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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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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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 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.

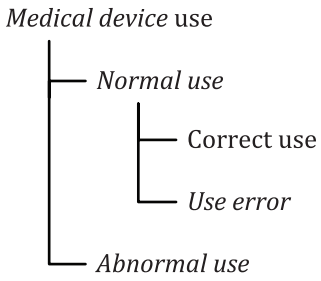


Figure 1 — Relationship of the types of use

[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 devices* 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:

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal or human tissues;

— devices for *in vitro* fertilization or assisted reproduction technologies.

[SOURCE: ISO 13485:2016, 3.11, modified — changed “and/or” to “or”, “human being” and “human body” to “patient” “devices” to “medical devices” and “may” to “can”.]

3.19
medical gas pipeline system
combination of a supply system, monitoring and alarm system and a pipeline distribution system with terminal units for provision of medical gases or vacuum

[SOURCE: ISO 4135:2022, 3.2.1.1]

3.20
normal condition
condition of a *medical device* or *accessory* in which all means provided for protection against *hazards* are intact

[SOURCE: IEC 60601-1:2005+AMD1:2012+AMD2:2020, 3.70]

3.21
normal use
operation, including stand-by, routine inspection and adjustments by any user in accordance with the instructions for use or with generally accepted practice for those *medical devices* provided without instructions for use

Note 1 to entry: *Normal use* should not be confused with *intended use*. While both include the concept of use as intended by the *manufacturer*, *intended use* focuses on the medical purpose while *normal use* incorporates not only the medical purpose, but maintenance, service, transport, etc. as well.

Note 2 to entry: *Use error* can occur in *normal use*.

Note 3 to entry: *Medical devices* that can be used safely without instructions for use are exempted from having instructions for use by some *authorities with jurisdiction*.

Note 4 to entry: Some *medical devices* or *accessories* have generally accepted practices that are not documented in the *instructions for use*. Those practices should be considered *normal use*.

Note 5 to entry: Figure 1 shows the relationships of the types of use.

[SOURCE: IEC 62366-1+AMD1:2020, 3.9, modified—added note 4 and moved ‘for those *medical devices* provided without instructions for use’.]

3.22
particulate matter
PM
particulates
solid particles suspended in a gas

3.23
patient
living being (person) undergoing a medical, surgical or dental procedure

[SOURCE: IEC 62366-1:2001+AMD1:2020, 3.10]

3.24
process
set of interrelated or interacting activities that use inputs to deliver an intended result

Note 1 to entry: Whether the "intended result" of a *process* is called output, product or service depends on the context of the reference.

Note 2 to entry: Inputs to a *process* are generally the outputs of other *processes* and outputs of a *process* are generally the inputs to other *processes*.

Note 3 to entry: Two or more interrelated and interacting *processes* in series can also be referred to as a *process*.

[SOURCE: ISO 14971:2019, 3.14]

3.25
processing
<preparation of *medical device*, *accessory*> activity to prepare a new or used *medical device* or *accessory* for its *intended use*

Note 1 to entry: Some *authorities having jurisdiction* refer to *processing* between uses as reprocessing.

[SOURCE: ISO 20417:2021, 3.20, modified —, added note.]

3.26
residual risk
risk remaining after *risk control* measures have been implemented

[SOURCE: ISO 14971:2019, 3.17]

3.27
risk
combination of the probability of occurrence of harm and the severity of that harm

[SOURCE: ISO 14971:2019, 3.18]

3.28
risk analysis
systematic use of available information to identify *hazards* and to estimate the *risk*

[SOURCE: ISO 14971:2019, 3.19]

3.29
risk assesssment
overall *process* comprising a *risk analysis* and a *risk* evaluation

[SOURCE: ISO 14971:2019, 3.20]

3.30
risk control
process in which decisions are made and measures implemented by which *risks* are reduced to, or maintained within, specified levels

[SOURCE: ISO 14971:2019, 3.21]

3.31
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring *risk*

[SOURCE: ISO 14971:2019, 3.24]

3.32
risk management file
set of records and other documents that are produced by *risk management*

[SOURCE: ISO 14971:2019, 3.25]

3.33
semi-volatile organic compound
SVOC
organic substance whose boiling point is greater than or equal to 250 °C , at a standard atmospheric pressure of 101,3 kPa

3.34
shelf-life
period of time until the expiry date during which a *medical device* or *accessory* in its original packaging maintains its *stability* under the conditions specified in the information supplied by the *manufacturer*

[SOURCE: ISO 20417:2021, 3.24]

3.35
simulated-use extraction
extraction using a method that simulates clinical use

Note 1 to entry: A *simulated-use extraction* is performed to estimate the type and amount of substances that are expected to be released from a *medical device* during its clinical use. A *simulated-use extraction* is designed to produce an extractables profile that represents the worst-case *leachables* profile, meaning that all *leachables* are also extractables and the levels of all individual extractables are at least equal to the level of all individual *leachables*.

[SOURCE: ISO 10993-18:2020, 3.25]

3.36
threshold of toxicological concern
TTC
level of exposure for a constituent below which there would be no appreciable *risk* to human health where there is no toxicological data for that constituent

Note 1 to entry: A *TTC* (expressed as µg/kg body mass/d or µg/d) is used for an unknown or insufficiently characterized compound.

[SOURCE: ISO/TS 21726:2019, 3.5 modified — added "where there is no toxicological data for that constituent" and note 1 to entry.]

3.37
tolerable exposure
TE
level of exposure for a constituent below which there would be no appreciable *risk* to human health where there is toxicological data for that constituent

Note 1 to entry: *TE* is also referred to as “allowed dose to patient”. This amount is specific to a particular *patient* or *patient* group of a given body mass.

Note 2 to entry: *TE* is calculated by multiplying *tolerable intake* by the body mass. *TE* is expressed in µg/d to the *patient.*

3.38
tolerable intake
TI
estimate of the daily exposure of an identified constituent over a specified time period (e.g., acute, subacute, subchronic, or chronic), on the basis of body mass, that is considered to be without appreciable *harm* to health

Note 1 to entry: *Tolerable intake* is normally expressed as microgram per kilogram of body mass per day (µg/kg/d). It is derived to establish a toxicological exposure limit for a *medical device* constituent.

