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Anaesthetic and respiratory equipment — Nebulizing systems and components

Matériel d'anesthésie et de réanimation respiratoire — Systèmes de nébulisation et leurs 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 of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 121, *Anaesthetic and respiratory equipment*, Subcommittee SC 2, *Airways and related equipment*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 215, *Respiratory and anaesthetic equipment,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces the third edition (ISO 27427:2013), which has been technically revised.

The main changes are as follows:

— Alignment with the general standard for airway devices, ISO 18190;

— updating of references.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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 are 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* is specified by the manufacturer and in the accompanying documentation.

This document 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 document 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.

This document is written following the format of ISO 18190, which is the general standard for airways and related *equipment.* The requirements in this device-specific standard take precedence over any conflicting requirements in ISO 18190.

Anaesthetic and respiratory equipment — Nebulizing systems and components

1 Scope

This document 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 document 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 document does not specify the electrical requirements of *electrically powered nebulizers*.

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

This document does not apply to:

a) devices intended for nasal deposition;

b) devices intended solely to provide humidification or hydration by providing water in *aerosol* form.

NOTE 1 ISO 80601-2-74 and ISO 20789 cover these devices.

c) drug-specific *nebulizers* or their components (e.g. metered dose inhalers, metered liquid inhalers, dry powder inhalers).

NOTE 2 ISO 20072 covers these devices.

NOTE 3 See Annex A for rationale.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. 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 7396-1, *Medical gas pipeline systems — Part 1: Pipeline systems for compressed medical gases and vacuum*

ISO 18190:2016, *Anaesthetic and respiratory equipment — General requirements for airways and related equipment*

ISO 18562-1, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 1: Evaluation and testing within a risk management process*

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

ISO 80369-2, *Small-bore connectors for liquids and gases in healthcare applications — Part 2: Connectors for breathing systems and driving gases applications*

3 Terms and definitions

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

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

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

3.3
aerosol outlet port
outlet of the *nebulizing system* through which the *aerosol* is emitted

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
parts, 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, 9.3.2 j) and k), Annex C, and Annex D.

3.19
test substance
active ingredient contained in the *test solution*

4 General requirements and requirements for test

4.1 General

ISO 18190:2016, Clause 4 applies.

NOTE See Annex E for a list of hazards than can be used as guidance in risk assessment.

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.

Check conformance by inspection of the technical file/documentation.

4.2.1.2 The type-test methods shall use a *test solution* of albuterol 0,1 % (mass/mass or volume/volume (m/m or V/V)) concentration in 0,9 % sodium chloride solution or 2,5 % (m/m OR V/V) sodium fluoride in distilled water with the provision that its use is declared in the accompanying documents. See 9.3.2 j).

Check conformance by inspection of the technical file/documentation and the accompanying documents.

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, provided that any:

a) alternative test methods are validated against the test methods in Annexes C and D to demonstrate equivalency and that

b) the demonstration of equivalency is included in the technical documentation of the manufacturer.

Check conformance by inspection of the technical file/documentation.

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.

5 Materials

5.1 General

ISO 18190:2016, Clause 5 applies.

5.2 Biocompatibility

Materials used to manufacture *nebulizing systems* shall be evaluated for biocompatibility. The breathing gas pathways shall be evaluated for biocompatibility as specified in ISO 18562-1 and tested as appropriate.

Check conformance by inspection of the technical file/documentation.

6 Design Requirements

6.1 General

ISO 18190:2016, Clause 6 applies.

6.2 Inlet and outlet ports

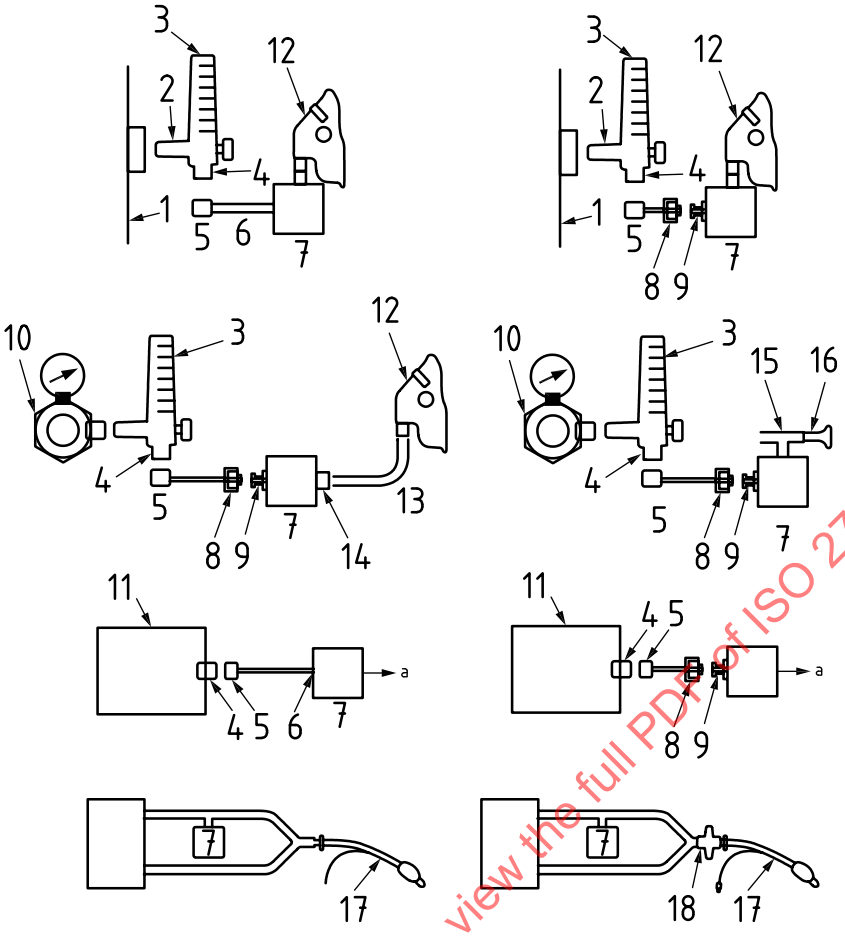
6.2.1 Inlet ports

The driving gas inlet port of a *nebulizing system* shall be compatible with the gas delivery system to which it is intended to be connected and shall be one of the following (see Figure 1):

a) a socket R2 connector conforming to ISO 80369-2; or

b) permanently attached (i.e. not removable without the use of a tool).

Check conformance by inspection of the technical file/documentation.



