International Standard

ISO 18562-1

Second edition
2024-03

Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 1: Evaluation and testing within a risk management process

Évaluation de la biocompatibilité des chemins de gaz respiratoire utilisés dans le domaine de la santé —

Partie 1: Évaluation et essais au sein d'un processus de gestion du risque

Reference number
ISO 18562-1:2024(en)

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Published in Switzerland

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Foreword

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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 document 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).

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This document was prepared by Technical Committee ISO/TC 121, *Anaesthetic and respiratory equipment*, Subcommittee SC 3, *Lung ventilators 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 second edition cancels and replaces the first edition (ISO 18562-1:2017), which has been technically revised.

The main changes are as follows:

— added informative mapping annexes to relevant regulatory requirements;

— clarified terms and definitions used in the document;

— expanded the *patient* groups to include: premature, small child, child, and adolescent;

— introduction of inhalation dose;

— the *threshold of toxicological concern* is changed;

— expanded the range of *volatile organic substances* that are tested;

— clarified the appropriate breathing gas volumes to be used in testing for *VOS*; and

— clarified the appropriate breathing gas volumes to be used in the analysis.

A list of all parts in the ISO 18562 series can be found on the ISO website.

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

This document represents the application of the best-known science, in order to improve *patient* safety, by addressing the *risk* of potentially hazardous substances being conveyed to the *patient* by the gas stream.

This document is intended to cover the biological evaluation of *gas pathways* of *medical devices* within a *risk management process*, as part of the overall *medical device* evaluation and development. This approach combines the review and evaluation of existing data from all sources with, where necessary, the selection and application of additional tests.

In general, the ISO 10993 series is intended to cover the biological evaluation of *medical devices*. However, the ISO 10993 series does not sufficiently address the biological evaluation of the *gas pathways* of *medical devices*.

Before this document was developed, some *authorities having jurisdiction* interpreted the ISO 10993-1:2009, Table A.1 to mean that as materials in the *gas pathway* form "indirect contact" with the *patient*, they should be subjected to tests equivalent to those required for tissue contact parts of *medical devices*. This interpretation can lead to tests that are not optimized for evaluation of *gas pathways* including possible *hazards* not being detected.

ISO 10993-1:2018 states that it is not intended to provide a rigid set of test methods as this might result in an unnecessary constraint on the development and use of novel *medical devices*. ISO 10993-1:2018 also states where a particular application warrants it, experts in the product or in the area of application concerned can choose to establish specific tests and criteria, described in a product-specific vertical standard. This series of standards is intended to address the specific needs for the evaluation of *gas pathways* that are not adequately covered by ISO 10993-1:2018.

This document provides a guide to the development of a biological evaluation plan that minimizes the number and exposure of test animals by giving preference to chemical constituent testing and *in vitro* models.

The initial version of this series of standards was intended to cover only the most commonly found potentially harmful substances. It was felt that it was best to get a functioning document published that would test for the bulk of the currently known substances of interest. With the use of the *TTC* (*threshold of toxicological concern*) approach, this document has the potential to be used to assess the safety of essentially any compound released from the *gas pathways* of respiratory *medical devices*, with very few exceptions (e.g. PCBs, dioxins), and not just the most commonly found potentially harmful substances.

ISO 18562-1 does not address all possible biological *hazards* that can be associated with *gas pathways*. Other, additional evaluations can be appropriate. These evaluations can require further *risk control* before finishing the biological evaluation.

Future parts of this series might be added to this series to address other relevant aspects of biological testing including additional contamination that might arise from the *gas pathway* because of the presence of drugs and anaesthetic agents added to the gas stream, and potential contamination by emission of inorganic gases such as ozone, CO, CO_2, and NO_x.

NOTE Some *authorities having jurisdiction* require evaluation of these *risks* as part of a biological evaluation.

This document has been prepared in consideration of:

— the *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices,* IMDRF/GRRP WG/N47:2018[13] as indicated in Annex B;

— the *Labelling Principles for Medical Devices and IVD Medical Devices,* IMDRF/GRRP WG/N52:2019[14] as indicated in Annex B;

— the *essential principles of safety and performance* of a *medical device* according to ISO 16142-1:2016 as indicated in Annex C; and

— the general safety and performance requirements of a *medical device* according to regulation (EU) 2017/745[15].

In this document, the following verbal forms are used:

— “shall” indicates a requirement;

— “should” indicates a recommendation;

— “may” indicates a permission;

— "can" indicates a possibility or capability.

Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 1:
Evaluation and testing within a risk management process

1 Scope

This document specifies:

— the general principles governing the biological evaluation within a *risk management process* of the *gas pathways* of a *medical device*, its parts or *accessories,* which are intended to provide respiratory care or supply substances via the respiratory tract to a *patient* in all environments;

— the general categorization of *gas pathways* based on the nature and duration of their contact with the gas stream;

— the evaluation of existing relevant data from all sources;

— the identification of gaps in the available data set on the basis of a *risk analysis*;

— the identification of additional data sets necessary to analyse the biological safety of the *gas pathway*;

— the assessment of the biological safety of the *gas pathway*.

This document covers general principles regarding *biocompatibility* assessment of *medical device* materials, which make up the *gas pathway*, in *normal use* and *normal condition*. This document does not cover biological *hazards* arising from mechanical damage.

The other parts of ISO 18562 cover specific tests that address potentially hazardous substances that are added to the respirable gas stream and establish acceptance criteria for these substances.

This document addresses potential contamination of the gas stream arising from the *gas pathways* within the *medical device*, which might then be conducted to the *patient*.

This document applies over the *expected lifetime* of the *medical device* when operated according to the instructions for use. This includes degradation arising from exposure to environmental conditions as well as cleaning, disinfection and sterilisation (i.e. *processing*). It also includes user action or inaction (omission) that leads to an unintended or unexpected outcome (result) (i.e. *use error*). It does not include conscious/intentional action or inaction that violates the instructions for use and is beyond reasonable *risk control* by the *manufacturer* (i.e. *abnormal use*).

This document does not address biological evaluation of the surfaces of *medical devices* that have direct contact with the *patient* or *user*. The requirements for direct contact surfaces are found in the ISO 10993 series.

Medical devices, parts or *accessories* containing *gas pathways* that are addressed by this document include, but are not limited to, ventilators, anaesthesia workstations (including gas mixers), breathing systems, oxygen conserving equipment, oxygen concentrators, nebulizers, low-pressure hose assemblies, humidifiers, heat and moisture exchangers, respiratory gas monitors, respiration monitors, masks, medical respiratory personal protective equipment[23][25][28-30], mouth pieces, resuscitators, breathing tubes, breathing system filters and Y-pieces as well as any breathing *accessories* intended to be used with such *medical devices*. The enclosed chamber of an incubator, including the mattress, and the inner surface of an oxygen hood are considered to be *gas pathways* and are also addressed by this document.

This document does not address contamination already present in the gas supplied from the gas sources while *medical devices* are in *normal use*.

EXAMPLE Contamination arriving at the *medical device* from gas sources such as *medical gas pipeline systems* (including the non-return valves in the pipeline outlets), outlets of pressure regulators connected or integral to a medical gas cylinder, or room air taken into the *medical device* is not addressed by ISO 18562 (all parts).

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 10993-1:2018, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-17:2023, *Biological evaluation of medical devices — Part 17: Toxicological risk assessment of medical device constituents*

ISO 14971:2019, *Medical devices — Application of risk management to medical devices*

ISO 18562-2:2024, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 2: Tests for emissions of particulate matter*

ISO 18562-3:2024, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 3: Tests for emissions of volatile organic substances*

ISO 18562-4:2024, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 4: Tests for leachables in condensate*

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/

NOTE For convenience, an alphabetized index of terms and their sources used in this document is found in Annex D.

3.1
abnormal use
conscious, deliberate act or deliberate omission of an act that is counter to or violates *normal use* and is also beyond any further reasonable means of *user interface*-related *risk control* by the *manufacturer*

EXAMPLE Reckless use or sabotage or intentional deliberate disregard of information for SAFETY are such acts.

Note 1 to entry: An intended but erroneous action that is not *abnormal use* is considered a type of *use error*.

Note 2 to entry: *Abnormal use* does not relieve the *manufacturer* from considering non-*user interface*-related means of *risk control*.

Note 3 to entry: Figure 1 shows the relationships of the types of use.

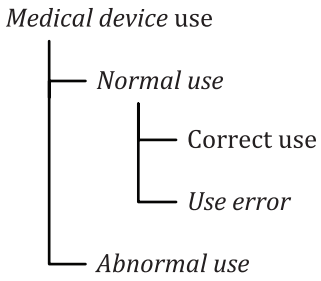

Figure 1 — Relationship of the types of use

[SOURCE: IEC 62366-1+AMD1:2020, 3.1, modified — deleted note 1.]

3.2
accessory
item, intended specifically by its *manufacturer*, to be used together with one or more *medical device*s to specifically enable or assist those *medical devices* to be used in accordance with their *intended use*

Note 1 to entry: An *accessory* is typically a consumable or separate item for use with one or more *medical devices*.

Note 2 to entry: Some *authorities having jurisdiction* consider an *accessory* to be a *medical device*.

