International Standard

ISO 18562-4

Second edition
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Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 4: Tests for leachables in condensate

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

Partie 4: Essais concernant les relargables dans le condensat

Reference number
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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, *Respiratory devices and related equipment used for patient care* 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 18562-4:2017), 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;

— clarified the stepwise test procedure;

— required determination of volume of condensate that can reach the *patient*; and

— required calculating resulting *exposure dose*.

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 is intended to protect *patients* connected to *medical devices* from harmful amounts of substances that might be dissolved in water that has condensed in the *gas pathways* of those *medical devices*. This document represents the application of the best-known science by addressing the *risks* from potentially hazardous substances in the condensate being conveyed to the *patient* by the *gas pathway*. The condensate itself will be distilled water, having condensed from the vapour phase. But substances from within the *medical device* could leach into the liquid water (condensate) present in the breathing system.

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 appropriately address the biological evaluation of the *gas pathways* of *medical devices*.

It is not within the scope of this document to address contamination arising from the source of the breathing gases entering such *medical devices*, but rather only address the potential contamination generated from within the *medical device* itself. This contamination might be from the original manufacturing *process* or generated by the *medical device* itself during use.

This document is concerned with substances that could be conveyed to the *patient* by liquid condensate forming in the *medical device* and then subsequently reaching the *patient*. Potentially harmful substances that could be found in condensate include organic compounds and elements (such as metals). Condensate management is part of most healthcare institution protocols, with the primary aim of preventing the condensate reaching the *patient* in the first place. The absolute volume of liquid reaching a *patient* by this route should therefore be low, but it might happen. This document outlines tests for substances contained in the liquid.

The methods to determine the acceptable levels of contamination are contained in ISO 18562-1.

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[16] as indicated in Annex B;

— the *Labelling Principles for Medical Devices and IVD Medical Devices,* IMDRF/GRRP WG/N52:2019[17] 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[18].

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 4:
Tests for leachables in condensate

1 Scope

This document specifies tests for substances leached by liquid water condensing in *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 chemical characterization methods described in this document apply to chemical substances that could leach from the *medical device*, its parts or *accessories* into the condensate. This document establishes verifiable acceptance criteria for these tests. The identity and quantity of each chemical released is intended for toxicological *risk assessment* as described in ISO 18562-1:2024.

This document addresses potential contamination of the gas stream arising from the *gas pathways*, which deliver breathing gas to the *patient*.

This document applies over the *expected lifetime* of the *medical device* in *normal use* and takes into account the effects of any intended *processing*.

This document does not address biological evaluation of the surfaces of *gas pathways* that have direct contact with the *patient*. 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 devices, oxygen concentrators, nebulizers, low-pressure hose assemblies, humidifiers, heat and moisture exchangers, respiratory gas monitors, respiration monitors, masks, medical respiratory personal protective equipment, mouth pieces, resuscitators, breathing tubes, breathing systems filters, Y-pieces and any breathing *accessories* intended to be used with such 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*.

This document does not address contact with drugs or anaesthetic agents. If a *medical device* or *accessory* is intended to be used with anaesthetic agents or drugs, then additional testing can be required. This document is intended to quantify hazardous water-soluble substances that are leached from the *medical device*, its parts or *accessories* by condensate and then conveyed by that liquid to the *patient*.

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 10993-5:2009, *Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity*

ISO 10993-10:2021, *Biological evaluation of medical devices — Part 10: Tests for skin sensitization*

ISO 10993-12:2021, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-18:2020+AMD1:2022, *Biological evaluation of medical devices — Part 18: Chemical characterization of materials within a risk management process*

ISO 10993-23:2021, *Biological evaluation of medical devices — Part 23: Tests for irritation*

ISO 18562-1:2024, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 1: Evaluation and testing within a risk management process*

ICH Q3D(R2):2022,[1)] *Guideline for elemental impurities*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 18562-1:2024 and the following 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 all defined terms and their sources used in this document are given in Annex D.

3.1
exaggerated extraction
extraction that is intended to result in a greater amount of a chemical constituent being released as compared to the amount generated under the simulated conditions of use

Note 1 to entry: It is important to ensure that the *exaggerated extraction* does not result in a chemical change of the material.

