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Anaesthetic and respiratory equipment — Nebulizing systems and components

Matériel d'anesthésie et de réanimation respiratoire — Systèmes de nébulisation et ses composants

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 121, *Anaesthetic and respiratory equipment*, Subcommittee SC 2, *Airways and related equipment*.

This third edition cancels and replaces the second edition (ISO 27427:2010), of which it constitutes a major revision.

Introduction

Nebulizers are widely used to deliver drugs and vaccines in an aerosol form to humans through the respiratory system. **Nebulizers** are also used for diagnostic purposes using radioisotopes for lung challenge tests. These drugs can be in the form of a solution, suspension or emulsion. **Aerosol** inhalation is the preferred route of administration for some drugs. Some drugs are intended for treatment of systemic diseases and other drugs are intended to treat respiratory diseases. To achieve the intended treatment, **aerosol** particles have to be deposited in specific parts of the respiratory tract. Different size particles tend to deposit in different parts of the respiratory system; therefore, the performance profile and the intended use of the **nebulizer** have to be defined by the manufacturer and specified in the accompanying documentation.

This International Standard is based on Reference.[29] This International Standard was developed to cover "general purpose" **nebulizers** and is based on adult test parameters which are likely to be different than stated when testing for paediatric or infant patient populations. It was specifically written to ensure that the results of the various tests declared by the manufacturer are meaningful to the users and buyers of **nebulizers**.

The objectives of this International Standard are to ensure

— suitability of the **nebulizers** for the intended use as disclosed by the manufacturer,

— safety, particularly for **electrically powered nebulizers**,

— compatibility between the materials of the components and the dispensed liquid, and

— biocompatibility of the materials of the components that come into contact with the human body.

Important changes were made to the original EN standard in recognition of the advances in test devices such as lasers and low-flow impactors that allow manufacturers to use different test methods, provided these alternate methods are validated against the methods specified in this International Standard.

Terms defined in this International Standard are set in **bold type**.

Throughout this International Standard, text for which rationale is provided in Annex A is indicated by an asterisk (*).

Anaesthetic and respiratory equipment — Nebulizing systems and components

1 Scope

*This International Standard specifies requirements for the safety and performance testing of general purpose **nebulizing systems** intended for continuous or breath-actuated delivery of liquids, in **aerosol** form, to humans through the respiratory system.

This International Standard includes **gas-powered nebulizers** which can be powered by, e.g., compressors, pipeline systems, cylinders, etc., and **electrically powered nebulizers** [e.g., spinning disc, ultrasonic, vibrating mesh (active and passive), and capillary devices] or **manually powered nebulizers**.

This International Standard does not specify the minimum performance of **nebulizing systems**.

*This International Standard does not apply to devices intended for nasal deposition.

This International Standard does not apply to devices intended solely to provide humidification or hydration by providing water in **aerosol** form.

NOTE ISO 8185 covers this.[3]

*This International Standard does not apply to drug-specific **nebulizers** or their components (e.g., metered dose inhalers, metered liquid inhalers, dry powder inhalers).

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 5356-1, *Anaesthetic and respiratory equipment — Conical connectors — Part 1: Cones and sockets*

ISO 5356-2, *Anaesthetic and respiratory equipment — Conical connectors — Part 2: Screw-threaded weight-bearing connectors*

ISO 5367, *Anaesthetic and respiratory equipment — Breathing sets and connectors*

ISO 7396-1, *Medical gas pipeline systems — Part 1: Pipeline systems for compressed medical gases and vacuum*

ISO 9170-1, *Terminal units for medical gas pipeline systems — Part 1: Terminal units for use with compressed medical gases and vacuum*

ISO 10524-1, *Pressure regulators for use with medical gases — Part 1: Pressure regulators and pressure regulators with flow-metering devices*

ISO 10524-3, *Pressure regulators for use with medical gases — Part 3: Pressure regulators integrated with cylinder valves*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO 11137-3, *Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 15001, *Anaesthetic and respiratory equipment — Compatibility with oxygen*

ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 23328-1, *Breathing system filters for anaesthetic and respiratory use — Part 1: Salt test method to assess filtration performance*