Key

1	terminal unit conforming to ISO 9170-1
2	probe, conforming to ISO 9170-1
3	flow meter conforming to ISO 15002
4	body of 9/16 UNF DISS connector conforming to CGA V-5-2008, or body of 3/4 UNF DISS connector conforming to CGA V-5-2008 or a nipple conforming to ISO 17256
5	9/16-18UNF-2A-RH socket connector conforming to CGA V-5-2008 or 3/4-16UNF-2A-RH socket connector conforming to CGA V-5-2008 or a funnel conforming to ISO 17256
6	permanently attached
7	nebulizer
8	cone R2 connector conforming to ISO 80369-2
9	socket R2 connector conforming to ISO 80369-2
10	pressure regulator conforming to ISO 10524-1
11	compressor conforming to this document (ISO 27427)
12	aerosol mask vented
13	breathing tube conforming to ISO 5367
14	connector conforming to ISO 5356-1
15	T-piece with connectors conforming to ISO 5356-1
16	mouthpiece
17	tracheal tube conforming to ISO 5361
18	HME conforming to ISO 9360-1
a	To the patient.

Figure 1 — Examples of inlet and outlet ports for *nebulizer systems*

6.2.2 Outlet port

6.2.2.1 If intended for use in breathing systems, the *aerosol outlet port* shall conform to ISO 5356-1.

Check conformance by inspection of the technical file/documentation.

6.2.2.2 If not intended for use in breathing systems, the *aerosol outlet port* shall not misconnect with connectors conforming to ISO 5356-1, or ISO 80369-1.

Check conformance by inspection of the technical file/documentation.

6.3 Flow-direction-sensitive components

Any flow-direction-sensitive, operator-detachable component shall be designed so that it cannot be fitted in such a way as to present a hazard to the patient.

Check conformance by functional testing.

6.4 Cleaning and disinfection or sterilization

Nebulizing systems and components intended for reuse shall be constructed so as to enable dismantling for cleaning and disinfection or sterilization.

NOTE See also ISO 17664 -1.

Check conformance by testing the disassembly/assembly procedure according to the manufacturer's instructions.

6.5 Rotary controls

The manufacturer should ensure consistency regarding the direction of movement of rotary controls of the device.

7 Requirement for *nebulizing systems* and components supplied sterile

ISO 18190:2016, Clause 7 applies.

8 Packaging

ISO 18190:2016, Clause 8 applies.

9 Information supplied by the manufacturer

9.1 General

ISO 18190:2016, Clause 9 applies.

9.2 Marking

9.2.1 General

9.2.1.1 Marking shall be durable following exposure to typical substances in contact during its intended use and remain legible for the intended duration of use.

NOTE The durability requirements for markings that are exposed to saliva or mucus over a prolonged period differ from the durability requirements for markings that are not exposed to prolonged exposure. Also, certain markings might not be exposed to saliva or mucus but can come in intermittent contact with the skin oil.

Check compliance by exposing the appropriate marking areas of the product to the applicable substances listed for a cumulative duration of time equivalent to the expected exposure duration in use:

— Drugs or chemicals which will contact the product in use and are listed in the Instructions for Use (IFU).

— If applicable, artificial saliva

— If applicable, artificial mucus

— If applicable, artificial skin oil

9.2.1.2 Marking shall be legible after cleaning to the manufacturer's instructions.

9.2.2 Marking of the *nebulizing system*:

The following shall be marked either on the *nebulizer* or its components as applicable:

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;

NOTE See 6.3 Flow-direction sensitive components

b) the *maximum fill volume* on the *liquid container*.

If applicable, controls and instruments shall be legibly marked with:

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

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

c) the flow in litres per minute (l/min);

d) the air entrainment/oxygen dilution valves, in percent oxygen (% O_2);

and

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

Check conformance by inspection.

9.2.3 Marking on the packaging or individual pack

In addition to the marking requirements specified in 9.2, the packaging or individual pack shall:

a) differentiate between the same or similar products, both sterile and non-sterile, placed on the market by the same manufacturer;

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

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

Check conformance by inspection.

9.3 Instructions for use

9.3.1 General information

In addition to the marking requirements specified in 9.2, components of *nebulizing systems*, shall be accompanied by instructions for use, inserts, or accompanying documents that include:

a) a statement that the *nebulizing system* is or is not suitable for use in an anaesthetic breathing system or a ventilator breathing system. See ISO 80601-2-12 and ISO 80601-2-13;

b) if applicable, the maximum temperature above ambient reached in the liquid chamber under all operating conditions;

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

d) the *maximum fill volume*;

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

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

g) a warning to the effect 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;

h) 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;

i) the mass of the *nebulizer system* in kilograms (kg);

j) the expected service lifetime of the reusable parts.

9.3.2 Performance disclosures

a) a statement to the effect that the following disclosures for 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 as outlined in Annex B 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 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 *breath-actuated nebulizers*, the method of operation and relevant sensitivity;

m) the maximum A-weighted sound pressure level, as derived from the test method in IEC 60601-1:2005+AMD1:2012+AMD2:2020, 9.6.2.1;

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 the basis to determine the correct dosage and that the *aerosol output* can differ when the *nebulizer* is used in combination with a ventilator.

9.3.3 Driving gas supply information

a) the recommended driving gas(es);

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

c) if applicable, a warning that oxygen or oxygen mixtures (with the O_2 > 23 %) should not be used as the driving gas[19];

d) if applicable, the composition and dryness specification for all gases to be supplied to the *nebulizer*;

Annex A
(informative)

Rationale

A.1 General

This annex provides a concise rationale for the important requirements of this document and is intended for use by those who are familiar with the subject of this document but who have not participated in its development. An understanding of the reasons for the main requirements is considered essential for its proper application. Furthermore, as clinical practices and technologies change, it is believed that rationales for the present requirements will facilitate any revisions of this document necessitated by those developments.

A.2 Rationale for Clause 1 — Scope

The essence of this document is to describe the characteristics and requirements of a general-purpose *nebulizer* that can be used with a variety of medicinal substances. It is expected that the selection of the *nebulizer* will be based on the requirements and characteristics developed in this document and declared in the manufacturer's instructions for use.

Nasal deposition devices are excluded, as they are not considered general-purpose *nebulizers*.

There can be times when a device falls under the scope of either this document or ISO 20072. The committee envisioned that the intended use of the product and the risk assessment of the device will determine which standard the manufacturer chooses to qualify the device.

General-purpose *nebulizers* are considered to be semi-critical devices. Semi-critical devices are devices that contact intact mucous membranes or non-intact skin. They do not ordinarily penetrate tissues or otherwise enter normally sterile areas of the body. These devices should be reprocessed to be free from all microorganisms.