[SOURCE: ISO 10993-12:2021, 3.3]

3.2
extractable
substance that is released from a *medical device* or material of construction when the *medical device* or material is extracted using laboratory extraction conditions and vehicles

[SOURCE: ISO 10993-18:2020+AMD1:2022, 3.16]

4 General principles

All *gas pathways* that are exposed to water or that are exposed to humidified gas, and within which water vapour can condense and subsequently reach the *patient* in liquid form shall be evaluated using the principles detailed in ISO 18562-1:2024.

NOTE Some parts of the expiratory *gas pathways* can allow condensed water to settle, and subsequently flow under gravity back towards the *patient*.

1) Available at: https://database.ich.org/sites/default/files/Q3D-R2_Guideline_Step4_2022_0308.pdf

5 *Leachables* in condensate

5.1 Identifying applicable *gas pathway* surfaces

a) A *medical device*, its parts or *accessories* shall not add *leachables* to the condensate at levels that create an unacceptable *risk* to the *patient.*

b) All *gas pathways* of *medical devices* or *accessories* in *normal use* and *normal condition* shall be evaluated for *leachables* in condensate, where

— gas in the *gas pathway* can reach 100 % saturation with water at some point in the *gas pathway*,

— condensate can form on or flow along the *gas pathway* surfaces, and

— that liquid condensate can reach the *patient*.

NOTE 1 Some parts of the expiratory *gas pathways* can allow condensed water to settle, and subsequently flow under gravity back towards the *patient*.

NOTE 2 Condensate, which in itself is water, can form in *gas pathways* and can take the form of liquid drops or a film of water on the *gas pathway* walls. This liquid water can extract substances from the materials of the walls that would not be extracted by the breathing gas alone. If this liquid condensate can reach the *patient,* it could potentially convey harmful substances to the *patient*.

1) Reasonably foreseeable *use errors* that can affect condensate reaching the *patient* should also be considered one *use error* at a time.

NOTE 3 Reasonably foreseeable *use errors* can include incorrect equipment set up.

c) Containers for water (e.g. water tanks) where that water in liquid form can reach the *gas pathway* and then reach the *patient* shall be evaluated for *leachables* in the water.

5.2 Determining if testing is required

a) The evaluation shall use the *risk management process* to assess if testing is required.

b) Sections of the *gas pathway* from which the *patient* cannot be exposed to condensate need not be tested.

EXAMPLE An exhaust *gas pathway* separated by a check valve preventing backflow of condensate to the *patient*.

1) The rationale for excluding *gas pathways* where the *patient* cannot be exposed to condensate shall be documented in the report.

c) If the *medical device* part or *accessory* is identical or sufficiently similar in *formulation*, geometry, manufacturing *processes* or application *processes*, packaging and any subsequent *processing* to an existing *medical device* with the same *intended use* and worst case clinically relevant conditions, an evaluation may conclude that no further testing is required. Refer to ISO 18562-1:2024, Figure 2 and ISO 10993-18:2020+AMD1:2022, C.2.

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

1) Any differences between the *medical device* part or *accessory* and existing *medical device* part or *accessory*

i) shall be documented in the report, with

ii) a rationale provided in the report for why the changes do not negatively impact the condensate volume and *leachable* profile.

d) If the *medical device* under evaluation has already been evaluated as an external communicating *medical device* with contact to tissue/bone/dentin in accordance with ISO 10993-1:2018, then the tests in 5.3 need not be performed.

EXAMPLE 2 A tracheal tube, because of its direct contact with the *patient*, is evaluated utilizing ISO 10993-1. In this case, the tests of this document are not required.

NOTE 2 Some *authorities having jurisdiction* might require the tests of 5.3 if the *medical device* is intended for use on particularly vulnerable *patient* populations, such as neonates.

e) If the *risk management process* determines that testing is required, the tests of 5.3 shall be performed.

5.3 Test methods

5.3.1 General

The condensate evaluation of *gas pathways* shall include

a) establishing the worst-case clinically relevant maximum volume of condensate that can be conveyed to the *patient.*

NOTE 1 There is guidance and rationale for this list item contained in Clause A.2.