Note 3 to entry: Some *authorities having jurisdiction* have a different definition of *accessory*.

[SOURCE: ISO 20417:2021, 3.1]

3.3
accompanying information
information accompanying or marked on a *medical device* or *accessory* for the user or those accountable for the installation, use, *processing*, maintenance, decommissioning and disposal of the *medical device* or *accessory*, particularly regarding safe use

Note 1 to entry: The *accompanying information* shall be regarded as part of the *medical device* or *accessory*.

Note 2 to entry: The *accompanying information* can consist of the label, marking, instructions for use, technical description, installation manual, quick reference guide, etc.

Note 3 to entry: *Accompanying information* is not necessarily a written or printed document but could involve auditory, visual, or tactile materials and multiple media types (e.g., CD/DVD-ROM, USB stick, website).

[SOURCE: ISO 20417:2021, 3.2, modified — deleted note 4.]

3.4
authority having jurisdiction
regulatory authority
governmental agency or office assigned to oversee the regulation of a regulated product within a country, jurisdiction, or assigned territory

[SOURCE: ISO 16142-1:2016, 3.1]

3.5
benefit
positive impact or desirable outcome of the use of a *medical device* on the health of an individual, or a positive impact on *patient* management or public health

Note 1 to entry: *Benefits* can include positive impact on clinical outcome, the *patient's* quality of life, outcomes related to diagnosis, positive impact from diagnostic devices on clinical outcomes, or positive impact on public health.

[SOURCE: ISO 14971:2019, 3.2]

3.6
biocompatibility
ability of a *medical device*, *accessory* or material to perform with an appropriate host response in a specific application

Note 1 to entry: A *medical device* or *accessory* may produce some level of adverse effect, but that level may be determined to be acceptable when considering the *benefit* provided.

[SOURCE: ISO 10993-1:2018, 3.1, modified — added *accessory* and note.]

3.7
essential principles
essential principles of safety and performance
fundamental high-level requirements that when complied with ensure a *medical device* or *accessory* is safe and performs as intended

[SOURCE: ISO 16142-1:2016, 3.3, modified — added 'or *accessory*'.]

3.8
expected lifetime
expected service life
period specified by the *manufacturer* during which the *medical device* or *accessory* is expected to maintain basic safety and essential performance

Note 1 to entry: The *expected lifetime* can be affected by the stability of the *medical device* or *accessory* or by the materials in the *medical device* or *accessory*.

Note 2 to entry: Maintenance, repairs or upgrades (e.g., safety or security modifications) can be necessary during the *expected lifetime*.

Note 3 to entry: Some *medical devices* have an absolute lifetime (e.g., 5 y), whereas other *medical devices* (e.g., software) have a relative lifetime (e.g., the time between two major releases).

[SOURCE: ISO 20417:2021, 3.7, modified — added note 1 and deleted notes 3 and 4.]

3.9
exposure dose
quantity of a chemical constituent that does, or could contact the body by an exposure route over a specified time period

Note 1 to entry: *Exposure dose* is normally expressed as microgram per kilogram of body mass per day (µg/kg/d) or microgram per day (µg/d).

Note 2 to entry: *Exposure dose* is different from an absorbed dose. The absorbed dose is the quantity of the constituent that traverses the portal of entry, which is dependent on the absorption rate of the constituent.

[SOURCE: ISO 10993-17:2023, 3.7, modified — deleted from note 1 'or as microgram per centimetre squared (µg/cm^2)' and added ' or microgram per day (µg/d)'.]

3.10
formulation
base polymer or alloy, including additives, colours, etc. used to establish a property or the stability of the material

Note 1 to entry: This does not include *processing* aids, mould release agents, residual contaminants, or other manufacturing aids that are not intended to be a part of the material.

Note 2 to entry: The term "chemical composition" is commonly used as a synonym for *formulation*.

[SOURCE: US FDA Deciding When to Submit a 510(k) for a Change to an Existing Device[18], reformatted.]

3.11
gas pathway
interior surfaces over which gases or liquids pass that can be inspired

EXAMPLE 1 The ventilator breathing system, inlet filter, gas mixer, blower and internal piping.

EXAMPLE 2 Enclosed chamber of an incubator including the mattress or the inner surface of an oxygen hood.

EXAMPLE 3 The inner surfaces of breathing tubes, tracheal tubes or masks and mouthpieces.

Note 1 to entry: The *gas pathway* is bounded by the ports through which gases or liquids enter the *medical device* or *accessory*. This can include the *patient* interface or the interior surfaces of enclosures that are in contact with gases or liquids that can be inspired.