A.3 Rationale for *aerosol outlet port* (3.3)

Mass is directly traceable to the active ingredient which is the fundamental deliverable. Volume is a secondary measure because it is dependent on evaporation (see A.4).

A.4 Rationale for *aerosol output rate* (3.4)

The *aerosol output rate* can be greatly influenced by the evaporation of the *aerosol* droplets. The following is provided to explain the sources and types of evaporation associated with nebulized *aerosol*:

Type 1 evaporation: Evaporation inside jet *nebulizers*. Compressed air (which is dry and on re-expansion to atmosphere is always dry) draws up and mixes with *nebulizer liquid container* solution sprayed within the *nebulizer*. The residence time of the de-compressed air (flow e.g. 6 l/min or 0,1 l/s) within the *nebulizer* (internal volume, approximately 100 ml) is short (around 1/10 of a second). Even so, the massive wet surface area of *aerosol* and rapid evaporation of solvent to the decompressed air ensures that the air leaving the *nebulizer* is nearly saturated with water vapour (approximately 100 %). Further, because of the latent heat lost to evaporation, the *nebulizer liquid container* cools relative to its initial ambient temperature (from 20 °C to approximately 10 °C) and the *aerosol*-laden air leaves the *nebulizer* in this cooled state. In this cooled saturated air cloud, the nebulized *aerosol* is stable until it either mixes with ambient air (see Type 2 evaporation) or increases in temperature (see Type 3 evaporation).

Type 2 evaporation: Evaporation of nebulized *aerosol* solvent when mixed with ambient air. Nebulized *aerosol* leaving a jet or ultrasonic *nebulizer* exists in a cloud of 100 % relative humidity (RH) air. This *aerosol* cloud is relatively stable with regard to evaporation until it mixes with ambient air. Mixing is inherent in the design of constant output *nebulizers* where the nebulized *aerosol* is emitted into a T-piece where the patient's inhalation flow causes ambient air at lower humidity to be drawn into the T-piece. The ambient air mixes with the nebulized *aerosol*-laden air and temporarily reduces the relative humidity. The relative humidity quickly rises to 100 % by evaporation of water from the nebulized *aerosol.* This evaporation effectively occurs in milliseconds, or using another reference, this evaporation happens by the time the *aerosol* passes through the T-piece and tubing and exits from the *nebulizer* (or very shortly thereafter). Of course, this volume loss implies that the size distribution of the nebulized *aerosol* has shifted downwards. Further, this shift could not be constant, as smaller droplets have the propensity to evaporate more readily than larger ones, so the distribution shift is not homogenous. In any case, after the nebulized *aerosol* gives up solvent to re-saturate the air, the nebulized *aerosol* is again stable. It is important to note that this form of evaporation is a feature of constant output *nebulizers* and not "breath-enhanced *nebulizers*" whose design causes entrained ambient air to draw solvent vapour from the *nebulizer liquid container*. For constant output *nebulizers*, the drier the ambient air, the greater the effect of evaporation on the nebulized *aerosol*. Further, the lower the rate of *aerosol output* relative to the flow of ambient air, the greater the effect of this evaporation on the nebulized *aerosol.*

Type 3 evaporation: Evaporation of nebulized *aerosol* solvent within a cascade impactor. Nebulized *aerosol*, after mixing with ambient air, equilibrates to 100 % RH and is relatively stable. However, it is cool (e.g. 10 °C) due to the latent heat of evaporation. The cool stable nebulized *aerosol* passes into a cascade impactor. If the cascade impactor is at ambient temperature (e.g. 20 °C), the cooled air is in contact with the cascade, which can act like a kind of radiator warming up the nebulized *aerosol*-laden air. As the air warms up and travels through the cascade, the capacity of the warmer air to hold moisture increases. In order to maintain 100 % RH, further evaporation occurs from the nebulized *aerosol* during its flight through the cascade. As with the type 2 evaporation, the smaller the size of the particles in the nebulized *aerosol*, the more significant the losses and the greater the size change.[24]

A.5 Rationale for *percentage of fill volume emitted* (3.15)

The *percentage of fill volume emitted* is an important value to be disclosed to the user, because it can influence the decisions of dosage intended for delivery in terms related to the expected amount of drug given to the patient.

The *percentage of fill volume emitted* per minute, when expressed as a rate, is an important value to disclose to the user, because it can influence the decisions of dosage intended for delivery in terms related to the expected duration of the therapy.

A.6 Rationale for *residual volume* (3.16)

The *residual volume* is an important value to disclose to the user because it can influence the decisions on the dosage intended for delivery.

A.7 Rationale for *respirable fraction* (3.17)

The *respirable fraction* was harmonized with the European Pharmacopoeia, Chapter 2.9.18.[21] The *respirable fraction* is an important parameter because, along with the *aerosol output*, it gives a single physical characteristic that allows the comparison of the performance of *nebulizing systems*.

A.8 Rationale for *test solution* (3.18)

The *test solution* is used throughout the type-test requirements and Annex test methods to allow flexibility, if permitted by a local competent authority, in the use of alternative aqueous solution media to characterize *nebulizer* performance. Some of the alternative aqueous solutions cost less and can be analysed using simpler means (e.g. electrochemistry, conductivity, etc.).

A.9 Rationale for type-test methods, representative samples (4.2.1.1)

Testing to verify performance specifications that characterize the intersample and intrasample variability in terms of particle specifications would also be beneficial. See ISO 20072:2009, 6.1.

A.10 Rationale for test solutions (4.2.1.2)

The use of sodium fluoride rather than albuterol as the *test substance* is recommended as it is considered to provide more comparable outcomes. Albuterol (also known as salbutamol) can be difficult to obtain in some countries.

US FDA 1993 guidance states that testing should be conducted on drugs from three of the following drug classes: beta-agonist bronchodilators, anticholinergic bronchodilators, steroids, antiallergics, mucokinetic agents, and anti-inflammatories. While other drugs can be appropriate, testing with ipatropium bromide (anti-cholinergic bronchodilator), albuterol (beta-agonist bronchodilator) and cromolyn sodium (anti-inflammatory) is suggested[22].

A.11 Rationale for alternative test methods (4.2.2)

Various methods for presenting *aerosol output* and particle size distribution of *nebulizers* are in use (see Annex B).

A.12 Rationale for small-bore connectors [6.2.1 d)]

The ISO 80369 series of small-bore connectors has been developed to prevent misconnections between devices of varying applications that previously used Luer connectors. ISO 80369-2 includes two connectors for respiratory applications: the R1 for low pressure devices such as breathing systems and the R2 for high pressure devices such as respiratory therapy equipment including *nebulizers*.