1) This shall be done by one of the following:

i) experimentally determining in *normal use* and *normal condition* under worst-case clinically relevant parameters (e.g., temperature, gas flowrate, etc.) the volume of condensate reaching the *patient*; or

I) *Normal use* shall include reasonably foreseeable *use errors* that contribute to condensate reaching the *patient*, one *use error* at a time (e.g., selection of incorrect settings for a *patient* or incorrect equipment set up).

NOTE 2 Normal use assumes the implementation of specific measures described in the instructions for use intended to avoid or reduce patient exposure to condensate. The worst-case amount of condensate that can be formed and reach the patient from simultaneous use errors is not relevant. A lower volume can then be justified for the toxicological risk assessment.

II) All reasonably foreseeable *use errors* shall be documented in the report with the respective condensate volumes generated.

III) If the experimentally determined volume of condensate reaching the *patient* establishes that no more than 0,1 ml in 24 h reaches the *patient* under worst case clinical conditions, then no further testing is required.

IV) The experimental methods shall be justified in the report.

NOTE 3 Breathing *gas pathways* are systems that commonly include multiple *medical devices* and *accessories*, often from different *manufacturers*. The subject *medical device* or *accessory* needs to be evaluated in its *intended use* as part of a system and might not be the part that determines the volume of condensate forming and being delivered to the *patient*.

ii) by justified arguments in the report.

NOTE 4 Some *authorities having jurisdiction* can require experimental testing.

b) the chemical characterization of the *leachables* in the condensate.

c) performing a toxicological *risk assessment* on the *leachables* in condensate with respect to systemic effects.

NOTE 5 For guidance on which effects (endpoints) are covered in a toxicological *risk assessment*, see Annex A of ISO 10993-1:2018.

NOTE 6 Concerns regarding materials mediated pyrogenicity can be addressed by using well known materials for which a pyrogenic effect is not expected.

d) condensate testing of the *leachables* with respect to the following local endpoints:

1) cytotoxicity;

2) sensitization; and

3) irritation.

5.3.2 Sample collection

a) The duration of sample collection shall be justified and documented in the report based on worst-case clinically relevant *patient* exposure in *normal use*.

b) If a *medical device* is intended to be used repeatedly for long-term duration, the extraction protocol shall be adequate to assess the impact from repeated use (over the *expected lifetime*).

NOTE 1 Some *authorities having jurisdiction* can require aqueous exhaustive extraction for prolonged and long-term exposure *medical devices* or *accessories*.

c) For chemical characterization, the sample shall be collected by:

1) producing and collecting condensate under worst-case clinically relevant conditions; or

i) the worst-case clinically relevant conditions shall be justified by rationale, and

ii) the rationale shall be documented in the report.

2) performing an aqueous extraction on the gas contact surface materials using *exaggerated extraction* (e.g., higher temperature or longer duration).

NOTE 2 Some *authorities having jurisdiction* can require exaggerated extraction to include higher temperature and longer duration relative to clinical use conditions.

i) If performing the *exaggerated extraction* on just the gas contact surface is not technically feasible, the extraction may be performed on the *medical device* or component as a whole,

ii) When the *exaggerated extraction* is performed on the *medical device* or component as a whole, the calculated surface area shall be limited to the gas contact surface area.

d) The sample collection shall facilitate the determination of the worst-case *exposure dose* (in one day).

1) The worst-case *exposure dose* shall be justified by rationale.

NOTE 3 There is guidance and rationale for this list item contained in Clause A.2.

2) The rationale shall be documented in the report.

e) For biological testing for irritation and sensitization, the sample shall be collected by performing a water extraction on the internal gas contact surfaces identified in 5.1 b), in accordance with ISO 10993-12:2021, Clause 10.

NOTE 4 There is guidance or rationale for this list item contained in Clause A.2.

1) Saline extraction shall not be used.

2) If performing the exaggerated extraction on just the gas contact surface is not technically feasible, the extraction may be performed on the *medical device* or *accessory* as a whole.

f) For biological testing for cytotoxicity on the *medical device* or *accessory* itself, the sample shall be collected by performing an extraction in cell culture medium or water on the internal gas contact surfaces in accordance with ISO 10993-5:2009, 4.2.