[SOURCE: ISO 10993-17:2023, 3.26]

3.39
total exposure period
period in days between first and last use of a *medical device* or *accessory* or a replacement of the same *medical device* or *accessory*

Note 1 to entry: The *total exposure period* is the number of elapsed calendar days between first and last use, whether or not the *medical device* or *accessory* is used every day, and regardless of the duration of exposure on each day.

Note 2 to entry: A *medical device* or *accessory* that has an infrequent use has a *total exposure period* that is determined for a single treatment episode.

3.40
type test
test on one or more representative samples, as designed and manufactured, with the objective of determining conformity to a requirement

Note 1 to entry: A representative sample shall be taken from production or be production equivalent.

Note 2 to entry: If the final *medical device* is not used for the assessments, all differences between the "representative sample" and the final *medical device* need to be described and a justification provided for why the differences do not affect the outcome of the testing.

3.41
use error
user action or lack of *user* action while using the *medical device* or *accessory* that leads to a different result than that intended by the *manufacturer* or expected by the *user*

Note 1 to entry: *Use error* includes the inability of the *user* to complete a user task.

Note 2 to entry: *Use errors* can result from a mismatch between the characteristics of the *user*, *user* interface, user task, or use environment.

Note 3 to entry: *Users* might be aware or unaware that a *use error* has occurred.

Note 4 to entry: An unexpected physiological response of the *patient* is not by itself considered *use error*.

Note 5 to entry: A malfunction of a *medical device* or *accessory* that causes an unexpected result is not considered a *use error*.

Note 6 to entry: Figure 1 shows the relationships of the types of use.

[SOURCE: IEC 62366-1:2015+AMD1:2020, 3.21, modified — added "or accessory" and replaced "task" with "user task".]

3.42
very volatile organic compound
VVOC
volatile organic substance whose boiling point is in the range of 0 °C to 50 °C, at a standard atmospheric pressure of 101,3 kPa

Note 1 to entry: Boiling points of some compounds are difficult or impossible to determine because they decompose before they boil at atmospheric pressure.

3.43
volatile organic compound
VOC
volatile organic substance whose boiling point is in the range of 50 °C to 250 °C, at a standard atmospheric pressure of 101,3 kPa

Note 1 to entry: There are many varied definitions of *VOC*. For the purposes of this document, a *VOC* is a substance that has a boiling point less than 250 °C, at a standard atmospheric pressure of 101,3 kPa.

Note 2 to entry: Boiling points of some compounds are difficult or impossible to determine because they decompose before they boil at atmospheric pressure.

Note 3 to entry: Compounds still exert a vapour pressure, and so could enter the breathing gas, at temperatures lower than their boiling point.

3.44
volatile organic substance
VOS
any organic substance with a saturation pressure at standard temperature of 20 °C that exceeds current analytical detection threshold

Note 1 to entry: *Volatile organic substances* include *VOCs*, *SVOCs* and *VVOCs*.

4 General principles applying to *biocompatibility* evaluation of *medical devices*

4.1 General

a) The *biocompatibility* evaluation of breathing *gas pathways* intended for use in healthcare shall form part of a structured *biocompatibility* evaluation programme within a *risk management process*. For *medical devices* in general, ISO 10993-1 describes how to perform this *process*. For breathing *gas pathways* in *medical devices*, *accessories* or their parts, the ISO 18562 series describes the appropriate process. Figure 2 illustrates this *process* for breathing *gas pathways*.

b) All *medical devices* shall be evaluated for *biocompatibility* in *normal use* and *normal condition*.

c) All *medical devices* shall be evaluated for *biocompatibility*, but evaluation does not necessarily imply testing.

d) The *biocompatibility* evaluation shall be planned, carried out and documented by knowledgeable and experienced professionals.

e) The evaluation programme shall include documented, informed decisions that assess the advantages/disadvantages and relevance of:

   1) the physical and chemical characteristics of the various candidate materials over the *expected lifetime* of the *medical device*;

      NOTE 1 Where this information is already documented within the *risk management file* for the *medical device*, it can be included by reference.

   2) effects of operation, handling, and environment during use over the *expected service life;*

      NOTE 2 For a reusable *medical device* or *accessory*, issues such as wear and material degradation apply over the *expected service life* and not only the exposure period.

   3) effects of aging and environment during storage over the *shelf-life;*

   4) effects of cleaning, disinfection and sterilisation (i.e. *processing*) in accordance with the *accompanying information*;

      i) Considerations shall include the agents impact to degradation of *gas pathway* components and the cleaning and sterilization methods that add potentially harmful substances to the *gas pathway*.

