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BIOLOGICAL EVALUATION OF GAS PATHWAYS IN MEDICAL DEVICES

The ISO 10993 series provides a framework for the biological evaluation of all medical devices (MDs) that come into direct or indirect contact with the patient's body. But for many medical devices, biological evaluation doesn't stop there.

In fact, medical devices incorporating a gas-transport system whose intended use involves the patient inhaling gas, or the risk that the gas circulating within it will be inhaled by the latter, must undergo special treatment for their biological evaluation. These include emergency ventilators, reanimation equipment, breathing tubes, nebulizers and inhalers, as well as mouthpieces, nosepieces, masks, and personal respiratory protection equipment.

This newsletter outlines the methodology for assessing the biological risk of gas pathways, as set out in the ISO 18562 series, revised in 2024.

What is a gas pathway?

ISO 18562-1:2024 §3.11 defines a gas pathway as "the interior surfaces over which gases or liquids that can be inspired" in a medical device. A gas pathway is "bounded by the ports through which gases or liquids enter the medical device or accessory", and may include the patient interface, or the inner surfaces of envelopes in contact with gases or liquids that can be inhaled, or certain surfaces of the expiratory path.

A THE STANDARDS FRAMEWORK

The ISO 18562 series of standards applies to respiratory gas pathways used in medical devices. ISO 10993-1:2018 refers to it for gas pathway device components with indirect patient contact, to determine the relevant type of biological risk assessment.

The reader's attention is drawn to the fact that:

- ISO 18562-1 replaces ISO 10993-1 when it comes to characterizing and assessing the biological safety of gas pathways when the gases are intended for or likely to be inhaled by patients;

- On the other hand, ISO 10993-1 does apply to all parts of the medical device that come into direct contact with the patient. For example, in the case of a mouthpiece, nosepiece or mask, the manufacturer must assess the biological risks separately from the gas pathway.

The biological assessment of a medical device including a gas pathway may therefore involve a dual assessment approach with more or fewer steps. These are to be integrated into a structured and clinically relevant biological risk assessment plan, within a risk management process, in accordance with ISO 14971.

B ISO 18652-1 AND ISO 10993-1: WHAT THEY HAVE IN COMMON

- A risk-based approach, combining the collection and evaluation of existing data with, where appropriate, the performance of tests, to carry out an analysis of the toxicological risks to which the patient is exposed, and ultimately to rule on the biological safety of the medical device;

- Similar steps:

1) Detailed presentation of the MD and/or gas pathway (components, raw materials, characteristics, claimed clinical use, target population, expected lifespan, manufacturing process, treatment or reprocessing process if applicable, packaging, storage conditions, aging, etc.);
2) Categorization of the MD and/or gas pathway, taking into account its duration of use and its claimed normal clinical use;
3) Identification of biological parameters, taking into account the previously defined categorization and the conditions of patient exposure to device constituents or other potential contaminants;
4) Collection of existing data, literature review, consideration, if available, of post-market data and/or results of tests previously carried out on the device or on device(s) representative of the device under evaluation...;
5) Analysis of data and data gaps, to rule on the acceptability of all risks associated with the biological parameters identified;
6) Definition and implementation of a chemico-physical test program to obtain additional data to adequately characterize the MD or gas pathway;
7) Toxicological assessment for all substances to which the patient could be exposed, and conclusion on the acceptability of each risk;
8) Definition and realization of a biological testing program, if the data or results of the toxicological evaluation are not sufficient to conclude on the acceptability of certain risks;
9) Compilation of all data collected and generated, and overall risk analysis;
10) Final conclusion on the biological safety of the medical device and the benefit of its use for the patient;
11) Reassessment in the event of changes to the medical device or new data affecting the previous assessment.

- Requirements to carry out chemical analyses in the first instance, before any biological testing, and to limit animal testing if alternatives exist;

- If chemical extractions are to be carried out (aqueous phase extraction of internal surfaces in contact with the gas, for example), if toxicological results are to be interpreted (calculation of a tolerable dose or safety margin), or if biological tests are to be carried out for a gas pathway (evaluation of cytotoxicity, irritation, allergic reactions, identification of degradation products, etc.), the recommendations of the ISO 10993 series of standards remain relevant.

C SPECIFIC FEATURES OF ISO 18652 SERIES

The ISO 18652 series adds requirements to the ISO 10993 series in order to better understand the risks generated by gas pathways and to simplify their biological evaluation by providing appropriate test methods and guidelines for toxicological assessments based on inhalation data.

The ISO 18652 series contains 4 parts:

- **Part 1: Evaluation and testing within a risk management process**
→ General strategy for the biological assessment of gas pathways and instructions for determining tolerable inhalation doses (basis for toxicological assessment) and for interpreting the results.
- **Part 2: Tests for emissions of particulate matter**
→ Analysis of particles contained in gases passing through the device and definition of acceptable limits according to their size and dimensions.
- **Part 3: Tests for emissions of volatile organic substances**
→ Detection and characterization of volatile organic substances that may be released by the gas pathway and then inhaled by the patient.
- **Part 4: Tests for leachables in condensate**
→ Assessment of condensate (drops, water films, liquids) formed in the gas pathway which may contain contaminants and be carried to the patient for inhalation or ingestion.

D ISO 18652 SERIES, NEW FEATURES

→ 1. Standard 2024 updates

The ISO 18562:2024 standards include major revisions compared to the 2017 versions. These evolutions allow:

- **Adding terms, clarifying others, and clarifying the general assessment methodology;**

- Broadening patient typologies to include more vulnerable groups, and redefining their criteria, which invites the manufacturer to question itself more about the clinical target population of its medical device, in order to **carefully consider the parameters** (default volume of air breathed, patient weight, etc.) **that may influence the calculation of the acceptable dose to which the patient may be exposed;**

- Gaining in relevance with the introduction of the concept of inhalation by which compounds (particles, condensates…) may come into contact with the patient, and the widening of the range of organic volatile substances tested. The standard no longer encourages testing only of common potentially dangerous substances, but, similar to ISO 10993-18 practice, **the recommendation is to detect as many substances as possible and quantify them in order to calculate an estimated inhalation dose and compare it with a tolerable exposure dose or a threshold of toxicological concern** (SPT aka TTC, cf. ISO 18562-1:2024 §3.36 or ISO/TS 21726:2019);

- Rewriting the **assessment of condensates, recommending that the risk of irritation be taken into account in addition to cytotoxicity and sensitivity, and enabling an approach closer to clinical use:** imitating as closely as possible clinical use in the laboratory to generate as much condensate as possible, then testing it to detect and quantify the semi-volatile and non-volatile organic compounds present, as well as inorganic compounds;

- Extending ISO 18562-2 testis to the emissions of semi-volatile and highly volatile organic compounds, whereas the previous version focused on emissions of volatile organic compounds only (the distinction is made via the compound's boiling point at atmospheric pressure);

- **Providing guidelines, adjustments and threshold values for toxicological concern adapted to inhalation exposure and to the typology of the patient targeted by the medical device.**

All these updates aim to **better align the biological evaluation of medical devices with their clinical use.** Tables of values and decision trees are a valuable aid to step-by-step assessment.

→ 2. How to proceed with a study based on the 2017 version?

Advancements in the state-of-the-art encourage regular reassessment of the acceptability of the biological risk, previously concluded for a given medical device, ensuring its continued market presence.

Demonstrating compliance with a new version of a standard involves:
- An analysis of discrepancies and impacts between the old standard and the revised version;
- Then, a justification of the adequacy of the historical biological evaluation;
- Or, an action plan to revise the risk assessment and conclude again on its acceptability in light of the clinical benefit.

Similarly, any modification to a medical device (including its design, manufacturing process, usage, etc.) requires reexamining its risk assessment as well as its balance regarding clinical benefit.

The conduction of new tests is not systematically required. It must be justified based on an in-depth analysis of relevant risks using existing data.

→ 3. Duration and frequency of use, and tolerable exposure: What does the standard say?

The definition of biological phenomena likely to affect the patient through the gas pathway and the scope of risk assessment depend on the duration and frequency of use, as well as the patient's exposure conditions.

ISO 18562-1:2024 §3.37 defines "tolerable exposure" as the "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."
This quantity, also referred to as the "allowed dose to the patient," is specific to each type of patient. Expressed in µg/day for the patient, it depends on a given body mass and is obtained by multiplying this body mass by the "tolerable intake" of the constituent. The "tolerable intake" is "the estimate of daily exposure," expressed in µg/kg/day for this constituent, "considered to be without appreciable harm to health " (see ISO 18562-1:2024 §3.38 or ISO 10993-17:2023 §3.26).

The principle of contact duration is not aligned between ISO 18562 and ISO 10993.

According to ISO 18562, the "intended duration of use" for a patient is the exposure duration to the original medical device (MD) and its replacements, rather than the duration of use of an individual MD. The total duration or "total exposure period" is defined in ISO 18562-1:2024 §3.39 as the number of calendar days "between first and last use of an MD or an accessory or a replacement thereof, whether or not the MD or accessory is used every day and regardless of the daily exposure duration."

Therefore, special attention should be paid to the duration of use of certain consumables, components, or accessories; the frequency at which they are replaced will influence the patient's exposure and the risk assessment of the gas pathway.

The 2024 revision introduces the concept of "infrequent use"* of the MD (cf. ISO 18562-1 §3.13), which could help avoid overly conservative categorization: in this case, the total exposure duration would not be the number of days between the first and last use, but rather the duration of a specific use, reduced to a minimum of 24 hours. However, a relevant demonstration will be required to justify that there is no risk of substances released (leachable) by the medical device accumulating between uses and thus being cumulatively delivered to the patient.

Conclusion

The biological evaluation of a medical device with a gas pathway requires a clear and comprehensive understanding of the medical device and its clinical use. This ensures the ability to define a relevant evaluation plan and determine whether tests need to be conducted to successfully evaluate the gas pathway.

If tests are indeed necessary for the gas pathway, standards ISO 18562-2, ISO 18562-3, and ISO 18562-4 must be strictly followed, and testing should be performed under clinically relevant conditions and criteria.
For toxicological evaluation, the ISO 10993-17 methodology is applicable, taking into account the specific characteristics of the gas pathway, which differ from the other parts of the device: The Tolerable Exposure of a substance released by the gas pathway or present in a condensate should be based on a Point Of Departure (POD) or tolerable exposure value from the literature that is relevant for inhalation, or on a toxicological concern threshold value presented in ISO 18562-1, relevant to the target patient and duration of use.
And if biological tests are to be carried out, the recommendations of the specific standards of the ISO 10993 series should be applied.

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*This concept might appear in the upcoming revised version of ISO 10993-1, currently under development.

To go further

TRAININGS FOR AMERICA REGION

European Medical Device Regulation (EU) 2017/745
2-day training session | Virtual Classroom

→ REGISTER FOR THE UPCOMING TRAINING

European in Vitro Diagnostic Device Regulation (EU) 2017/746
2-day training session | Virtual Classroom

→ REGISTER FOR THE UPCOMING TRAINING

TRAININGS FOR OTHER REGIONS

Conduct a biological assessment of medical devices
SA21B | 2-day training session | On demand

→ CONTACT GMED TRAINING CENTER

Manage the risks applied to medical devices in accordance with ISO 14971
SA02 | 2-day training session | On demand

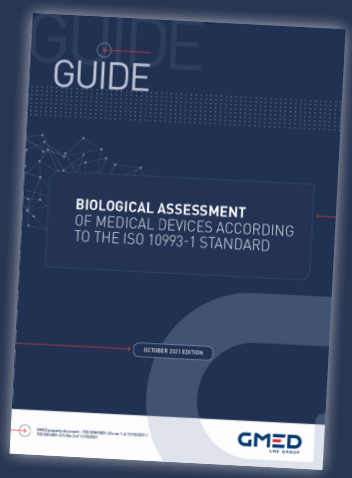
→ CONTACT GMED TRAINING CENTER

Apply the requirements of European Medical Device Regulation (EU) 2017/745 on medical devices
SA56 | 2-day training session | On demand

→ CONTACT GMED TRAINING CENTER

GUIDE

Biological assessment of medical devices according to the ISO 10993-1 standard



The GMED teams have prepared this document in an aim to guide the medical device manufacturers in the presentation and demonstration of their biological assessment according to the ISO 10993-1 standard.

This guide, applicable to all medical devices (whatever their class and type), reviews the general principles, proposes a 7-step methodology corresponding to each section of GMED's biological evaluation report. The guide also sets out the conditions for a biological evaluation file re-assessment.

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