1) If performing the exaggerated extraction on just the gas contact surface is not technically feasible, the extraction may be performed on the *medical device* or *accessory* as a whole.

2) Where cytotoxicity testing is conducted on a water extract of components including exposed metallic parts, the concentration of the cell culture medium shall be corrected to account for dilution (e.g., use of 10X MEM solutions).

NOTE 5 There is guidance and rationale for this list item contained in Clause A.2.

NOTE 6 Some *authorities having jurisdiction* require that the extraction is performed with cell culture medium.

g) For biological testing for cytotoxicity on the condensate, the sample collection conditions shall represent worst-case clinically relevant conditions including temperature and duration of contact.

h) This document is not intended to be prescriptive in the selection of *medical device* configuration, test methods or the conditions used to produce the sample. Choices shall be justified and documented in the report.

5.3.3 Chemical characterization of *leachables* in condensate

a) Identify and quantify in the condensate or extract,

1) organic *leachable substances*, using appropriate analytical techniques such as

i) gas chromatography-mass spectrometry (GC/MS); or

ii) liquid chromatography - mass spectrometry (LC/MS).

2) elemental (e.g. metal ions) *leachable substances*, using appropriate analytical techniques such as

i) inductively coupled plasma/mass spectroscopy (ICP-MS); or

ii) inductively coupled plasma atomic emission spectroscopy (ICP-AES); or

iii) a combination of ICP-MS and ICP-AES.

NOTE 1 Elemental *leachables* are sometimes referred to as inorganic *leachables*.

NOTE 2 ISO 10993-18 extensively covers chemical characterisation of *medical device* extracts.

b) For all analytical chemistry testing methods used, the analytical sensitivity of the testing approach shall be justified and documented in the report.

NOTE 3 Analytical sensitivity can be determined by a combination of the limit of quantification and a reporting threshold such as by using analytical evaluation threshold (AET) according to ISO 10993-18.

1) The analytical approaches used shall be sensitive enough to permit identification and quantification of chemical constituents that could present a toxicological *risk*, including both expected and unexpected *leachables*.

2) If the methods are inadequate to address the cohorts of concern chemicals, these shall be addressed separately.

c) If it is required to achieve detection of concentrations at the limits specified, enrich the organic impurities in the condensate or extract using established methods, such as

1) stir bar sorptive extraction,

2) solid phase microextraction,

3) liquid-liquid extraction or

4) a demonstrably equivalent method.

5.3.4 Calculation of *tolerable exposure*

a) The assignment of the route of exposure (inhalation or oral) for the *medical device* shall be justified in the report.

b) For organic *leachables*, establish a *tolerable intake*, in accordance with ISO 18562-1:2024.

1) This may also require the application of the *threshold of toxicological concern* concept, as described in ICH M7:2023-09[14].

c) Establish which of the identified elemental *extractables* require *risk assessment* in accordance with ICH Q3D(R2):2022, [15] Table 5.1.

NOTE 1 Some *authorities having jurisdiction* can require review of additional *medical device*-specific elements (e.g. manufacturing contaminants) not listed in ICH Q3D(R2):2022, Table 5.1.

d) For elements requiring *risk assessment* in accordance with ICH Q3D(R2):2022, Table A.2.1, establish the permitted daily exposure with respect to:

1) inhalation; or

2) oral.

NOTE 2 Some *authorities having jurisdiction* can require review of additional limits for *patient* populations not listed in ICH Q3D(R2):2022, Table A.2.1.

5.3.5 Calculation of *exposure dose* estimate

a) Perform an evaluation of the *leachables* using the methods of ISO 18562-1:2024, Clause 8.

b) 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 as established in 5.3.1 and assume the total quantity is released each day.

NOTE If the volume of the condensate that can reach the *patient* cannot be established, the worst-case condition is that all detected substances reach the *patient*.

5.3.6 *Risk assessment*

a) Confirm if the *exposure dose* of each identified substance delivered to the *patient* in the established amount of condensate or extract is less than the chemical-specific tolerable exposure.

1) If no chemical-specific toxicity data is available, use the *threshold of toxicological concern* derived from the method of ISO 18562-1:2024, 8.1 c).