The standard for respiratory tubing and connectors, ISO 17256, has mandated a cone R2 respiratory connector at the outlet of the tubing. *Nebulizers* designed to be driven by gas using this therapy tubing must therefore be equipped with a socket R2 respiratory connector as specified in 6.2.1 e).

A.13 Rationale for maximum temperature of the *liquid container* [9.3.1 b)]

Disclosure of the maximum temperature of the *liquid container* is important because certain active ingredients, such as nebulized proteins or DNA components, can be sensitive to temperature and degrade within the *liquid container*[23].

A.14 Rationale for alternative test methods [9.3.2 k)]

Alternative test methods, such as laser diffractometry, electrochemistry,[24] high-performance liquid chromatography (HPLC), or spectrophotometry,[25] can be used for the repeated performance assessment, once these methods have been validated against the cascade impaction method during the initial testing.

A.15 Rationale for sound pressure levels [9.3.2 m)]

See also information and alternative test methods in ISO 3744 and IEC 61672-1.

A.16 Rationale for test principle C.1

A treatment session using a *nebulizer* requires the patient to breathe in and out of the *nebulizer* for a duration of approximately 5 min to 15 min (depending on the medication used) while the *nebulizer* is

running. During this time, the *nebulizer* is continuously producing *aerosol*. When the patient inhales *aerosol*, it is taken up in the lungs. However, when the patient exhales, some *aerosol* is driven out of the *nebulizer* and lost. Thus, only a certain fraction of *aerosol* produced by the *nebulizer* can be taken up by the patient. The test described in this Clause collects the *aerosol* exiting at the *nebulizer* mouthpiece while the *nebulizer* is subjected to a simulated breathing pattern. The mass of the collected albuterol is extracted and measured. The volume of *aerosol* delivered is calculated and expressed as *aerosol output rate* in millilitres of *test solution* 0,1 % (m/m or V/V) per minute.

A.17 Rationale for test conditions C.2

The committee chose these conditions to represent the conditions affecting the majority of general *nebulizers* and cannot represent the use of *nebulizers* within breathing systems, where higher temperatures, pressures, and humidity can affect the *nebulizer* performance.

A.18 Rationale for test equipement C.3

A breathing simulator is used when determining the *aerosol output* from a *nebulizer* in order to reasonably estimate the mass of aerosolized active pharmaceutical ingredient provided at the outlet of the *nebulizing system* under simulated conditions of breathing. For *nebulizers* intended for use over wide patient populations, it could be useful to analyse multiple breathing patterns associated with different patient populations[26].

A.19 Rationale for test method C.4

Measurements of mass rather than volume alone correct for evaporative losses.

A.20 Rationale for test principle D.1

A continuous suction pump is used for nebulized *aerosol* size testing because impactors for performing these measurements need to operate at a constant “inhalation” flow rate to reasonably estimate *aerosol* size.

Annex B
(informative)

Diameters of *respirable fraction* particles

In general, it is considered that *aerosol* particles with an aerodynamic diameter of

— >5 µm are deposited in the upper airways,

— 2 µm to 5 µm are deposited in the lower airways, and

— <2 µm are deposited in the alveoli[27][28].

Aerosol particle sizing can be defined in terms of *mass median aerodynamic diameter (MMAD)* and geometric standard deviation (GSD). These values can be interpolated from the cumulative particle size distribution curve as follows.

MMAD: Note the particle size at which the line crosses the 50 % mark.

GSD: This should be calculated only if the particle size distribution curve is reasonably straight between 10 % and 90 %, showing that the *aerosol* is log-normally distributed. Where a straight line is a good fit to the data, the calculation of GSD is performed by noting the particle size X at which the line crosses the 84,13 % mark and the particle size Y at which the line crosses the 15,87 % mark.

Then, the GSD = $(X/Y)^{0,5}$.

Methods of deriving information from data that are based on interpolation from a graph are inevitably subject to some degree of approximation.

Rigorous mathematical methods of analysis are described in ISO 9276-1 and ISO 9276-2. These methods are readily performed by a computer, including the generation of the particle size distribution graph.

Annex C
(normative)

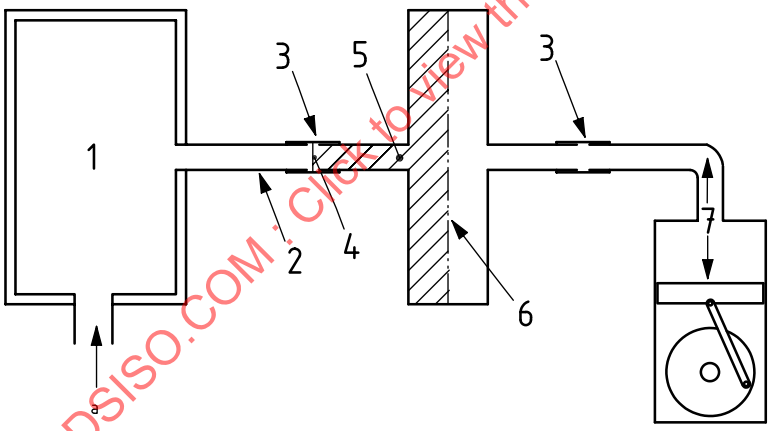
Test methods for *aerosol output* and *aerosol output rate*

C.1 Test principle

The *nebulizer* is filled with the required volume of *test solution*, connected to a breathing simulator (e.g. a sine-wave pump or volumetric ventilator that creates a sinusoidal waveform) to simulate respiratory flow (see Figure C.1). During operation of the *nebulizer*, the *aerosol* emitted at the patient interface is collected on a filter. This filter can be extracted to analyse the mass of the collected test substance using an appropriately validated analytical method [high-performance liquid chromatography (HPLC), UV-spectroscopy, gravimetric or electrochemical analysis, or other].[29][20][24][25]

During the experiment, the nebulization is conducted for a known time (e.g. 1 min), after which the filter is exchanged and analysed. Dividing the mass of test substance by this time gives the *aerosol output rate*.

The experiment is then continued to collect the total mass of test substance emitted at the *aerosol outlet port*. Collection filters can be replaced several times to avoid saturation of the filter. At the end of the nebulization, the *aerosol output* is determined by adding up the results from all collection filters.



Key

1 *nebulizing system* filled with *test solution* and (if required) an inlet for entrained ambient air or exhaust gases
2 connection to the *aerosol outlet port*
3 dismountable connectors
4 *aerosol outlet port*
5 dead space
6 collection filter
7 breathing simulator
a Inlet for driving gas.