ISO 80369-1, *Small-bore connectors for liquids and gases in healthcare applications — Part 1: General requirements*

IEC 60601-1:2005, *Medical electrical equipment — Part 1: General requirements for basic safety and essential performance*

IEC 60601-1-2:2006+A1:2012, *Medical electrical equipment — Part 1-2: General requirements for basic safety and essential performance — Collateral standard: Electromagnetic compatibility — Requirements and tests*

IEC 60601-1-6, *Medical electrical equipment — Part 1-6: General requirements for basic safety and essential performance — Collateral standard: Usability*

IEC 60601-1-8, *Medical electrical equipment – Part 1-8: General requirements for basic safety and essential performance – Collateral Standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems*

IEC 62366, *Medical devices — Application of usability engineering to medical devices*

EN 556-1, *Sterilization of medical devices — Requirements for medical devices to be designated "STERILE" — Part 1: Requirements for terminally sterilized medical devices*

EN 13544-2, *Respiratory therapy equipment — Part 2: Tubing and connectors*

EN 15908, *Anaesthetic and respiratory equipment. Non-interchangeable screw-threaded (NIST) low-pressure connectors for medical gases*

ENV 737-6, *Medical gas pipeline systems — Part 6: Dimensions and allocation of probes for terminal units for compressed medical gases and vacuum*

CGA V-5-2005, *Diameter Index Safety System — Noninterchangeable Low Pressure Connections for Medical Gas Applications*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
aerosol
suspension of particles in gas

Note 1 to entry: Particles can be liquid or solid.

Note 2 to entry: The gas can be the driving gas or ambient air.

3.2
aerosol outlet port
outlet of the **nebulizing system** through which the **aerosol** is emitted

3.3
***aerosol output**
mass or volume of **aerosol** emitted by the **nebulizing system** at the **aerosol outlet port** for the given fill volume

3.4
***aerosol output rate**
mass or volume of **aerosol** emitted by the **nebulizing system** per unit of time

3.5
breath-actuated nebulizer
nebulizer triggered by a respiratory parameter

Note 1 to entry: Examples of this classification are found in Annex F.

3.6
continuous nebulizer
nebulizer in which **aerosol** is delivered continuously over multiple inhalation/exhalation breathing cycles or over long periods

3.7
electrically powered nebulizer
nebulizer that operates by means of electrical power

Note 1 to entry: **Electrically powered nebulizers** include ultrasonic, vibrating mesh and capillary-type devices.

3.8
gas-powered nebulizer
nebulizer in which the **aerosol** is generated by compressed gas

3.9
liquid container
part of the **nebulizer** that contains the liquid for nebulization

3.10
manually powered nebulizer
nebulizer that operates by means of human power

3.11
mass median aerodynamic diameter
MMAD
particle size at which 50 % of the mass of the active component are contained in droplets of smaller or equal aerodynamic diameter

3.12
maximum fill volume
maximum volume of liquid, expressed in millilitres, in the **liquid container** when the **nebulizer** is filled to its maximum filling level

3.13
nebulizer
device that converts a liquid to an **aerosol**

Note 1 to entry: A nebulizer is also known as an **aerosol** generator.

3.14
nebulizing system
device, including the **nebulizer** and all other components, up to and including the **aerosol outlet port**, required to make the **aerosol** available for inhalation

Note 1 to entry: Airway devices (e.g., masks, tracheal and tracheostomy tubes, supralaryngeal airways) and breathing systems are not part of the **nebulizing system**.

3.15
***percentage of fill volume emitted**
aerosol output expressed as a percentage of the fill volume recommended by the manufacturer that is emitted by the **nebulizer**

3.16
***residual volume**
estimated volume of liquid remaining in the **nebulizing system** when the **nebulizer** stops generating an **aerosol**

3.17
***respirable fraction**
fraction of **aerosol** droplets below 5 µm in diameter expressed as a percentage of the total **aerosol distribution**

Note 1 to entry: The **respirable fraction** can be converted to a percentage (%) by multiplying by 100.

3.18
***test solution**
aqueous solution used for the type-tests to characterize **aerosol output**, **aerosol output rate**, and particle sizing

Note 1 to entry: See 4.2.1.2, 5.4.2 j) and k), Annex C, and Annex D.

