ISO/FDIS 18562-4:2024(E)

ISO/TC 121/SC 3/WG 13

Date: 2023-11-27

Secretariat: ANSI

Date: 2023-12-05

Biocompatibility evaluation of breathing gas pathways in healthcare applications

Part 4:
Tests for leachables in condensate

Évaluation de la biocompatibilité des voieschemins de gaz respiratoiresrespiratoire utilisés dans les applicationsle domaine de soins delala santé

Partie 4: Essais concernant les substances relargables dans le condensat

FDIS stage

ISO copyright office
Case postale 56 • CP 401 • Ch. de Blandonnet 8
CH-1211 1214 Vernier, Geneva 20
Tel. Phone: + 41 22 749 01 11

Fax + 41 22 749 09 47

E-mail: copyright@iso.org

Web www.iso.org

Website: www.iso.org

Published in Switzerland.

Contents

Foreword

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

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO 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).

ISO draws attention to the possibility that the implementation of this document may involve the use of (a) patent(s). ISO takes no position concerning the evidence, validity or applicability of any claimed patent rights in respect thereof. As of the date of publication of this document, ISO had not received notice of (a) patent(s) which may be required to implement this document. However, implementers are cautioned that this may not represent the latest information, which may be obtained from the patent database available at www.iso.org/patents. ISO shall not be held responsible for identifying any or all such patent rights.

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

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 121, *Anaesthetic and respiratory equipment*, Subcommittee SC 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 lungs of 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][16] as indicated in Annex B;

— ——the *Labelling Principles for Medical Devices and IVD Medical Devices,* IMDRF/GRRP WG/N52:2019[17][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],[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:—[1], *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 1: Evaluation and testing within a risk management process*

ICH Q3D(R2):2022,[2] *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 terminological databases for use in standardization at the following addresses:

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

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

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]

[1] Under preparation. Stage at the time of publication: ISO/FDIS 18562-1:2023.
[2] Available at: https://database.ich.org/sites/default/files/Q3D-R2_Guideline_Step4_2022_0308.pdf

2 © ISO 2023 – All rights reserved

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*.

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*.

- 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:—, 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.