Figure C.1 — Schematic diagram showing the equipment for testing the *aerosol output* and *aerosol output rate*

C.2 Test conditions

The ambient test conditions shall be:

— temperature: (23 ± 2) °C;

— relative humidity: 45 % to 75 %;

— pressure: from 86,0 kPa to 106,0 kPa (i.e. absolute atmospheric pressure).

C.3 Test equipment

The test equipment (see the schematic diagram in Figure C.1) shall comprise:

— the *nebulizing system* under test;

NOTE 1 The *nebulizing system* under test can be connected to a patient interface component (e.g. a mouthpiece or facemask). The dismountable connector (3 in Figure C.1), at the inlet to the filter holder, provides a matching adaptor to make a leak-free joint.

— a *test solution* of albuterol 0,1 % (m/m or V/V) concentration in 0,9 % sodium chloride solution or, if allowed or required by local competent authorities, 2,5 % (m/m or V/V) sodium fluoride in distilled water, with the provision that its use is declared in the accompanying documents [see 9.3.2 k)];

— a filter holder;

— a breathing system filter conforming to ISO 23328-1 with a filtration efficiency of >98 % of particles less than 10 µm;

— a breathing simulator (e.g. a sine-wave pump or volumetric ventilator that creates a sinusoidal waveform to simulate respiratory flow, or for infants a 40:60 pattern), which creates a cycle of frequency, f, = 15 breaths/min; I/E ratio = 1:1; and tidal volume (V_t) = 500 ml measured at the outlet of the filter;

— a dead space (between the *aerosol outlet port* and the filtering surface) of 10 % or less of the tidal volume;

— for *gas-powered nebulizers*, a driving gas of medical air as defined in ISO 7396-1, unless the *nebulizer* is designed to be powered exclusively by a compressor, at ambient conditions described in C.2, and driven by the gas at the flow rate recommended by the manufacturer;

— a means of extracting the *test substance* from filters and other components and quantitative analysis apparatus calibrated to an accuracy of ±5 % of reading.

NOTE 2 The quantitative analysis apparatus is validated and can include high-performance liquid chromatography (HPLC), UV spectroscopy, gravimetric, or electrochemical analysers.[29][24][25]

C.4 Test method

a) Pre-weigh the *nebulizing system* before filling with the *test solution*.

b) Stabilize all parts of the *nebulizer system*, fluids, and test equipment at the ambient conditions, as described in C.2, before use.

c) Perform the test with the *nebulizer* filled with *test solution* to the fill volume recommended by the manufacturer or 2 ml if no fill volume is recommended.

d) By means of a dismountable connector, connect the *aerosol outlet port* to the filter and its holder, and the latter to the breathing simulator (sine pump), as shown in Figure C.1.

e) Switch on the breathing simulator and, 10 s later, the *nebulizer*.

f) Run the *nebulizer* for (60 ± 1) s, switch off the *nebulizer* and, 5 s later, the pump.

g) Dismantle the filter, the filter holder, and the dismountable connectors from the *aerosol outlet port* to the filter holder.

h) Extract and measure the mass of *test substance* in the components downstream of the *aerosol outlet port*, including the filter, and use this result to calculate the *aerosol output rate*.

i) Assemble a new filter and its holder and continue the experiment until the end of nebulization to measure the total *aerosol output*. The end of nebulization, for *gas-powered nebulizers*, is 1 min after the beginning of sputtering, and for *electrically-powered nebulizers*, the end of the operation, as specified by the manufacturer.

j) Stop the nebulization and re-weigh the *nebulizing system*.

k) *Residual volume* is calculated by subtracting the initial dry weight from the final weight of the *nebulizing system* and multiplying this mass by the specific gravity of the *test solution*.

l) All type-test methods shall be performed on at least three representative test devices. See 4.2.1.1.

C.5 Test results

The test results shall include:

a) for a *gas-powered nebulizer*, the test gas employed;

b) the *test solution*;

c) the *filling volume* and flow rate used;

d) the *aerosol output*, expressed as the mass of test substance collected on the filter(s);

e) the *aerosol output rate*, expressed as the mass of *test substance* collected on the filter(s) per minute;

f) nebulization time;

g) *residual volume*;

h) the *percentage of fill volume emitted* in 1 min, expressed as the *aerosol output* in 1 min divided by the fill volume recommended by the manufacturer or 2 ml if no fill volume is recommended (e.g. 20 % of fill volume per minute).

NOTE *Aerosol output* is directly measured as the mass of *test substance* by the test lab and can be converted to % of total mass loaded into the *nebulizer* for the disclosure of the results [see also 9.3.2 e)]. Likewise, *aerosol output rate* is directly measured as the mass of *test substance* per minute and can be converted to ml/min for disclosure, while *percentage of fill volume emitted* in 1 min or %/min expresses *aerosol output rate* as a percentage of the fill volume recommended by the manufacturer or 2 ml if no fill volume is recommended.

Annex D
(normative)

Test methods for particle sizing

D.1 Test principle

The *nebulizing system* is tested for particle size by capturing the *aerosol output* in a cascade impactor driven by air and analysing the results.

Two different sets of test equipment and test methods are described that allow the use of either

— a high-flow cascade impactor (calibrated at 15 l/m), or

— a low-flow cascade impactor (calibrated at flows less than 15 l/m).

The two test methods differ in the use of a T-piece and/or air entrainment port that serves as a means to allow more gas to be emitted by the *nebulizer* than that which is drawn into the cascade impactor. Test conditions, calculations, and expressions of test results are otherwise identical between the two methods.

NOTE Several types of cascade impactors are available (e.g. Marple, Anderson, and Next Generation Impactor (NGI™[1)]).

D.2 Test conditions for all test methods

The ambient test conditions for all tests shall be:

— temperature: (23 ± 2) °C;

— relative humidity: 45 % to 75 %;

— pressure: from 86,0 kPa to 106,0 kPa.

D.3 Test using a cascade impactor calibrated and operating at 15 l/min

D.3.1 Test equipment

The test equipment (see the schematic diagram in Figure D.1) shall comprise:

a) the *nebulizing system* under test;

b) a cascade impactor:

1) with at least eight stages to estimate the *respirable fraction*;

2) with sufficient loading capacity on each stage to estimate the *respirable fraction* without overloading any stage;

3) with no measurable heat transfer-related droplet evaporation;

NOTE 1 The impactor can be chilled to avoid this cause of inaccuracy.

1) NGI™ is the trademark of a product supplied by MSP Corporation, Shoreview, MN, USA. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named. Equivalent products may be used if they can be shown to lead to the same results.