NOTE The route of exposure can be into the lung or by oral ingestion. A *medical device* connected to the *patient* by a tube into the trachea is exposed by inhalation whereas if the *medical device* is connected via a mask or a tube into the nose, the exposure is via oral ingestion (the condensate is swallowed).

b) If the *exposure dose* of an identified substance delivered to the *patient* is more than the *tolerable intake* or *threshold of toxicological concern*, calculate a margin of safety (MoS), where the margin of safety equals the *tolerable intake* divided by the *exposure dose*.

1) Consider whether the *risks* indicated by such margin of safety values (i.e. <1) can be addressed.

2) Conduct a *benefit-risk* analysis utilizing ISO 18562-1:2024, Clause 10.

5.3.7 Biological evaluation according to ISO 10993 standards

a) *Gas pathways* that have potential to convey *leachables* in condensate to the *patient* may be evaluated as externally communicating in contact with tissue/bone/dentin in accordance with ISO 10993-1:2018 with respect to evaluation of condensates.

b) The chemical characterization and toxicological *risk assessment* [see 5.3.1 c)] are used to address systemic effects (e.g., acute, subacute, subchronic and chronic systemic toxicity), genotoxicity, and carcinogenicity. However, this evaluation method is not appropriate to address local endpoints, such as cytotoxicity, sensitization, and irritation, and can be inconclusive for systemic effects.

NOTE 1 An aqueous extraction is sufficient since this document does not address contact with drugs or anaesthetic agents.

NOTE 2 Concerns regarding materials mediated pyrogenicity can be addressed by using well known materials for which a pyrogenic effect is not expected.

1) For complex *medical devices* made of many different components, *simulated-use extractions* may be used. See ISO 10993-12:2021, 10.3.1.

c) If the *risk management process* determines that testing is required, perform a cytotoxicity test in accordance with ISO 10993-5:2009.

NOTE 3 There is guidance or rationale for this list item contained in Clause A.2.

NOTE 4 Some *authorities having jurisdiction* can require extraction with cell cure media.

d) If the *risk management process* determines that testing is required, perform a sensitization test in accordance with ISO 10993-10:2021.

NOTE 5 There is guidance or rationale for this list item contained in Clause A.2.

NOTE 6 The local lymph node assay (LLNA) is not accepted by some *authorities having jurisdiction* as an appropriate method. Refer to Reference [21] for more information on the limitations of LLNA.

e) If the *risk management process* determines that testing is required, perform an irritation test in accordance with ISO 10993-23:2021.

NOTE 7 There is guidance or rationale for this list item contained in Clause A.2.

NOTE 8 The reconstructed human epidermis (RhE) assay is not accepted by some *authorities having jurisdiction* as an appropriate method.

f) Where the use of biological test methods is appropriate, testing shall be in accordance with ISO 10993-1 (see ISO 18562-1:2024, 4.5 Note 1) using sample preparation in accordance with ISO 10993-12 or be otherwise justified in the report.

1) *Biocompatibility* endpoints not addressed by chemical characterization and toxicological *risk assessment* shall be addressed in accordance with ISO 10993-1:2018 (see ISO 18562-1:2024, 4.5 Note 1) using sample preparation in accordance with ISO 10993-12:2021.

6 Reporting

a) The reporting shall include:

1) a description of the *medical device* or *accessory* subject to evaluation (i.e., the sample or samples tested);

2) the description and rationale for the test article including any differences between it and the final *medical device*;

3) the sampling system components;

4) a description of the testing methods utilized for the chemical evaluations and their qualification (e.g., calibration data or accreditation);

5) the testing results (e.g. which substances were detected and what were their concentrations) including a reference to the subclauses which explain how the results were calculated;

6) derivation of the *exposure dose* estimates;

7) a description and rationale of the testing methods utilized for the biological evaluation and the test results;

8) any deviations from the *procedures* indicated in this standard;

9) the test parameters (e.g., flow rate, temperature, pressure, run time duration);

10) any unusual features observed;

11) a dated reference to this standard (the standard used for the evaluation); and

12) the dates of the testing.

b) The chemical evaluations report shall include descriptions and justifications in accordance with:

1) ISO 10993-18:2020+AMD1:2022, 7 a) to 7 g);

2) ISO 10993-18:2020+AMD1:2022, F;

3) ISO 10993-18:2020+AMD1:2022, G.2; and

4) ISO 10993-18:2020+AMD1:2022, G.5.

c) The chemical evaluations report shall clearly state the details and purpose of:

1) the test article in accordance with ISO 10993-18:2020+AMD1:2022, G.3; and

2) the extract preparation in accordance with ISO 10993-18:2020+AMD1:2022, G.4.