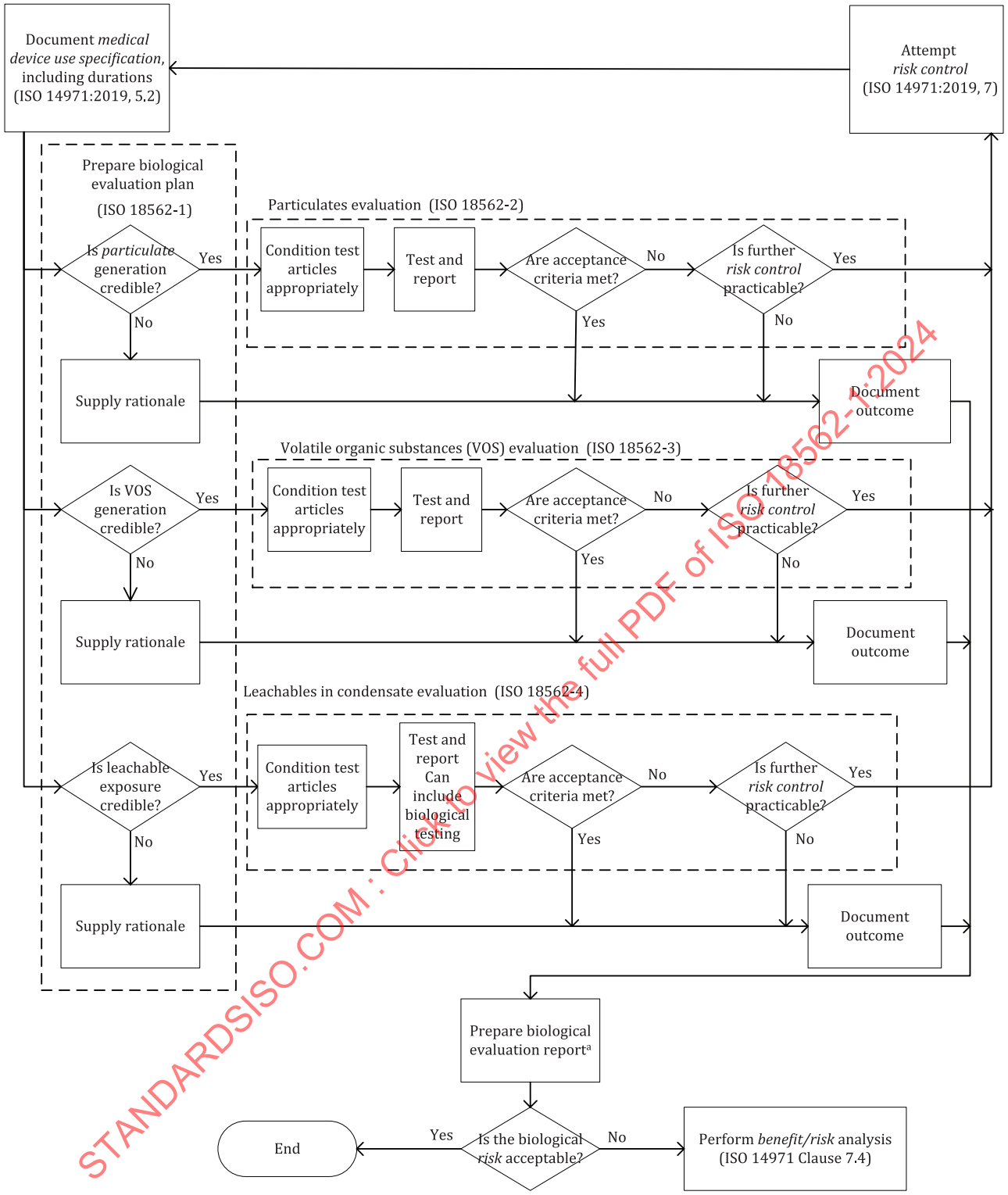
   5) effects from exposure to the rated environmental conditions;

   6) any history of human exposure data;

7) any existing toxicology and other *biocompatibility* safety data on product and component materials, breakdown products and metabolites.

f) This series of documents shall not be used to mandate re-testing of historical products assessed previously using the appropriate edition of this document at the time of the assessment. Nevertheless, conformity to this new edition shall be shown, by providing a justification for omission of further testing. Where recommendations for endpoint assessment are different from prior published versions of this document, a history of safe clinical use can be used to document why additional testing on a commercially-marketed *medical device* or *accessory* is not required. However, if any of the changes described in ISO 10993-1:2018, 4.9, occur, an evaluation of the biological *risks* related to the change shall be performed using the current version of this document.

Conformity is established by inspection of the biological evaluation *plan, risk management file* and biological evaluation report.



a ISO 18562-1 does not address all possible biological *hazards* that can be associated with *gas pathways*. Other, additional evaluations can be appropriate. See 4.5, note 4. These evaluations can require further *risk control* before preparation of the biological evaluation report.

Figure 2 — *Risk management process* for biological evaluation of *gas pathways*

4.2 *Type tests*

NOTE 1 There is guidance or rationale for this subclause contained in Clause A.2.

The tests described in this document are *type tests*. *Type tests* are performed on the final *medical device*, a component of the *medical device* or a representative sample of the *medical device*, part or *accessory* being evaluated.

a) If representative samples are used (i.e. manufactured and processed by equivalent methods), consideration shall be given to whether or not the differences between the representative sample and the final *medical device* or component could affect the results of the test.

b) Testing of representative samples (manufactured and processed by equivalent methods) instead of the final *medical device* shall:

   1) be supported by a description of any differences between the representative sample and the final *medical device*; and

   2) include a detailed rationale for why each difference is not expected to impact the *biocompatibility* of the final *medical device*.

      NOTE 2 Some *authorities having jurisdiction* evaluate these differences and rationales.

c) *Type tests* are only required for *medical device* or *accessory* prior to releasing a product or a change to a product for production. There is no requirement for ongoing testing throughout the production lifetime of a product.

4.3 *Biocompatibility hazard* identification

a) Identify all the possible *biocompatibility*-related *hazards* that might reach the *patient* via the *gas pathways* during the use of the *medical device*.

b) All known *biocompatibility*-related *hazards* shall be taken into account for every material and final *medical device*, part or *accessory* in the *gas pathway.* This does not imply that testing for all possible *hazards* is necessary or practical.

   NOTE 1 For a *medical device* (such as a mask) that has direct *patient* contact in addition to *gas pathway* contact, assessment for conformity to both ISO 18562-1 and ISO 10993-1 can be required.

c) The following shall be taken into account for their relevance to the overall biological evaluation of the *gas pathway*:

   1) the material(s) of manufacture;

      i) In the selection of materials to be used in *gas pathway* manufacture, consideration shall be given for fitness for purpose with regard to toxicological properties in addition to other characteristics and properties (e.g. physical, chemical and mechanical) of the material.

   2) intended additives, *process* contaminants and residues;

   3) substances or particles released in *normal use*;

      NOTE 2 *Normal use* can include use with heated and humidified breathing gas. Tests are done on the "worst case" configuration. This can mean testing with and without heat and humidification to establish the worst case.

      NOTE 3 Humidified air can affect the measurements of *VOS* and *particulates*, necessitating testing without humidification.

4) degradation products from *normal use* during the *shelf-life* and the *expected service life* that might pass into the *patient* via the *gas pathways*;

   i) Considerations should include degradation caused by wear and environmental effects such as temperature, humidity, pressure as well as exposure to sunlight or ultraviolet light.

   NOTE 4 The tests of ISO 18562 series cannot alone evaluate degradation.