3.19
test substance
active ingredient contained in the test solution

3.20
validation
confirmation through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The term “validated” is used to designate the corresponding status.

Note 2 to entry: The use conditions for **validation** can be real or simulated.

4 General requirements and requirements for test

4.1 Risk management

4.1.1 General

Nebulizing systems and **nebulizers** shall, when transported, stored, installed, operated in normal use, and maintained according to the instructions of the manufacturer, present no risks that are not reduced

to an acceptable level using the risk management procedures in accordance with ISO 14971 and which are connected with their intended application, in normal and in single fault condition.

NOTE A situation in which a fault is not detected is considered a normal condition. Fault conditions/hazardous situations might remain undetected over a period of time and, as a consequence, might lead to an unacceptable risk. In that case, a subsequent detected fault condition needs to be considered as a single fault condition. Specific risk control measures need to be determined within the risk management process to deal with such situations.

4.1.2 Clinical evaluation

If applicable, a clinical evaluation shall be performed and the results documented in the technical documentation of the device.

Compliance is checked by inspecting the technical documentation of the device.

4.2 Test methods and alternatives

4.2.1 Test methods for aerosol output, aerosol output rate, and particle sizing

The type-test methods for **aerosol output**, **aerosol output rate**, and particle sizing in air are specified in Annexes C and D.

4.2.1.1 *All type-test methods shall be performed on at least three representative devices of the same type.

4.2.1.2 *The type-test methods shall use a **test solution** of albuterol 0,1 % (M/V) concentration in 0,9 % sodium chloride solution or 2,5 % (M/V) sodium fluoride in distilled water with the provision that its use is declared in the accompanying documents. See 5.4.2 j).

4.2.2 *Alternative test methods

The manufacturer can use type-test methods for **aerosol output**, **aerosol output rate**, and particle sizing different from those specified in Annexes C and D.

Alternative test methods shall be **validated** against the test methods in Annexes C and D to demonstrate equivalency.

Demonstration of equivalency shall be included in the technical documentation of the manufacturer.

Evidence shall be provided (e.g. to regulatory authorities) upon request.

4.2.3 Calibration and setup

To establish confidence in the test method, it is recommended that mass balance procedures be incorporated during initial determinations. It is also recommended that occasional checks for system leaks and overall efficiency of analysis be performed.

4.3 Electrical safety

A **nebulizing system** that utilizes electrical power shall meet the requirements given in IEC 60601-1, in addition to the requirements given in this International Standard.

Compliance is checked by applying the tests given in IEC 60601-1.

4.4 Mechanical safety

Nebulizing systems shall comply with Clause 9 of IEC 60601-1:2005.

Compliance is checked by inspection.

4.5 Pneumatic safety

If it is declared by the manufacturer that a **nebulizing system** is intended to be connected directly to a pipeline system complying with ISO 7396-1 or a pressure regulator complying with ISO 10524-1 or ISO 10524-3, the **nebulizing system** shall meet the requirements of this International Standard for a pneumatic power supply having a range of 280 kPa (2,8 bar) to 600 kPa (6 bar) and shall cause no hazardous situation under single fault conditions of the medical gas supply, [i.e. up to 1 MPa (10 bar) inlet pressure].

4.6 Protection against inadvertent adjustments

Means of protection against inadvertent adjustment of controls which can create a hazardous output shall be provided.

EXAMPLE Acceptable mechanical control techniques include locks, shielding, friction loading, detents, pressure-sensitive finger pads, capacitive finger-switched microprocessor-oriented "soft" controls, and a specific sequence of key or switch operations.

Compliance is checked by visual inspection following the instructions for use.

4.7 Usability

4.7.1 The manufacturer shall address, in a usability engineering process, the risk resulting from poor usability according to IEC 60601-1-6 and IEC 62366.

4.7.2 The ON/OFF switch and/or control devices shall be positioned in such a way as to be safely operated without hesitation or loss of time and without ambiguity.

4.7.3 Control devices (if fitted) shall be so arranged that their layout, travel, and resistance to operation are compatible with the action to be performed, taking account of ergonomic principles.