Annex A
(informative)

Rationale and guidance

A.1 General guidance

This annex provides rationale for 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 clauses and subclauses in this document. The numbering is, therefore, not consecutive.

— **5.3.1 —General**

a)

In any assessment, the most important consideration is the actual *exposure dose,* which is calculated by taking the concentrations multiplied by the liquid condensate volume that the *patient* ingests per day.

The experts on the committee discussed at length the amount of liquid condensate that might reach the *patient* per day. The committee noted that it is established clinical practice to have methods in place to prevent liquid water as condensate from reaching the *patient*. These methods include heated breathing hoses, water traps and mounting a humidifier below the *patient*. The committee concluded that having condensed water reaching the *patient* was bad clinical practice and was an anomalous event, not a regular occurrence.

The committee agreed that the ISO 18562 series requires consideration of *normal use* in *normal condition* under worst-case clinically relevant conditions, the daily permitted volume of water entering a *patient* should be established experimentally. Reasonably foreseeable *use errors* that can affect the volume of condensate reaching the *patient* should also be considered one *use error* at a time. If the volume of condensate reaching the *patient* from a *use error* is so large that it is an unacceptable *risk* irrespective of leached substances (i.e. might result in aspiration pneumonia or drowning the *patient*), that *use error* should not be considered in the toxicological *risk assessment.* The results from testing are used in the calculations to derive the *exposure dose*. The condensate enters the lungs or is swallowed. The *exposure dose* is therefore compared with derived limits for inhalation or oral ingestion.

— **5.3.2 — Sample collection**

d)

The following are examples of the appropriate considerations for determining the *exposure dose* reaching the *patient*.

If a *medical device* is only intended to be used on a *patient* for 20 min then the extraction duration of 24 h might not be representative of the *leachables* profile. However, a safety factor should be considered for extraction durations less than 24 h.

If a *medical device* could be used multiple times in a 24 h period (with or without *processing*) then the maximum likely cumulative use time should be considered as the extraction duration.

If the *medical device* or *accessory* is single use and replaced consecutively, the 24 h exposure should reflect the number of *medical devices* or *accessories* used.

The underlying principle remains, the determination of the worst-case dose of condensate reaching the *patient* in one day.

e)

The extraction ratio of the *gas pathway* is typically 3 cm^2/ml to 6 cm^2/ml 0,1 g/ml to 0,2 g/ml as described in ISO 10993-12. However, this is not always possible and in such a case extraction conditions should be representative of the worst-case clinical conditions (e.g., *gas pathway* filled to capacity with water).

Care should be taken if the bulk material of the walls of the *gas pathway* are non-homogeneous. For example, a tube with a coating or a co-extruded tube could have different materials on the inner gas contact surfaces from the materials forming the outer surfaces. In this case, grinding up the bulk material to perform the extraction will not give results representative of an intact tube.

Also, be aware that with some materials, fresh cut surfaces can have different properties from the surfaces resulting from the actual manufacturing *process*. For example, extruded foamed materials typically have a closed film surface, while the inner bulk material has a foam structure with a much greater surface area. These two different physical forms of the same material may well give different results when a typical extraction is performed.

Some *authorities having jurisdiction* recommend exhaustive extraction for prolonged and long-term exposure *medical devices*.

f) 2)

The tissue contact by condensates from the *gas pathways* is generated by condensation of water vapor. The extraction of substances from the *medical device* is thus by pure water, which is an adequate extraction solution. To minimize dilution of the water extract, a concentrated MEM solution is required to be used. By using a 10 x or 20 x MEM solution the dilution is kept below 10 % compared to using a MEM solution for the extraction.