5) other components and their interactions in the final *medical device*, part or *accessory*;

6) the performance and characteristics of the final *medical device*, part or *accessory*;

7) physical characteristics of the final *medical device*, part or *accessory* including, but not limited to, size, porosity and shape;

8) the effects of any *processing* steps (e.g. cleaning/disinfection/sterilization) required before use or between uses, if applicable.

Check conformity by inspection of the biological evaluation plan, *risk management file* and biological evaluation report.

4.4 Extent of *risk assessment*

a) An analysis shall be made of the *hazards* identified in 4.3

   1) The results shall be documented in the biological evaluation report.

   NOTE 1 Figure 2 is a graphical representation of the *risk assessment process*.

b) The *risk* that each *hazard* poses to the *patient* shall be determined.

   1) The results shall be documented in the biological evaluation report.

c) The rigour necessary in the biological evaluation is principally determined by the duration and frequency of the exposure and the *hazards* identified for the *medical device*. The information needed to support a biological evaluation, including any test data, shall consider:

   1) the physical and chemical characteristics of the materials,

   2) the electromechanical nature of the *medical device*,

   3) as well as the frequency, duration and conditions of exposure of the *patient* to the gas from the *gas pathway*.

   This enables the categorization of uses to facilitate the selection of appropriate tests, if required.

NOTE 2 ISO 10993-1:2018, Clause 5 contains additional requirements.

4.5 Biological evaluation plan

a) Having identified the possible *biocompatibility hazards* and determined the *risks* that they might pose to the *patient*, a biological evaluation plan shall be created.

   1) This plan shall detail what is currently known about:

      i) the material *formulation*;

      ii) additives; and

      iii) *process* aids

   used in the manufacture of the *gas pathways* of the *medical device*.

2) This plan shall identify gaps in knowledge that shall be filled by further work.

b) If a potential *hazard* has been identified, but the *risk* it poses to the *patient* can be shown to be negligible (for example, the dose the *patient* receives is less than the *tolerable exposure*), then no further work on the *hazard* is required.

1) This decision shall be documented in the biological evaluation report.

c) If a potential *hazard* has been identified and the *risk* it poses to the *patient* is not negligible, or the *risk* is unknown, then further work to characterize or mitigate the *hazard* is required.

1) This step may involve:

i) referring to previous similar *medical devices* and manufacturing methods;

ii) accessing reliable information in the public domain; or

iii) performing tests to gather the necessary data.

d) All *medical devices* shall be evaluated for *biocompatibility,* but evaluation does not automatically imply testing.

1) Depending on the final *formulation*, manufacturing *processes* and application *processes*, an evaluation may result in the conclusion that no testing or no additional testing is needed.

NOTE 1 Manufacturing and application *processes* include *processing* (i.e., cleaning/disinfection/sterilization either prior to use or between uses).

EXAMPLE A *medical device* with the same *intended use* that has a demonstrable similarity in a specified function and physical form, has identical *formulation*, contains no additional chemicals, uses the same manufacturing *processes*, so that it is equivalent to a *medical device,* part or *accessory* that has already been evaluated as biocompatible, might not require additional testing.

2) Where there is appropriate evidence, testing of an existing *medical device* or *accessory* according to the ISO 18562 series may be unnecessary.

i) Appropriate evidence that allows for conclusions on specific endpoints can include a history of safe clinical use as well as testing or toxicological *risk assessment* conducted prior to the publication this document.

e) To reduce animal testing for *gas pathways* that can contact liquids, identification of material chemical constituents and consideration of chemical characterization shall be undertaken.

1) Only if results show the presence of substances, which do not have sufficient toxicological data to allow *risk assessment,* should any biological testing be considered.

NOTE 2 Some local effects including cytotoxicity, irritation, and sensitization might not be adequately assessed using a chemical characterization/*risk* assessment approach. As a result, it can be necessary to conduct biological testing to assess these end points. These endpoints are evaluated as a part of ISO 18562-4. Systemic effects including acute, subacute, subchronic and chronic toxicity, reproductive and developmental toxicity, genotoxicity and carcinogenicity can often be assessed using a chemical characterization/*risk* assessment approach.

f) An evaluation of *particulate matter* shall be included in the *biocompatibility* evaluation.

g) Test results cannot guarantee freedom from potential biological *hazards.* Therefore, production release shall be followed by post-market surveillance, to inform a continuous *risk management process*. Post-market surveillance plans are not required in the biological evaluation plan.

NOTE 3 The range of possible biological *hazards* is wide and can include short-term effects, as well as long-term or specific toxic effects.

h) The biological evaluation of a *gas pathway* shall take into account:

1) the nature and mobility of the chemical constituents in the materials used to manufacture the *medical device*, part or *accessory*;

2) information from other non-clinical tests;

3) information from clinical studies;

4) information from post-market experience; and

5) other relevant information.

NOTE 4 This series does not currently address *biocompatibility hazards* associated with the following substances being added to the respirable gas stream. Nonetheless, when applicable, some *authorities having jurisdiction* require the *manufacturer* to evaluate the following:

— ozone, for *gas pathways* in contact with active electromechanical or electrostatic parts in *normal condition*;

— CO, NO_x and CO_2, for *gas pathways* where inorganic gases are added, generated or concentrated;

— *leachables,* for *gas pathways* in contact with anaesthetic agents where the gas can be inspired in *normal condition*;

— *leachables,* for *gas pathways* in contact with substances intended to be delivered via the respiratory tract (e.g. inhalational drugs).

4.6 Selection of tests

a) The results of the biological evaluation plan might indicate that further information is required.

1) If this information is not available from other sources, then tests to complete the biological evaluation may be necessary.

b) Any selection of tests shall be based on the conditions of expected worst-case clinical use (which could include repeated use).

c) All tests:

1) shall be conducted according to recognized current/valid best laboratory/quality practices; and

NOTE Such test laboratories operate under a recognized quality system, for example, ISO/IEC 17025.

2) the data shall be evaluated by competent, informed professionals.

d) Biological testing shall conform to the relevant parts of the ISO 10993 series.

e) Tests, other than biological tests, shall be carried out:

1) under clinically relevant environmental conditions;

2) using clinically relevant flow rates and total flow volumes; and

3) for clinically relevant time durations.

i) For a clinical duration of use of equal or less than 24 h, the test duration shall be at least as long as the clinical duration of use.

ii) If a *medical device* could be used multiple times in a 24 h period (with or without *processing*) then the worst-case cumulative use time shall be considered as the test duration.

iii) For a clinical duration of use of greater than 24 h, the test duration shall be at least 24 h and adequate to represent the release of substances over the expected duration of use.

f) *In vitro* test methods, which are appropriately validated, reasonably and practically available, reliable and reproducible, shall be considered for use in preference to *in vivo* tests.

1) Whenever possible, *in vitro* screening shall be carried out before *in vivo* tests are commenced.

2) Test data, complete to the extent that an independent analysis could be made, shall be documented in the biological evaluation report.

f) Where further tests are required, the *process* depicted in Figure 2 shall be followed to identify the type of testing needed.

4.7 Subsequent evaluation

a) The materials or final *medical device*, part or *accessory* shall be re-evaluated if any of the following occurs:

1) any change in the *formulation* of the materials used in the manufacture, *processing* or primary packaging of the *medical device*, part or *accessory*;

2) change in *processing* methods, including sterilization;

3) any change in the *manufacturer's* instructions for use concerning storage (e.g. changes in *shelf-life* or transport);

4) any change in the *intended use* of the *medical device*, part or *accessory*; or

5) any other changes identified by the *risk management process.*

b) If the change is related to components of a complex *medical device*, conformity to this document may be shown by:

1) information (e.g., rationale) to support that *biocompatibility* of the other *medical device* components are not affected; and

2) one of the following:

i) evidence that the new materials do not show any increased *biocompatibility* concerns compared to the old ones;

ii) test and evaluation of the new components according to this document;

iii) comparison to components, which are identical in *formulation*, *processing*, preparation for use to an existing component of a *medical device* that has been previously tested and used in a comparable application (see e.g. ISO 18562-3:2024, 5.1); or

iv) re-test and re-evaluation of the complete product including the new component.

c) If there are multiple component changes of a complex *medical device*, each change shall be considered separately.

1) Additionally, the combination of changes and impact on the final *medical device* or *accessory* shall be considered.

5 Contamination of breathing gas from *gas pathways*

5.1 Duration of use

a) The tests that a *medical device*, part or *accessory* shall be subjected to depend on:

1) the nature of the components in the *gas pathway*;

2) their location in the *gas pathway*; and

3) their duration of use on a *patient*.

NOTE 1 The tests and specified limits for a *medical device* depend on its intended duration of use for a single *patient.*

c) Where there are components replaced every few days, the multiple sequential exposures to new replacement *medical devices* or *accessories* shall be considered for the *total exposure period*.

EXAMPLE 1 A single use breathing tube is replaced multiple times on a single *patient* over the period of treatment.

NOTE 2 A *medical device* or *accessory* that has an *infrequent use* has a *total exposure period* that is determined for a single treatment episode.

EXAMPLE 2 A *medical device* or *accessory* that is for resuscitation.

d) *Medical devices* shall be categorized according to the anticipated duration of contact as follows:

1) limited exposure: *medical device*, part or *accessory* that has a *total exposure period* of less than or equal to 24 h;

2) prolonged exposure: *medical device*, part or *accessory* that has a *total exposure period* of more than 1 d but be less than 30 d; and

3) long-term exposure: *medical device*, part or *accessory* that has a *total exposure period* of greater than or equal to 30 d.

e) Notwithstanding d), some *gas pathway medical devices* or *accessories* are considered transitory contacting with limited exposure (<24 h). They have very brief or transitory exposure to a single *patient* (e.g. single use inhalers, respiratory gas monitors, mouth pieces, masks, etc.). In these cases, an evaluation shall be completed with rationale.

NOTE 3 These types of medical devices and accessories do not typically require testing to address biocompatibility.

1) Coatings or lubricants that can be readily released into the air or could be left in contact with body tissues after the *medical device* or *accessory* is removed shall be considered.

2) Cumulative use, by a single *patient*, shall be considered.

5.2 *Particulate matter* (*PM*) emissions

All *gas pathways* of *medical devices* or *accessories* shall be:

a) evaluated for *PM* emissions; and

b) if required, tested according to ISO 18562-2:2024.

1) Water tanks in the *gas pathway* shall be evaluated to ISO 18562-2:2024 without water.

5.3 *Volatile organic substance* emissions

All *gas pathways* of *medical devices* or *accessories* shall be:

a) evaluated for the emission of *volatile organic substances*: and

b) if required, tested according to ISO 18562-3:2024.

1) Water tanks in the *gas pathway* shall be evaluated to ISO 18562-3:2024 without water.

NOTE Emission of *volatile organic substances* includes emissions of *VOCs*, *SVOCs* and *VVOCs*.

5.4 *Leachables* in condensate

a) If humidified gas or water is present in the *medical device* and can condense in the *medical device* and subsequently reach the *patient* in liquid form, then evaluation shall be performed for the presence of harmful *leachables* according to ISO 18562-4:2024.

1) Only sections of the *gas pathway* from which the *patient* can be exposed to water condensate need be evaluated.

2) Water tanks from which water can reach the *patient's* airway shall be evaluated to ISO 18562-4:2024.

3) If the *medical device* under evaluation has already been evaluated as tissue-contacting according to ISO 10993-1, then *leachables* testing need not be performed in addition.

6 Adjustment of *exposure dose* and *inhalation dose* for different *patient* groups

6.1 General considerations

a) If a compound has been detected in the gas stream or condensate, then it shall be determined if the amount that can reach the *patient* presents an acceptable *risk* to that *patient*.

b) The adjustments found in ISO 10993-17 may be used in calculating the *TI* to which a *patient* may be exposed for the tests of ISO 18562-4 (condensate) and the *TI* to be used to calculate the *TE* to which a *patient* may be exposed for the tests of ISO 18562-3 (*VOS*).

c) To estimate the ingested dose to the *patient* for the tests of ISO 18562-4 (condensate), convert the concentration of each substance to a total dose per *patient* per day based on the condensate volume.

d) Adjustments for *patient* groups are not applied to ISO 18562-2 (*particulates*), where allowable limits are taken from the US EPA 40 § CFR Part 50[17].

e) To estimate the inhalation dose to the *patient* for the tests of ISO 18562-3, convert the concentration of each substance to a total dose per *patient* per day based on the breathed volume.