Compliance is checked by inspecting the usability engineering file.

5 Marking

5.1 Symbols

ISO 15223-1 and 6.4 of IEC 60601-1:2005 apply.

Compliance is checked by inspection.

5.2 Marking on the device

Nebulizers, **nebulizing systems**, and components shall contain durable and legible marking on the device to include the following.

5.2.1 Marking of the nebulizer and components

The following shall be marked on the **nebulizer** and components:

a) an arrow showing the direction of gas flow on all operator-detachable flow direction-sensitive components, breathing attachments or parts (e.g. facemask or mouthpiece one-way valve, etc.), unless manufactured to prevent incorrect assembly;

b) the inlet and outlet, if gas-specific;

c) the **maximum fill volume** level on the **liquid container** of the **nebulizer**.

5.2.2 Marking of the controls and instruments

If applicable, controls and instruments shall be legibly marked as

a) the gas supply pressures, in kilopascals (kPa),

b) the pressures in breathing systems, in hectopascals (hPa),

c) the flows, in litres per minute (l/min),

d) if supplied, the air entrainment/oxygen dilution valves, in percent oxygen (% O_2), and

e) the power and/or control devices marked with the relevant symbols.

Compliance is checked by inspection. All displayed qualitative or quantitative information, values, functions, and/or markings shall be discernible or identifiable to an OPERATOR with 6-6 (20/20) vision (corrected, if necessary) from a distance of 1 m at a light level of 215 lx, when viewing the information, markings, etc., perpendicular to and including 15° above, below, left, and right of the normal line of sight of the OPERATOR. See IEC 60601-1, 7.1.2 and 7.1.3.

5.3 Labelling on the packaging or individual pack

The following shall be labelled on the packaging or individual pack:

a) the name or trademark and address of the manufacturer;

b) the device identification and content information;

c) the batch code, preceded by the word "LOT" or serial number;

d) the word "STERILE", if appropriate (It is recommended that the method of sterilization be given.);

e) if applicable, an indication that the device is for single use;

NOTE The manufacturer's attention is drawn to the regulatory provision, requiring that the indication of single use be consistent across the European Community.

f) the device packaging and/or labelling to differentiate between the same or similar products, both sterile and non-sterile, placed on the market by the same manufacturer;

g) the expiry date, expressed as the year and month, if the device is sensitive to storage or shelf life;

h) any special storage and/or handling conditions;

i) any warning and/or precaution (e.g. compatibility with the use of oxygen mixtures and compatibility between oxygen and administered drugs);

j) for packages containing parts made of antistatic or conductive material, the word "ANTISTATIC" or "CONDUCTIVE";

k) if natural rubber latex is incorporated in parts of the medical devices that come directly or indirectly into contact with the patient, the device shall be labelled accordingly;

l) if phthalates are incorporated in parts of the medical devices that come directly or indirectly into contact with the patient, the device shall be labelled accordingly;

m) for **nebulizing systems** intended to be connected to an electrical power source, the nominal power expressed in Watts (W) or kilowatts (kW), as appropriate;

n) for **nebulizing systems** intended to be connected to the supply mains, the rated supply voltage(s) or rated voltage range(s) to which they can be connected, expressed in Volts (V).

Compliance is checked by inspection.

5.4 Instructions for use, inserts, and accompanying documents

Nebulizers, **nebulizing systems**, and components shall be accompanied by instructions for use, inserts, or accompanying documents that include:

5.4.1 General information

a) the date of issue or the date of latest revision of the instructions, inserts, or accompanying documents;

b) the name or trademark and address of the manufacturer;

c) for devices imported into the European Union, the name and address of the person responsible and of the authorized representative of the manufacturer established within the European Community;

d) the purpose and the intended use of the device and parts thereof, as determined by the manufacturer, including the power and/or control devices;

EXAMPLE Intended use categories include, but are not limited to:

— patient populations,

— environment of use,

— single-use disposable,

— single-patient reuse, and

— multi-patient reuse.