— **5.3.7 —Biological evaluation according to ISO 10993 standards**

c), d) and e)

Historically, a *medical device* with a breathing *gas pathway,* which exposed a *patient* to *leachables* in condensate, was evaluated as externally communicating with contact to tissue/bone/dentin utilizing ISO 10993-1. As such, the *medical device* was evaluated for a range of biological effects, including local and systemic endpoints. The *tolerable intake* and *threshold of toxicological concern* methodologies can be used to address systemic toxicity (e.g. acute, subacute, subchronic, and chronic toxicity), genotoxicity and carcinogenicity.

Cytotoxicity testing has been retained, as these tests are very sensitive and serve as a screening test for local effects.

Sensitization and irritation testing have been retained as the *tolerable intake* and *threshold of toxicological concern* methodologies are not currently considered to be adequately predictive.

Annex B
(informative)

Reference to the IMDRF *essential principles* and labelling guidances

This document has been prepared to support the *essential principles of safety and performance* of *gas pathways* as components of *medical devices* according to International Medical Device Regulators Forum (IMDRF). This document is intended to be acceptable for conformity assessment purposes.

Conformity with this document provides one means of demonstrating conformity with the specific *essential principles* of IMDRF/GRRP WG/N47:2018[16] and labelling principles IMDRF/GRRP WG/N52:2019[17]. Other means are possible. Table B.1 maps the clauses and subclauses of this document with the *essential principles* of IMDRF/GRRP WG/ N47:2018. Table B.2 maps the clauses and subclauses of this document with the labelling principles of IMDRF/GRRP WG/N52:2019.

NOTE 1 When an *essential principle* does not appear in Table B.1, it means that it is not addressed by this document.

Table B.1 — Correspondence between this document and the IMDRF *essential principles*

***Essential principle* of IMDRF/GRRP WG/N47:2018[16]**	**Corresponding clause(s)/ subclause(s) of this document**	**Qualifying remarks/notes**
5.3.1 a)	Clause 4, Clause 5, Clause 6	Only the part relating to toxicity and *biocompatibility* of condensates from the *gas pathways* is addressed.
5.3.1 f)	Clause 4, Clause 5, Clause 6	Only condensates from the *gas pathways* are covered.
5.3.2	Clause 4, Clause 5, Clause 6	Only condensates from the *gas pathways* are covered.
5.3.3	Clause 4, Clause 5, Clause 6	Only condensates from the *gas pathways* are covered.
6.1.1	Clause 4, Clause 5, Clause 6	Only condensates from the *gas pathways* are covered.
6.1.2	Clause 4, Clause 5, Clause 6	Only condensates from the *gas pathways* are covered.

NOTE 2 When a labelling principle does not appear in Table B.2, it means that it is not addressed by this document.

Table B.2 — Correspondence between this document and the IMDRF labelling principles

Labelling principles of IMDRF/GRRP WG/N52:2019[17]	**Corresponding clause(s)/sub-clause(s) of this document**	**Qualifying remarks/Notes**
—	—	

Annex C
(informative)

Reference to the *essential principles*

This document has been prepared to support the *essential principles of safety and performance* of *gas pathways* as components of *medical devices* according to ISO 16142-1:2016. This document is intended to be acceptable for conformity assessment purposes.

Conformity with this document provides one means of demonstrating conformity with the specific *essential principles* of ISO 16142-1:2016. Other means are possible. Table C.1 maps the clauses and subclauses of this document with the *essential principles* of ISO 16142-1:2016.

NOTE 1 When an *essential principle* does not appear in Table C.1, it means that it is not addressed by this document.

Table C.1 — Correspondence between this document and the *essential principles*

***Essential principle* of ISO 16142-1:2016**	**Corresponding clause(s)/ subclause(s) of this document**	**Qualifying remarks/notes**
8.1 a)	Clause 4, Clause 5, Clause 6	Only the part relating to toxicity of condensates from *gas pathways* is addressed.
8.1 b)	Clause 4, Clause 5, Clause 6	Only the compatibility of condensates from the *gas pathways* is covered.
8.2	Clause 4, Clause 5, Clause 6	Only condensates from *gas pathways* is covered.
8.4	Clause 4, Clause 5, Clause 6	Only condensates from *gas pathways* is covered.
8.5	Clause 4, Clause 5, Clause 6	Only condensates from *gas pathways* is covered.