6.2 Adjustment for different patient groups

a) Table 1 describes *patient* groups and indicates the default body masses and default breathing volumes. These shall to be used in the calculation of *tolerable exposure* and in the calculation of *exposure dose* or *inhalation dose*.

1) For specific pathologies or *intended uses* different values may be applied, with rationale.

b) Use the row for the intended *patient* population with the lowest intended ideal body mass for leachables in condensates or breathing volume for *VOS*.

NOTE There is guidance or rationale for this list item contained in Clause A.2.

c) For the patient population chosen under 6.2 b), use the default breathing volume consistent with the *intended use* of the *medical device*—*patient* at rest or *patient* undergoing exercise.

EXAMPLE 1 A critical care ventilator for ventilator-dependent *patient* uses the default daily breathing volume (resting).

EXAMPLE 2 Home healthcare environment sleep apnoea therapy equipment uses the default daily breathing volume (resting).

EXAMPLE 3 For a homecare ventilator for a ventilator dependent adult, it is reasonable to expect duration of exercise of up to a maximum of 2 hours per day. This would result in breathed volume during this two hours totalling 9,2 m^3. For the other 22 h of the day, the breathed volume would be 11,5 m^3 times 22/24 that equals 10,5 m^3. The total breathed volume should be increased from 11,5 m^3 to 19,7 m^3.

Table 1 — Default body mass and breathing volume by *patient* group

***Patient* group**			**LPV[b]**	**Resting breath rate[c]**	**Default body mass**	**Default daily breathing volume (resting)**	**Maximum exercise ventilation[d]**
Label	**Typical age range[a]**	**Ideal body mass range[a]**					
	year	kg	ml/kg	breaths/min	kg	m^3/d	m^3/h
Premature neonate	Premature birth	<2,65	6	60	0,5	0,26	—
Infant	0 to 0,5	2,65 to 7,4	8	56	3,5	2,3	—
Small child	0,5 to 3	7,4 to 15	8	44	10	5,1	—
Child	3 to 10	15 to 32	8	26	20	6,0	1,8
Adolescent	10 to 18	32 to 56	8	21	32	7,7	2,6
Adult	>18	>56	8	20	60	11,5	4,6

[a] These values are descriptive and are not used for calculation.

[b] LPV is the lung protective ventilation strategy based on ideal body mass[24].

[c] The resting breath rate is the 90th percentile of the normal range as reported in Reference [22].

[d] This column has the maximal likely total ventilation during exercise, expressed in units of m^3/h. When the *intended use* of a *medical device* includes periods during which the *patient* is likely to be exercising, the *manufacturer* should determine the likely duration of such exercise (in hours per day) and use this to determine an additional breathing volume for the periods of exercise. The data in this column are the predicted resting minute ventilation multiplied by eight, based on clinical data that show minute ventilation during exercise increased by a factor of around 6 to 8 times.[19][26] Exercise ventilation data are not appropriate for small children and infants.

7 Deriving *tolerable exposure* (*TE*) for *VOS*

NOTE There is guidance or rationale for this Clause contained in Clause A.2.

7.1 General *process*

Derive an inhalational *TE* for each identified *VOS* above the reporting limit defined in ISO 18562-3:2024, 5.2 i) (see ISO 16000-6:2021) in accordance with the *process* illustrated in Figure 3.

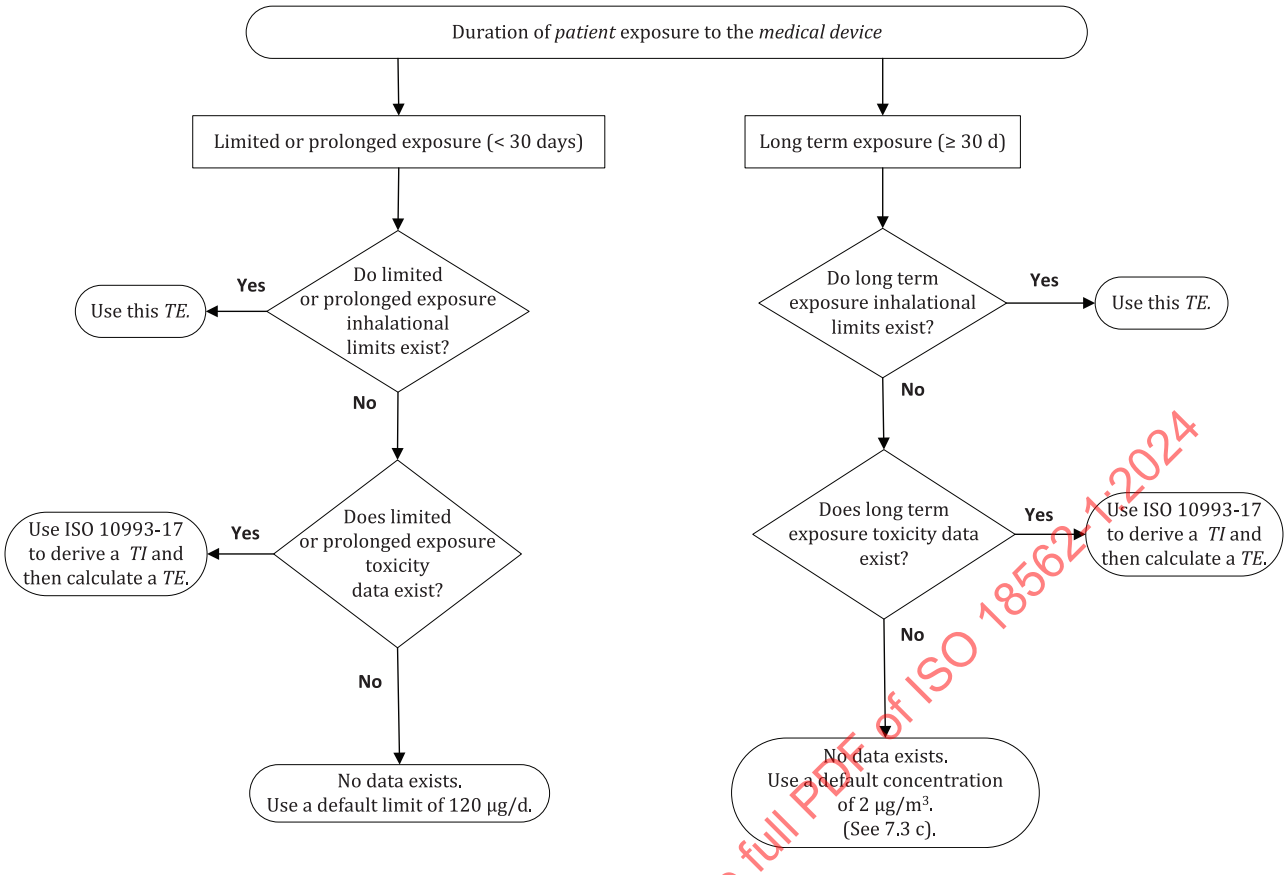


Figure 3 — Flowchart of *process* to derive inhalational *tolerable exposure* (*TE*) for each identified *VOS* compound

7.2 For *medical devices* intended for limited exposure use (≤24 h) and prolonged exposure use (>24 h but <30 d)

For each identified compound

a) if possible, obtain the limited or prolonged exposure inhalational limit for that compound from internationally available toxicological databases and the published peer reviewed literature.

   1) Use this exposure limit in the assessment of *biocompatibility.*

b) if a limited or prolonged exposure inhalational limit is not directly available for that compound, then use the procedure described in ISO 10993-17 to estimate the *TI* based on otherwise available toxicological information and use that *TI* to calculate a *TE*.

   1) Parenteral toxicological information may be used in the absence of inhalational toxicological information without modification.

   2) The use of non-inhalational or non-parenteral information shall be justified in the biological evaluation report.

c) if no toxicological information exists for limited or prolonged exposure or a compound is unidentified, then use 120 µg/d as the threshold for that compound (see ICH M7:2023-09, Table 2).

   1) This threshold shall not be scaled according to body mass.

      NOTE This limit is based on the value for systemic exposure. Exposure by inhalation is regarded as a systemic exposure.

7.3 For *medical devices* intended for long-term exposure (≥30 d)

For each identified compound

a) if possible, obtain the long-term exposure inhalational limit for that compound from internationally accepted toxicological databases.

   1) Use this exposure limit in the assessment of *biocompatibility.*

b) if a long-term exposure inhalational exposure limit is not directly available, then use the procedure described in ISO 10993-17 to estimate the *TI* based on otherwise available toxicological information and use that *TI* to calculate a *TE*.

   1) Parenteral toxicological information may be used in the absence of inhalational toxicological information without modification.

   2) The use of non-inhalational or non-parenteral information shall be justified in the biological evaluation report.

c) if no toxicological information exists for long-term exposure or a compound is unidentified, then use 2 µg/m^3 as the inhalational exposure limit for that compound.

   1) This inhalational exposure limit shall not be scaled according to body mass.

      NOTE This value is derived from the indoor air standard, ISO 16000-6:2021 and is considered safe as this standard applies for permanent exposure to indoor air.

8 Determining values for *leachables* in condensate

8.1 General

For each identified compound

a) if possible, obtain compound-specific toxicological data from internationally accepted toxicological databases or peer reviewed scientific literature.

   1) Use this toxicological data to derive a *TI* (µg/kg body mass/d) for this compound using the procedure described in ISO 10993-17:2023, 7.1, and use that *TI* to calculate a *TE*.

b) if compound-specific toxicological data is not available, then use the procedure described in ISO 10993-17:2023, 6.2.4, to estimate the *TI* based on otherwise available toxicological information and use that *TI* to calculate a *TE*.

c) If no toxicity data are available to derive a *TI*, then use the *TTC* value indicated in Table 2 (see ICH M7: 2023-09).

   1) The *TTC* value shall not be scaled according to body mass.

Table 2 — *TTC* values by *total exposure period*

Total exposure period	***TTC* value** µg/d
≤ 1 month	120
> 1 month to ≤ 1 year	20
>1 year to ≤ 10 years	10
> 10 years	1,5[a]
[a] The 1,5 µg/d value is based on 10^{-5} cancer risk and 60 kg (adult) body mass[20][27].	

8.2 Adjustments for different *patient* groups

a) *Patient*s, other than adults, cannot tolerate the same dose of a toxic substance as an adult. The *TE* for *patient* categories other than adults, are calculated by adjusting for their lower body mass compared to an adult.

EXAMPLE If the *TE* (in µg/d) for a substance is known for an adult, then the *TE* for an infant *patient* is 0,058 of that for an adult patient (because 3,5 kg divided by 60 kg is 0,058).

b) For the purposes of *TE* calculations in this document, a premature neonate or infant only remains in that category for 6 months. A *medical device* or *accessory*, only intended for use with premature neonatal or infant *patients*, with greater than 30 days of use may be evaluated based on a 1-year *total exposure period* instead of the lifetime exposure period.

c) For sensitive patient populations, the *TI* shall take into account ISO 10993-17:2023, C.2.2.2.

8.3 *Exposure dose* estimate for condensate

To estimate the *exposure dose* to the *patient*, convert the concentration of each substance to a total dose per *patient* per day based on the condensate volume reaching the *patient*.

9 *Risk control*

a) If the *exposure dose* or *inhalation dose* of one or more compounds exceeds the *tolerable intake*, then the materials and manufacture of the *medical device* shall be reviewed.

1) If *risk control* is practicable, then the design (e.g. shape, materials or *processes*):

i) shall be revised; and

ii) *biocompatibility* evaluation shall be repeated.

2) If *risk control* is not practicable, perform the *benefit-risk analysis* as described in Clause 10.

3) If the *manufacturer* determines that the *benefit* outweighs the *risks*, then the *medical device* conforms with this document.