Note 2 to entry: The *gas pathway* can include some surfaces in the expiratory pathway.

Note 3 to entry: *Patient* contact surfaces such as the outer surfaces of a tracheal tube or the cushion of a mask are evaluated according to the ISO 10993 series.

3.12
hazard
potential source of harm

[SOURCE: ISO 14971:2019, 3.4]

3.13
infrequent use
same or similar *medical device* or *accessory* used at different treatment occasions at intervals that are expected to be long relative to the elimination time of any *leachable* harmful substance from the *patient's* body

Note 1 to entry: If the *medical device* or *accessory* is intended to be used for a recurring condition, then the determination as to whether this is treated as *infrequent use* is based on the likelihood that the *patient* recovers from any toxicological effects of the between episodes. If there is likely to be a cumulative effect then the *total exposure period* across all treatment episodes shall be considered.

Note 2 to entry: If use of the *medical device* or *accessory* is deemed to be *infrequent use*, then the *total exposure period* is determined for a single treatment episode.

3.14
inhalation dose
quantity of a *VOS* that does, or could be inhaled into body in one day

Note 1 to entry: *Inhalation dose* is expressed as microgram per day (µg/day).

3.15
intended use
use for which a product, *process* or service is intended according to the specifications, instructions and information provided by the *manufacturer*

Note 1 to entry: The intended medical indication, *patient* population, part of the body or type of tissue interacted with, user profile, use environment, and operating principle are typical elements of the *intended use*.

[SOURCE: ISO 14971:2019, 3.6]

3.16
leachable
substance that is released from a *medical device* or material during its clinical use

Note 1 to entry: For many *medical devices*, a *leachables* study is not practical due to the challenges with reproducing actual clinical conditions, so *simulated-use extraction* studies are often performed instead. See definition for *simulated-use extractions*.

[SOURCE: ISO 10993-18:2020, 3.22]

3.17
manufacturer
organization with responsibility for the design or manufacture of a *medical device* or *accessory* with the intention of making the *medical device* available for use, under their name, whether or not such a *medical device* is designed or manufactured by that organization their self or on their behalf by another organization

Note 1 to entry: This organization has ultimate legal responsibility for ensuring compliance with all applicable regulatory requirements for the *medical device* in the countries or jurisdictions where it is intended to be made available or sold, unless this responsibility is specifically imposed on another organization by the *authority having jurisdiction*.

Note 2 to entry: The *manufacturer's* responsibilities are described in other GHTF/IMDRF guidance documents. These responsibilities include meeting both pre-market requirements and post-market requirements, such as adverse event reporting and notification of corrective actions.

Note 3 to entry: "Design or manufacture" can include specification development, production, fabrication, assembly, *processing*, packaging, repackaging, labelling, relabelling, sterilization, installation or remanufacturing of a *medical device* or *accessory*; or putting a collection of *medical devices* or *accessories*, and possibly other products, together for a medical purpose.

Note 4 to entry: Any organization who assembles or adapts a *medical device* or *accessory* that has already been supplied by another organization for an individual *patient*, in accordance with the instructions for use, is not the *manufacturer*, provided the assembly or adaptation does not change the *intended use* of the *medical device* or *accessory*.

Note 5 to entry: Any organization who changes the *intended use* of, or modifies, a *medical device* or *accessory* without acting on behalf of the original *manufacturer* and who makes it available for use under their own name, should be considered the *manufacturer* of the modified *medical device* or *accessory*.

Note 6 to entry: An authorised representative, distributor or importer who only adds their own address and contact details to the *medical device*, *accessory* or the packaging, without covering or changing the existing labelling, is not considered a *manufacturer*.

Note 7 to entry: To the extent that an *accessory* is subject to the regulatory requirements of a *medical device*, the organization responsible for the design or manufacture of that *accessory* is considered to be a *manufacturer*.

[SOURCE: ISO/IEC Guide 63:2019, 3.6, modified — Added "or accessory", replaced "and/or" with "or", replaced "natural or legal person" and "person with "organization" replaced "Regulatory Authority within that jurisdiction" with "authority having jurisdiction", inserted "IMDRF" and replaced "labelling" with "information supplied by the manufacturer".]

3.18
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the *manufacturer* to be used, alone or in combination, for *patients* for one or more of the following specific purpose(s) of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

— investigation, replacement, modification, or support of the anatomy or of a physiological *process;*

— supporting or sustaining life;

— control of conception;

— disinfection of *medical devices;*

— providing information by means of *in vitro* examination of specimens derived from the patient;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the *patient*, but which can be assisted in its function by such means

Note 1 to entry: Products which may be considered to be *medical devices* in some jurisdictions but not in others include: