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Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 1: Evaluation and testing within a risk management process

Évaluation de la biocompatibilité des voies de gaz respiratoires dans les applications de soins de santé —

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

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Foreword

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

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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

For an explanation on the voluntary nature of ISO 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 the following URL: www.iso.org/iso/foreword.html.

The committee responsible for this document is ISO/TC 121, *Anaesthetic and respiratory equipment*, Subcommittee SC 3, *Lung ventilators and related equipment*.

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

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 materials in the GAS PATHWAY form "indirect contact" with the PATIENT, and should be subjected to tests equivalent to those required for tissue contact parts of MEDICAL DEVICES. This interpretation can lead to tests with questionable benefit and also to possible HAZARDS not being detected.

ISO 10993-1:2009 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 10993-1:2009 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 new series of standards is intended to address the specific needs for the evaluation of GAS PATHWAYS that are not adequately covered by ISO 10993-1:2009.

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. Later amendments and additional parts are planned to explicitly cover less common substances.

In this document, the following print types are used:

— requirements and definitions: roman type;

— *test specifications: italic type*;

— informative material appearing outside of tables, such as notes, examples and references: in smaller type. Normative text of tables is also in a smaller type;

— terms defined in Clause 3 of this DOCUMENT or as noted: small capitals.

In this document, the conjunctive "or" is used as an "inclusive or" so a statement is true if any combination of the conditions is true.

The verbal forms used in this document conform to usage described in Annex H of the ISO/IEC Directives, Part 2. For the purposes of this document, the auxiliary verb:

— "shall" means that compliance with a requirement or a test is mandatory for compliance with this document;

— “should” means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this document;

— “may” is used to describe a permissible way to achieve compliance with a requirement or test.

An asterisk (*) as the first character of a title or at the beginning of a paragraph or table title indicates that there is guidance or rationale related to that item in Annex A.

The attention of Member Bodies is drawn to the fact that equipment manufacturers and testing organizations may need a transitional period following publication of a new, amended or revised ISO or IEC publication in which to make products in accordance with the new requirements and to equip themselves for conducting new or revised tests. It is the recommendation of the committee that the content of this publication be adopted for implementation nationally not earlier than 3 years from the date of publication for equipment newly designed and not earlier than 5 years from the date of publication for equipment already in production.

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, but does not cover biological HAZARDS arising from any mechanical failure, unless the failure introduces a toxicity RISK (e.g. by generating PARTICULATES). 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 SERVICE LIFE of the MEDICAL DEVICE in NORMAL USE and takes into account the effects of any intended processing or reprocessing.

This document does not address biological evaluation of the surfaces of MEDICAL DEVICES that are in 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 equipment, oxygen concentrators, nebulizers, low-pressure hose assemblies, humidifiers, heat and moisture exchangers, respiratory gas monitors, respiration monitors, masks, 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).

Future parts might be added 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.

NOTE 1 Some AUTHORITIES HAVING JURISDICTION require evaluation of these RISKS as part of a biological evaluation.

NOTE 2 This document has been prepared to address the relevant essential principles of safety and performance as indicated in Annex B.

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 7396-1:2016, *Medical gas pipeline systems — Part 1: Pipeline systems for compressed medical gases and vacuum*

ISO 10993-1:2009, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-17:2002, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

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

ISO 18562-3, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 3: Tests for emissions of volatile organic compounds (VOCs)*

ISO 18562-4, *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 terms and definitions given in ISO 7396-1, ISO 14971 and the following apply.

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

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

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

NOTE For convenience, an alphabetized index of all defined terms and their sources used in this document is given in Annex C.

3.1
ACCESSORY
additional part for use with a MEDICAL DEVICE in order to:

— achieve the INTENDED USE,

— adapt it to some special use,

— facilitate its use,

— enhance its performance, or

— enable its function to be integrated with those of other MEDICAL DEVICES

[SOURCE: IEC 60601-1:2005, 3.3, modified — substituted "MEDICAL DEVICE" for "equipment"]

3.2
BIOCOMPATIBILITY
ability to be in contact with a living system without producing an unacceptable adverse effect

Note 1 to entry: MEDICAL DEVICES may produce some level of adverse effect, but that level may be determined to be acceptable when considering the benefits provided by the MEDICAL DEVICE.

3.3
EXPECTED SERVICE LIFE
maximum period of useful life as defined by the MANUFACTURER

[SOURCE: IEC 60601-1:2005+AMD1:2012, 3.28]

3.4
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 510(k) Memorandum #K97-1]

3.5
GAS PATHWAY
interior surfaces, over which gases or liquids that can be inspired, in a MEDICAL DEVICE bounded by the ports through which gases or liquids enter and leave the MEDICAL DEVICE including the PATIENT interface or the interior surfaces of enclosures that are in contact with gases or liquids that can be inspired

Note 1 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.

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.

3.6
LEACHABLE SUBSTANCE
chemical removed from a MEDICAL DEVICE by the action of water, other liquids or other gases (e.g. anaesthetic agents or inhalational drugs) related to the use of the MEDICAL DEVICE

EXAMPLE Additives, sterilant residues, PROCESS residues, degradation products, solvents, plasticizers, lubricants, catalysts, stabilizers, anti-oxidants, colouring agents, fillers and monomers, among others.

[SOURCE: ISO 10993-17:2002, 3.10, modified — added "or other gases (e.g. anaesthetic agents or inhalational drugs)"]

3.7
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 human beings 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 human body;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may 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 and/or human tissues;

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

[SOURCE: ISO 13485:2016, 3.11]

3.8
NORMAL CONDITION
condition in which all means provided for protection against HAZARDS are intact

[SOURCE: IEC 60601-1:2005, 3.70]

3.9
NORMAL USE
operation, including routine inspection and adjustments by any user, and stand-by, according to the 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.

[SOURCE: IEC 60601-1:2005+AMD1:2012, 3.97, modified — replaced "OPERATOR" with "user"]

3.10
PARTICULATE MATTER
PM
PARTICULATES
solid particles suspended in a gas

3.11
PATIENT
living human undergoing a medical, surgical, or dental procedure

[SOURCE: IEC 60601-1:2005+AMD1:2012, 3.76, modified — removed reference to animal]

3.12
THRESHOLD OF TOXICOLOGICAL CONCERN
TTC
level of exposure for all chemicals, known or unknown, below which it is considered there is no appreciable RISK to human health

Note 1 to entry: A TTC is used as an acceptable value for a TE for an unknown or insufficiently characterized compound.

3.13
TOLERABLE EXPOSURE
TE
total amount of a substance (in units of µg/d) that a PATIENT can be exposed to per 24 h period that is considered to be without appreciable harm to health

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 weight.

Note 2 to entry: TE is calculated by multiplying TOLERABLE INTAKE by the body mass.

3.14
TOLERABLE INTAKE
TI
TOLERABLE INTAKE LEVEL
TIL
total amount of a substance per kilogram of body weight (in units of µg/kg body weight/d) that a PATIENT can be exposed to per 24 h period that is considered to be without appreciable harm to health

Note 1 to entry: This amount is applicable for all PATIENT groups.

3.15
TYPE TEST
test on a representative sample of the MEDICAL DEVICE with the objective of determining if the MEDICAL DEVICE, as designed and manufactured, can meet the requirements of this document

Note 1 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.

[SOURCE: IEC 60601-1:2005, 3.135, modified — substituted "MEDICAL DEVICE" for "me equipment" and added Note 1]

3.16
VOLATILE ORGANIC COMPOUND
VOC
organic compound whose boiling point is in the range of 50 °C to 260 °C

Note 1 to entry: There are many varied definitions of VOC. For the purposes of this document, a VOC is a compound that has a boiling point in the range of 50 °C to 260 °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.

Note 4 to entry: VOC does not include VERY VOLATILE ORGANIC COMPOUNDS (VVOCS) nor semi-volatile organic compounds (SVOCs). Additional parts of this document might be developed to address these substances in the future. Some AUTHORITIES HAVING JURISDICTION require evaluation of these RISKS as part of a biological evaluation.

3.17
VERY VOLATILE ORGANIC COMPOUND
VVOC
organic compound whose boiling point is in the range of 0 °C to 50 °C

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

4 General principles applying to BIOCOMPATIBILITY evaluation of MEDICAL DEVICES

4.1 General

The BIOCOMPATIBILITY evaluation of any material or MEDICAL DEVICE, part or ACCESSORY intended for use with PATIENTS shall form part of a structured BIOCOMPATIBILITY evaluation programme within a RISK MANAGEMENT PROCESS. The BIOCOMPATIBILITY evaluation shall be planned, carried out and documented by knowledgeable and experienced professionals. Figure 1 illustrates this PROCESS.

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

— the physical and chemical characteristics of the various candidate materials over the EXPECTED SERVICE LIFE of the MEDICAL DEVICE;

NOTE Where this information is already documented within the RISK MANAGEMENT FILE for the MEDICAL DEVICE, it can be included by reference.

— any history of human exposure data;

— any existing toxicology and other BIOCOMPATIBILITY safety data on product and component materials, breakdown products and metabolites.

All MEDICAL DEVICES should be evaluated for BIOCOMPATIBILITY, but evaluation does not necessarily imply testing everything. Depending on the final FORMULATION, manufacturing or application, an evaluation may result in the conclusion that no testing or no additional testing is needed.

EXAMPLE The MEDICAL DEVICE 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.

Check compliance by inspection of the RISK MANAGEMENT plan and RISK MANAGEMENT FILE.