10 *Benefit-risk analysis*

a) If substances are identified, and their quantities are in excess of the *tolerable exposure* levels derived above, then the *manufacturer* shall review the materials and manufacturing *processes*.

b) If that review cannot identify practicable alternative materials or *processes*, then a *benefit-risk* analysis according to ISO 14971:2019, 7.4, shall be carried out to determine if the *medical device* can still be considered suitable if the *benefits* arising from the use of the *medical device* outweigh the *risks* posed to the *patient* from this substance being present.

NOTE 1 *Benefit-risk analysis* can be particularly applicable to critical life-saving *medical devices* without which the *patient* will die or for *medical devices* for which there are no alternatives.

EXAMPLE The *residual risks* of the *medical device* are similar to the *residual risks* of other similar *medical devices* that are legally marketable.

c) When the *manufacturer* determines that the *benefits* outweigh the *risks*, the *manufacturer* shall disclose the *residual risk* in the *accompanying information*.

d) The *manufacturer* shall document in the biological evaluation report the results of *benefit-risk analysis*, if performed.

NOTE 2 Some *authorities having jurisdiction* evaluate this *benefit-risk analysis*.

Check conformity by inspection of the *risk management* plan and *risk management file*.

11 Biological evaluation report

a) The biological evaluation shall be documented in a report.

b) For *gas pathway medical devices* evaluated according to this document, the biological evaluation report shall include:

   1) a description of the *medical device* or *accessory* subject to evaluation;

   2) the biological evaluation plan;

   3) the description and rationale for the test articles any differences between them and the final *medical device*;

   4) the results of the *risk assessment* (see 4.4);

   5) for any testing performed:

      i) summary comparison of the acceptance criteria and *particulate matter* released, according to ISO 18562-2:2024, 5.1;

      ii) summary comparison of the acceptance criteria and *inhalation doses* for *volatile organic substances* according to ISO 18562-3:2024, 5.2;

      iii) summary comparison of the acceptance criteria and *exposure doses* for *leachable* residues in condensates according to ISO 18562-4:2024, 5.3.6; and

      iv) *risk assessment* of the findings according to ISO 14971:2019, including toxicological relevance of *volatile organic substances* and *leachable* residues in condensate according to ISO 10993-17:2023, Annex D; and

   6) the results of any *benefit-risk analysis*, if performed.

Annex A
(informative)

Rationale and guidance

A.1 General guidance

This Annex provides rationale for the some requirements of this document and is intended for 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 to be essential for its proper application. Furthermore, as clinical practice and technology change, it is believed that rationale for the present requirements will facilitate any revision of this document necessitated by those developments.

A.2 Rationale for particular clauses and subclauses

The numbering of the following rationales corresponds to the numbering of the clauses and subclauses in this document. The numbering is, therefore, not consecutive.

— **4.2 – *Type tests***

Some *medical devices* are provided in variants with small differences which have minor impact on their biological safety. It is therefore possible to use test results from one variant for the evaluation of the biological safety of other variants. This subclause requires a justification for the choice of which variant to test.

— **6.1 – General considerations**

— ***b) 2)***

In this revision, the committee has further stratified the potential *patient* population, to define groups based on clinical presentation and body mass with defined *risk* profiles. *Patient* populations are now considered in six strata:

— premature neonate;

— infant;

— small child;

— child;

— adolescent; and

— adult.

For each of these *patient* groups, the committee has defined the range of expected ideal body mass, together with a default body mass (applicable to calculations of *tolerable exposure*) and default breathing volume (applicable to calculations of *inhalation dose*). These default values are regarded as generally applicable within the *patient* group – for example, a premature neonate with a body mass of 1,0 kg breathes twice as much volume as the default premature neonate with body mass 0,5 kg, resulting in twice the *inhalation dose*; but that same scaling also applies to the *tolerable exposure*, as the *exposure dose* applies to twice the body mass, so the concentration at which the *tolerable intake* is reached is the same for both *patients*.

Furthermore, the committee assumes that the *patient* population with the lowest body mass represents the most vulnerable population, and in the absence of evidence to the contrary, determination of

allowable limits based on this population is considered conservatively protective for the older and heavier *patient* groups.

It should be noted that for some *medical devices* or *accessories*, the flow rate through the *medical device* or *accessory* might not correspond directly with the *patient* breathed volume, either due to the *patient* breathing some gas independently of the *medical device* or *accessory*, or due to flow required to achieve therapy exceeding that delivered to the *patient's* lungs. If the ratio of flowrate to *patient* breathed volume is significantly different for the different *patient* groups, it can be necessary to calculate *inhalation dose* for all applicable *patient* groups.

— **Clause 7 – Deriving *tolerable exposure (TE)* for *VOS***

The choice of a *TTC* level for unknown substances of 120 µg/d (limited exposure and prolonged exposure) were taken from ICH M7:2023-09.

The inhalation *TTC* value for prolonged (24 h to 30 d) exposure to *VOSs* released into the *gas pathway* is based on:

— the 5th percentile of a distribution of noncancer *tolerable intake* (*TI*) values derived from inhalation NOAEL (no observed adverse effect level) and LOAEL (lowest observed adverse effect level) values (exposure duration ≤30 d) reported in Reference [32] (135 µg/d);

— the acceptable intake of an individual mutagenic impurity in a pharmaceutical product with exposure to the *patient* for ≤30 d, per Reference [12] (120 µg/d).

The lower of the two values, 120 µg/d, was selected as the inhalation *TTC* value for limited and prolonged exposure and this value is intended to be protective for both cancer and noncancer effects.

Lastly, the committee considered long-term exposure limits and proposed 2 µg/m^3. This is also the reporting limit for non-targeted compounds for indoor air according to ISO 16000 and is thus considered safe for permanent exposure to indoor air. This limit is considered to be too restrictive for limited and prolonged exposure. Therefore, the *TTC* levels as defined by ICH M7:2023-09 were applied for these contact durations.

It is recognized that these limits can be adjusted in the future as more knowledge becomes known and analytical measurement techniques improve. However, on the balance of probabilities, the committee felt that the proposed limits were reasonably conservative and would not expose *patients* to unacceptable *risks*.

These limits apply only to substances added by the *medical device* to gases supplied to *patients*. The proposed limits are not relevant to any other type of *patient* exposure.