e) if applicable, the interdependence of controls;

f) a statement that the **nebulizing system** is or is not suitable for use in a anaesthetic breathing system or a ventilator breathing system, see References [26] and [27];

g) *if applicable, the maximum temperature above ambient reached in the nebulizing chamber under all operating conditions;

h) the types of liquid (e.g. solution, suspension, and/or emulsion) the device is designed to nebulize;

i) the **maximum fill volume** level, as marked on the **liquid container** of the **nebulizer**;

j) if appropriate, the recommended fill volume for use;

k) if handheld, an indication of the spatial orientation (e.g. vertical, horizontal, inverted) at which the **nebulizer** functions as intended;

l) a statement that using a solution, suspension, or emulsion different from that recommended by the manufacturer, in particular, a suspension and/or high-viscosity solution, can alter the particle size distribution curve, the **mass median aerodynamic diameter (MMAD)**, **aerosol output**, and/or **aerosol output rate**, which can then be different from those disclosed by the manufacturer;

m) a statement that **nebulizing systems** intended to be connected to a power source (electrical or pneumatic) shall be disconnected from the power source after use;

n) the mass of the most usual configuration, in kilograms (kg).

5.4.2 Performance disclosures

a) a statement to the effect that the following disclosures for **nebulizer** performance are based upon testing that utilizes adult ventilatory patterns and are likely to be different from those stated for paediatric or infant populations;

b) the distribution of particles, in terms of percent of sampled mass, within each of the following size ranges: % >5 µm, % 2 µm to 5 µm, and % <2 µm when tested in accordance with Annex D;

c) the **mass median aerodynamic diameter (MMAD)** and the geometric standard deviation (GSD) only if the distribution is unimodal and log-normal, as derived from the particle size distribution curve, when tested in accordance with Annex D;

d) the **respirable fraction** performance of the nebulizer, when tested in accordance with Annex D;

e) the **aerosol output** and **aerosol output rate** at the fill volume recommended by the manufacturer or 2 ml if a recommended fill volume is not provided, expressed as the mass of test substance collected and the mass of test substance collected per minute, when tested in accordance with Annex C;

f) for **gas-powered nebulizers**, the **aerosol output** and **aerosol output rate** at the minimum, nominal, and maximum driving gas flows with the corresponding pressures, when tested in accordance with Annex C;

g) the **percentage of fill volume emitted** per minute (e.g. 20 % of fill volume per minute) as the **aerosol output** in one minute divided by the fill volume recommended by the manufacturer or 2 ml if no fill volume is recommended, when tested in accordance with Annex C;

h) for **gas-powered nebulizers**, the **percentage of fill volume emitted** and **percentage of fill volume emitted** per minute at the minimum, nominal, and maximum driving gas flows with the corresponding pressures, when tested in accordance with Annex C;

i) the **residual volume** (in millilitres), when tested in accordance with Annex C;

NOTE **Aerosol output** fraction can then be calculated as the **aerosol output** divided by the mass (weight) of the liquid placed in the **nebulizer**.

j) the **test solution** used to carry out the **nebulizer** performance type-tests in Annexes C and D;

k) *if alternative test methods or **test solutions** have been used to demonstrate **nebulizer** performance, a demonstration of equivalency shall be included in the technical documentation of the manufacturer and shall be made available upon request;

l) for a **breath-actuated nebulizer**, the method of operation and relevant sensitivity;

m) *the maximum A-weighted sound pressure level, as derived from the test method in 9.6.2.1 of IEC 60601-1:2005;

n) for **nebulizers** intended for use with ventilators, a statement to the effect that the measured **aerosol output** and **aerosol output rate** are not intended to be used as basis to determine the correct dosage and that the **aerosol output** can differ when the nebulizer is used in combination with a ventilator.

5.4.3 Driving gas supply information

a) the recommended driving gas(es);

b) the minimum and maximum recommended driving gas pressures and flows;

c) the pressure and flow characteristics of any gas power outlet under the worst-case conditions stated by the manufacturer;

d) if applicable, a warning that oxygen or oxygen mixtures (O_2 > 23 %) should not be used as driving gas;[36]

e) if applicable, a statement of the composition and dryness specification for all gases to be supplied to the **nebulizer**;

f) the service lifetime of the reusable parts.