Annex D
(informative)

Terminology — Alphabetized index of defined terms

Term	Source
accessory	ISO 18562-1:2024, 3.2
authority having jurisdiction	ISO 18562-1:2024, 3.4
benefit	ISO 18562-1:2024, 3.5
biocompatibility	ISO 18562-1:2024, 3.6
essential principles	ISO 18562-1:2024, 3.7
essential principles of safety and performance	ISO 18562-1:2024, 3.7
expected lifetime	ISO 18562-1:2024, 3.8
exaggerated extraction	3.1
exposure dose	ISO 18562-1:2024, 3.9
extractable	3.2
formulation	ISO 18562-1:2024, 3.10
gas pathway	ISO 18562-1:2024, 3.11
hazard	ISO 18562-1:2024, 3.12
intended use	ISO 18562-1:2024, 3.15
leachable	ISO 18562-1:2024, 3.16
manufacturer	ISO 18562-1:2024, 3.17
medical device	ISO 18562-1:2024, 3.18
normal condition	ISO 18562-1:2024, 3.20
normal use	ISO 18562-1:2024, 3.21
patient	ISO 18562-1:2024, 3.23
process	ISO 18562-1:2024, 3.24
processing	ISO 18562-1:2024, 3.25
risk	ISO 18562-1:2024, 3.27
risk assessment	ISO 18562-1:2024, 3.29
risk management	ISO 18562-1:2024, 3.31
simulated-use extraction	ISO 18562-1:2024, 3.35
threshold of toxicological concern	ISO 18562-1:2024, 3.36
tolerable intake	ISO 18562-1:2024, 3.38
type test	ISO 18562-1:2024, 3.40
use error	ISO 18562-1:2024, 3.41

Bibliography

[1] ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

[2] ISO 10993-3, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

[3] ISO 10993-9, *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products*

[4] ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

[5] ISO 10993-13, *Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices*

[6] ISO 10993-14, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from ceramics*

[7] ISO 10993-15, *Biological evaluation of medical devices — Part 15: Identification and quantification of degradation products from metals and alloys*

[8] ISO 10993-16, *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables*

[9] ISO/TS 10993-19, *Biological evaluation of medical devices — Part 19: Physico-chemical, morphological and topographical characterization of materials*

[10] ISO/TS 10993-20, *Biological evaluation of medical devices — Part 20: Principles and methods for immunotoxicology testing of medical devices*

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

[12] ISO 16142-1:2016[2)], *Medical devices — Recognized essential principles of safety and performance of medical devices — Part 1: General essential principles and additional specific essential principles for all non-IVD medical devices and guidance on the selection of standards*

[13] ISO/TS 21726, *Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents*

[14] ICH M7:2023-09, *Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - Scientific guideline*

[15] ICH Q3D(R2):2022, *Guideline for elemental impurities*

[16] IMDRF/GRRP WG/N47:2018,[3)] *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices*

[17] IMDRF/GRRP WG/N52:2019,[3)] *Labeling Principles for Medical Devices and IVD Medical Devices*

[18] (EU) 2017/745, (2017) Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices. *OJ L 117, Official Journal of the European Union,* pp. 1-175

[19] USP 35 — NF 30, Chapter 233-Elemental impurities-procedures, February 1, 2013. Available (viewed 2021-03-12) at: https://www.usp.org/sites/default/files/usp/document/our-work/chemical-medicines/key-issues/c233_final.pdf

2) Withdrawn

3) Available at https://www.imdrf.org/documents/documents.asp.

[20] USP 35 — NF 30, Chapter 232-Elemental impurities-limits, February 1, 2013. Available (viewed 2021-03-12) at: https://www.usp.org/sites/default/files/usp/document/our-work/chemical-medicines/key-issues/c232_final.pdf

[21] OECD GUIDELINES FOR THE TESTING OF CHEMICALS. Section 4: Test No. 429: Skin Sensitization, July 23, 2010[4)]

4) Available at: https://www.oecd.org/.

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