4) calibrated at a flow of 15 l/min, either by the manufacturer or the user, and specifying:

— a D_{50} [the aerodynamic diameter of a particle having a 50 % probability of impacting on the collection stage, also called the effective cut-off diameter (ECD)];

— a D_{84} (the aerodynamic diameter of a particle having an 84 % probability of impacting on the collection stage) that is less than 1,3 × D_{50};

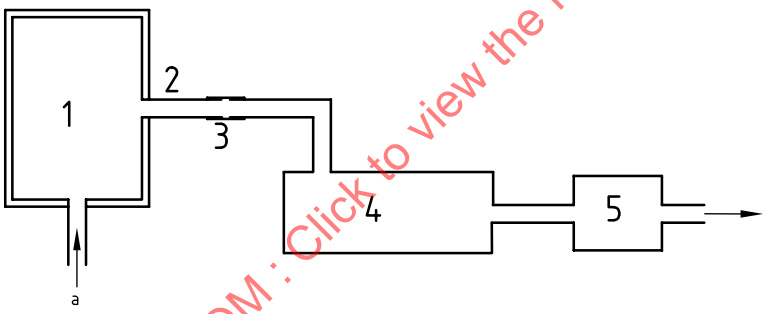
— a D_{16} (the aerodynamic diameter of a particle having a 16 % probability of impacting on the collection stage) that is greater than 0,77 × D_{50};

NOTE 2 Selection of the cut points (i.e. D_{50}) for the impactor includes at least two stages with D_{50}s greater than the *MMAD* of the *aerosol* from the *nebulizer* and two stages with D_{50}s less than the *MMAD* of the *aerosol* from the *nebulizer*.

c) a sampling pump and adjustable flowmeter capable of drawing air through the cascade impactor at a flow of 15 l/min;

d) a *test solution* (at stabilized temperature) of albuterol 0,1 % (m/m or V/V) concentration in 0,9 % sodium chloride solution or, if allowed or required by local competent authorities, 2,5 % (m/m or V/V) sodium fluoride in distilled water, with the provision that its use is declared in the accompanying documents. See 9.3.2 k);

e) for *gas-powered nebulizers*, a driving gas of medical air as defined in ISO 7396-1, unless the *nebulizer* is designed to be powered exclusively by a compressor, at ambient conditions described in C.2, and driven by the gas at the flow rate recommended by the manufacturer.



Key

1 *nebulizing system* filled with *test solution* with an entrained ambient air inlet (i.e. T-piece), if required
2 *aerosol outlet port*
3 dismountable connector
4 cascade impactor
5 sampling pump
a Inlet for driving gas.

Figure D.1 — Schematic diagram showing the equipment for testing the particle sizes

D.3.2 Test method

D.3.2.1 The *nebulizer* is filled with the *test solution* to the fill volume recommended by the manufacturer or 2 ml if no fill volume is recommended and connected to the test compressor or air supply in accordance with the manufacturer's instructions.

D.3.2.2 The cascade impactor is dismantled, cleaned (e.g. with distilled water, wiped and allowed to air dry), and reassembled, incorporating all the stages of impaction surfaces in accordance with the manufacturer's instructions.

D.3.2.3 Readily dismountable connectors are attached between the *nebulizer aerosol outlet port* and the inlet of the connector attached to the cascade impactor.

D.3.2.4 If required, an absolute filter is connected between the outlet of the cascade impactor (4 in Figure D.1) and the sampling pump (5 in Figure D.1), to prevent fine *aerosol* droplets from entering the sampling pump.

D.3.2.5 The flow of the sampling pump is set to (15 ± 5 %) l/min.

NOTE 1 During testing, the *nebulizer* and the cascade impactor are secured in the position specified by the manufacturer.

NOTE 2 Care should be taken to prevent vibration of the impactor and to minimize perturbation of flow through the test apparatus.

D.3.2.6 The sampling pump is turned on and allowed to stabilize at the required flow.

D.3.2.7 The *nebulizer* is started.

D.3.2.8 Sampling times can be varied for different *nebulizers* to allow for maximum deposition on each stage without overloading the stages.

NOTE Some experimentation could be needed to establish the optimum period of test, aided by visual recognition of "overloading" an impactor substrate.

D.3.2.9 After sampling for the required time, the *nebulizer* is switched off, and then a few seconds later, the sampling pump is switched off.

D.3.2.10 The cascade impactor is dismounted from the remainder of the apparatus.

D.3.2.11 The impactor is dismantled according to the manufacturer's instructions and the mass of *test solution* on the individual stages of the impactor, the input connection, and the outlet filter is determined (see also 4.2.3).

D.3.2.12 All type-test methods shall be performed on at least three representative test devices. See 4.2.1.1.

D.4 Test using a cascade impactor calibrated and operating at less than 15 l/min

D.4.1 Test equipment

The test equipment (see the schematic diagram in Figure D.2) shall comprise:

a) the *nebulizing system* under test containing, if required, an entrained ambient air inlet (i.e. T-piece) to allow more gas to be emitted by the *nebulizer* than that which is drawn into the cascade impactor;

b) a cascade impactor:

   1) with at least eight stages to estimate the *respirable fraction*;

   2) with sufficient loading capacity on each stage to estimate the *respirable fraction* without overloading stages;

   3) with no measurable heat transfer-related droplet evaporation;

      NOTE 1 The impactor can be chilled to avoid this cause of inaccuracy.

4) calibrated at a flow not exceeding 15 l/min, either by the manufacturer or the user, and specifying:

— a D_{50} (the aerodynamic diameter of a particle having a 50 % probability of impacting on the collection stage, also called the ECD);

— a D_{84} (the aerodynamic diameter of a particle having an 84 % probability of impacting on the collection stage) that is less than 1,3 × D_{50};

— a D_{16} (the aerodynamic diameter of a particle having a 16 % probability of impacting on the collection stage) that is greater than 0,77 × D_{50};

NOTE 2 Selection of the cut points (i.e. D_{50}) for the impactor includes at least two stages with D_{50}s greater than the *MMAD* of the *aerosol* from the *nebulizer* and two stages with D_{50}s less than the *MMAD* of the *aerosol* from the *nebulizer*.

c) a 22 mm T-piece connected to the inlet of the cascade impactor using a connector with a 22 mm internal diameter;

d) a sampling pump and adjustable flowmeter capable of drawing through the cascade impactor a flow specified in the calibration data of the cascade impactor;

e) a collection filter conforming to ISO 23328-1 with a filtration efficiency of >98 % of particles less than 10 µm and having minimal resistance connected to the T-piece to capture excess *aerosols*;

NOTE 3 Suitable filters are high-efficiency polypropylene filters (product K248 of 3M).[2)]

