the COVID-19 response and associated technical specifications, World Health Organization 2020.

Compliance with the monograph requires the performance of suitable tests to demonstrate that the gas meets the limits specified under "Production" or that the gas would meet the limits if tested. The additional tests using methods such as semi-quantitative indicator tubes are to be performed in the form of spot checks by healthcare facilities to verify the quality of the gas where needed and appropriate, e.g. in the distribution system or at the terminal outlet of the medical gas pipeline.

Requirements

Definition. Medicinal oxygen is Oxygen 93%, Oxygen 98% or Oxygen 99.5%. Other products with different oxygen concentrations and/or produced using different production methods may also be considered as Medicinal oxygen, if approved by the appropriate national or regional authority.

Oxygen 93%

Definition. Oxygen 93% contains not less than 90.0% and not more than 96.0% (V/V) of O_2, the remainder mainly consisting of argon and nitrogen.

Production. Oxygen 93% is produced from ambient air by pressure swing adsorption (PSA) or vacuum swing adsorption (VSA).

The production process ~~method~~ is validated to demonstrate that Oxygen 93% complies with the definition and the following limits: carbon dioxide: maximum 300 ppm (*V*/*V*); carbon monoxide: maximum 5 ppm (*V*/*V*); nitrogen monoxide and nitrogen dioxide: maximum 2 ppm (*V*/*V*) in total; sulfur dioxide: maximum 1 ppm (*V*/*V*); oil: maximum 0.1 mg/m3; water: maximum 67 ppm (*V*/*V*) and that viable and

non-viable particulates are eliminated or minimized and adequately controlled in the product.

During production, the oxygen content is continuously monitored.

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.

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 5 ppm (*V*/*V*).

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 ppm (*V*/*V*).

Water. Determine the content using a water vapour detector tube according to the manufacturer's instruction; not more than 67 ppm (*V*/*V*).

Assay. Determine the percentage content of Oxygen (O_2) using a paramagnetic analyser which electronically measures the molecule's interaction with magnetic fields.

Impurities

A. CO_2, carbon dioxide,

B. CO, carbon monoxide,

C. NO and NO_2, nitrogen monoxide and nitrogen dioxide

D. SO_2, sulfur dioxide

E. oil

F. H_2O, water.

Oxygen 98%

Definition. Oxygen 98% contains not less than 96.0% of O_2, the remainder mainly consisting of argon and nitrogen.

Production. Oxygen 98% is produced from ambient air in a two-stage adsorption plant, applying differential pressures to the adsorption vessels, using different zeolites/molecular sieves to reduce the levels of nitrogen and argon.

The production process is validated to demonstrate that Oxygen 98% complies with the definition and the following limits: carbon dioxide: maximum 300 ppm (*V*/*V*); carbon monoxide: maximum 5 ppm (*V*/*V*); nitrogen monoxide and nitrogen dioxide: maximum 2 ppm (*V*/*V*) in total; sulfur dioxide: maximum 1 ppm (*V*/*V*); oil: maximum 0.1 mg/m^3; water: maximum 67 ppm (*V*/*V*) and that viable and non-viable particulates are eliminated or minimized and adequately controlled in the product.

During production, the oxygen content and the above listed impurities are continuously monitored. A risk assessment must be performed to identify any additional impurities that may be present in the gas produced by the two-stage adsorption plant. Where applicable, special consideration should be given to identifying any potential impurities that could cause harm to the patient, related to:

- the environment in which the plant is situated;
- any emission within the plant that could lead to impurities;
- compression of the oxygen when filling high-pressure cylinders.

When indicated by the risk assessment, some or all of these additional impurities may need to be continuously monitored.

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.

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 5 ppm (*V*/*V*).

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 ppm (*V*/*V*).

Nitrogen monoxide and nitrogen dioxide. Determine the content using a nitrogen monoxide and nitrogen dioxide detector tube according to the manufacturer's instruction; not more than 2 ppm (*V*/*V*) in total.

Sulfur dioxide. Determine the content using a sulfur dioxide detector tube according to the manufacturer's instruction; not more than 1 ppm (*V*/*V*).

Oil. Determine the content using an oil detector tube according to the manufacturer's instruction; not more than 0.1 mg/m^3.

Water. Determine the content using a water vapour detector tube according to the manufacturer's instruction; not more than 67 ppm (*V*/*V*).

Assay. Determine the percentage content of Oxygen (O_2) using a paramagnetic analyser which electronically measures the molecule's interaction with magnetic fields.

Impurities

A. CO_2, carbon dioxide,

B. CO, carbon monoxide,

C. NO and NO_2, nitrogen monoxide and nitrogen dioxide,

D. SO_2, sulfur dioxide,

E. oil,

F. H_2O, water.

Oxygen 99.5%

Definition. Oxygen 99.5% contains not less than 99.5% (V/V) of O_2.

Production. Oxygen 99.5% is produced from ambient air by cryogenic distillation.

The production process ~~method~~ is validated to demonstrate that Oxygen 99.5% complies with the definition and the following limits: carbon dioxide: maximum 300 ppm (*V*/*V*), carbon monoxide: maximum 5 ppm (*V*/*V*), water: maximum 67 ppm (*V*/*V*).

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.

Water. Not more than 67 ppm (*V*/*V*) determine by water vapor detector tube or electrolytic hygrometer.

Assay. Determine the percentage content of Oxygen (O_2) using a paramagnetic analyser which electronically measures the molecule's interaction with magnetic fields.

Impurities

A. CO_2, carbon dioxide,

B. CO, carbon monoxide,

C: H_2O, water.

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