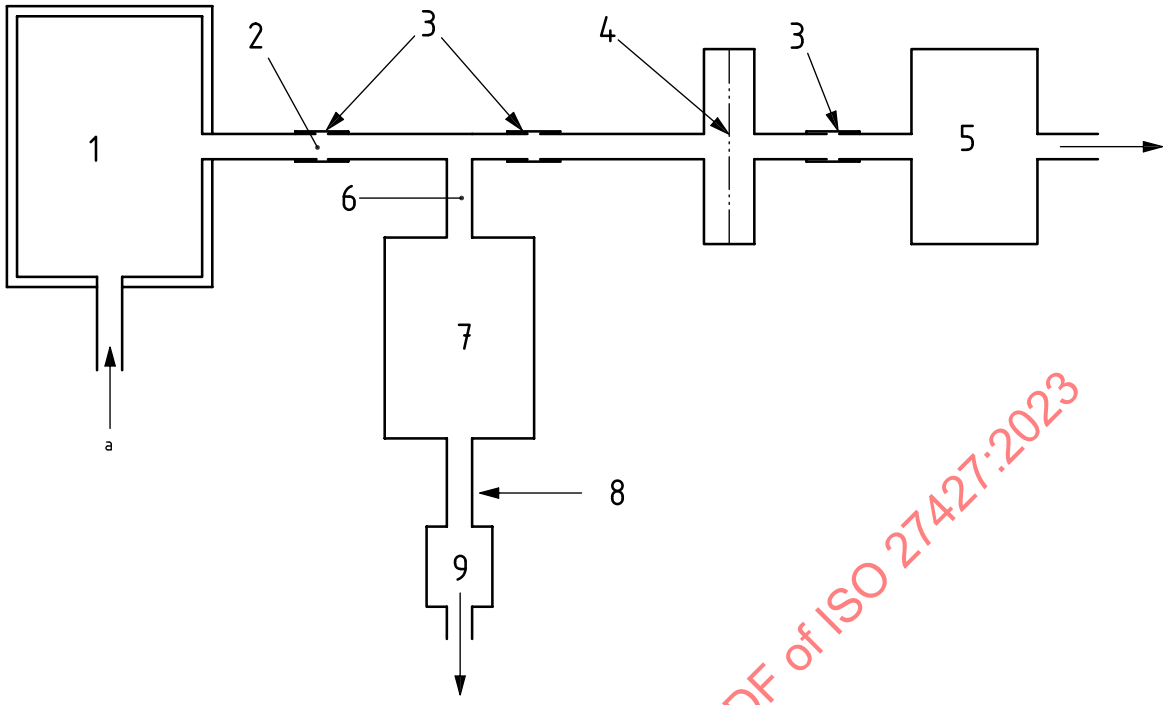
f) a suction pump that creates a continuous flow sufficient to raise the total flow through the T-piece (Figure D.2, item 6) to 15 l/min ± 1,5 l/min, the surplus flow above the sampling flow to the cascade impactor passing through the collection filter;

NOTE 4 This pump is not required if the cascade impactor is calibrated at 15 l/min.

g) the *test solution* (at stabilized temperature) of albuterol 0,1 % (m/m or V/V) concentration in 0,9 % sodium chloride solution or, if allowed or required by local competent authorities, 2,5 % (m/m or V/V) sodium fluoride in distilled water, with the provision that its use is declared in the accompanying documents. See 9.3.2 k);

h) for *gas-powered nebulizers*, the driving gas specified by the manufacturer (either compressed air from ambient conditions as described in C.2 or medical air as defined in ISO 7396-1).

2) This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named. Equivalent products may be used if they can be shown to lead to the same results.



Key

1 *nebulizing system* filled with *test solution* with an entrained ambient air inlet (i.e. T-piece), if required
2 *aerosol outlet port*
3 dismountable connectors
4 collection filter for excess *aerosol*
5 suction pump
6 T-piece
7 cascade impactor
8 connector to sampling pump
9 sampling pump
[a] Inlet for driving gas.

Figure D.2 — Schematic diagram showing the equipment for testing the particle sizes

D.4.2 Test method

D.4.2.1 The *nebulizer* is filled with the *test solution* to the fill volume recommended by the manufacturer or 2 ml if no fill volume is recommended and connected to the test compressor or air supply in accordance with the manufacturer's instructions.

D.4.2.2 A T-piece is attached to the *aerosol outlet port*.

D.4.2.3 The cascade impactor is dismantled, cleaned (e.g. with distilled water, wiped and allowed to air dry), and reassembled, incorporating all the stages of impaction surfaces in accordance with the manufacturer's instructions.

D.4.2.4 Readily dismountable connections are made from the T-piece to the inlet of the connector attached to the cascade impactor and from the outlet of this connector to the collection filter, which is connected to a suction pump.

D.4.2.5 An absolute filter (see D.3.2.4) is interposed between the outlet of the cascade impactor and the sampling pump, the flow of which is set to the calibration flow of the cascade impactor (e.g. 2 l/min ± 10 %.)

NOTE 1 During testing, the *nebulizer* and the cascade impactor are secured in the position specified by the manufacturer.

NOTE 2 Care is to be taken to prevent vibration of the impactor and to minimize perturbation of flow through the test apparatus.

D.4.2.6 The suction and sampling pumps are turned on and allowed to stabilize at the required flows.

NOTE The flow rate of the suction pump is adjusted in such a way that a total flow of 15 ml/min is drawn through the *nebulizer*, while at the same time, the sampling pump draws the flow rate which is required to operate the impactor (e.g. the suction pump for the excess *aerosol* is adjusted to produce an exhaust flow of (13 ± 10 %) l/min and the cascade impactor sampling pump is adjusted to the calibration flow of (2 ± 10 %) l/min .

D.4.2.7 The *nebulizer* is started.

D.4.2.8 Sampling times can be varied for different *nebulizers* to allow for maximum deposit on each stage without overloading the stages.

NOTE Some experimentation can be needed to establish the optimum period of test, aided by visual recognition of "overload" of an impactor substrate.

D.4.2.9 After sampling for the required time, the *nebulizer* is switched off, followed in a few seconds by the sampling pump and then the suction pump.

D.4.2.10 The cascade impactor is dismounted from the remainder of the apparatus.

D.4.2.11 The impactor is dismounted according to the manufacturer's instructions and the mass of *test solution* on the individual stages of the impactor, the input connection, and the outlet filter determined.

D.4.2.12 All type-test methods shall be performed on at least three representative test devices. See 4.2.1.1.

D.5 Test results

D.5.1 Calculations

Use of appropriate software to calculate and draw all the results is allowed.

a) Calculate the total mass of albuterol collected in the impactor as follows in the case of eight stages:

$$F = m_1 \text{ (including inlet assembly)} + m_2 + m_3 + m_4 + m_5 + m_6 + m_7 + m_8 + m_{\text{filter}} \quad \text{(D.1)}$$

b) Calculate the cumulative collection (%) of albuterol of particle mass under size as follows.

$$c_8 = m_{\text{filter}}/F \cdot 100 \quad \text{(D.2)}$$

Plot this (D.2) against the D_{50} of stage 8.

$$c_7 = c_8 + m_8/F \cdot 100 \quad \text{(D.3)}$$

Plot this (D.3) against the D_{50} of stage 7.

$$c_6 = c_7 + m_7/F \cdot 100 \quad \text{(D.4)}$$

Plot this (D.4) against the D_{50} of stage 6, and so forth,

where

F is the total mass of albuterol collected in the impactor, including the inlet assembly and the filter;

m_x is the mass collected on stage x;

c_x is the cumulative collection in percent of undersized particles.

NOTE A typical set of figures is shown in Table D.1, which includes mean values from the series of tests.

c) Plot the cumulative size distribution on log-probability graph paper, as shown in Figure D.3. The utility of the log-probability graph is that the cumulative size distribution can be represented by a straight line fitted through the data points. This is equivalent to the more familiar "S" curve fitted to the data on semi-log graph paper. The probability axis is a linear scale of the "z" values (standard deviation units associated with the cumulative area under a normal distribution).

d) Determine the *MMAD* and the GSD as illustrated in Figure D.3.

The *MMAD* is the diameter vertically below the horizontal intersection of the 50 % cumulative frequency value and the size distribution line. The GSD shall be calculated using the values $D(-1)$ or $D(1)$. The diameter $D(-1)$ is the diameter vertically below the horizontal intersection of the 16 % cumulative frequency value (or the value –1 on the probability axis) and the size distribution line; alternatively, the $D(1)$ value [the diameter vertically below the horizontal intersection of the 84 % cumulative frequency value (or the value 1 on the probability axis) and the size distribution line].

The GSD is then the $MMAD/D(-1)$ or $D(1)/MMAD$.

It is not necessary to plot all the results from the impactor stages to determine the *MMAD* of the *nebulizer*. It is only necessary to plot the two values, one above and one below the 50 % cumulative collection efficiency value, to find the *MMAD* and plot the line representing the size distribution. Plotting more points than that could result in the value being determined with less accuracy. Points farther away from the 50 % cumulative value have less accuracy because they represent a smaller fraction of the total mass. Points closer to the *MMAD* will have higher mass and should be determined therefore with greater accuracy. By weighting points with less accuracy with the same weighting as points with more accuracy (i.e. by drawing a best fit line through all the points), the overall accuracy of the determination is reduced. Using only the points representing the highest mass (i.e. those above and below the *MMAD*) to draw the line ensures higher accuracy even though only two points are used.

D.5.2 Expression of test results

The test results shall include

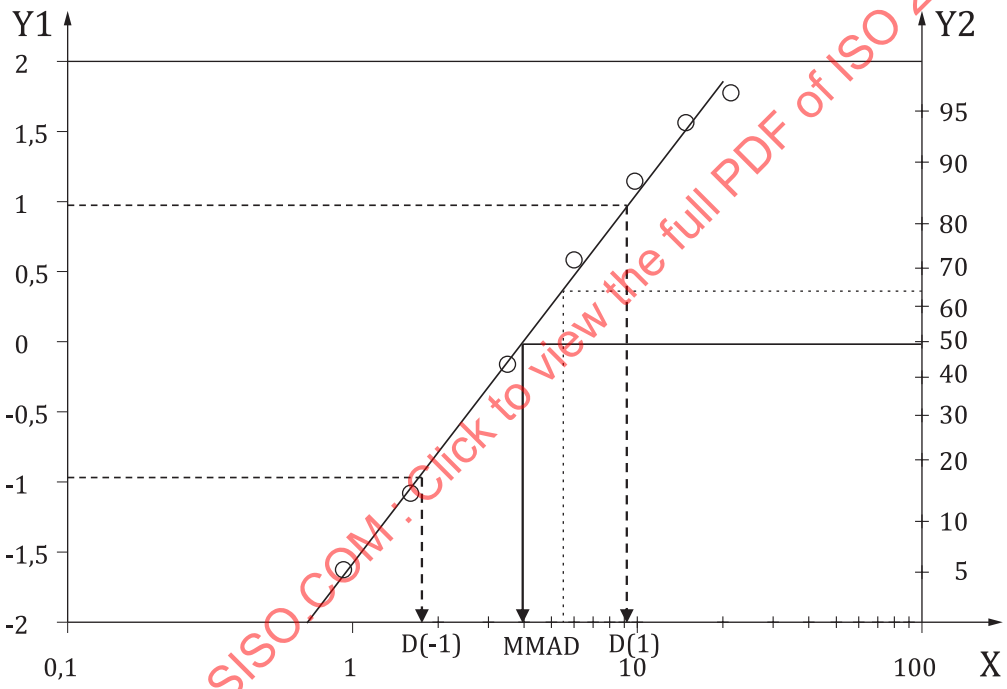
— for *gas-powered nebulizers*, the test gas employed,

— the filling volumes and flow rates used, and

— the mass of *test solution* deposited on the individual stages of the impactor (including the inlet assembly and the absolute filter).

Table D.1 — Typical sets of results from repeat measurement of a cascade impactor

Stage no.	Effective cut-off diameter µm	Cumulative particle mass of albuterol under size %				
		Mean	Test 1	Test 2	Test 3	Test 4
8	0,53	2,1	2,8	3,2	1,5	1,1
7	0,93	5,2	5,6	6,4	5,4	3,4
6	1,6	14,0	13,7	17,0	13,3	12,1
5	3,5	43,6	41,4	47,0	42,9	43,1
4	6,0	72,0	69,6	73,2	70,0	75,3
3	9,8	87,4	85,0	87,4	85,2	92,0
2	14,8	94,1	93,0	94,1	92,1	97,1
1	21,3	96,2	95,4	96,0	95,6	97,7



Key

X	diameter (µm)
Y1	probability (z values)
Y2	cumulative percent
———	*MMAD* (3,9 µm)
- - - - - - -	*MMAD*/*D*(−1) = GSD or *D*(1)/*MMAD* = GSD (2,06)
.....	cumulative % less than 5 µm (60 %)

NOTE Parameters such as the *MMAD* of 3,9 µm (shown with an arrow) and percent *aerosol* solute mass below 5 µm (in this case approximately 60 %) can be interpolated from the plot.

Figure D.3 — Example plot of cumulative size distribution from results in Table D.1