Biocompatibility of Breathing Gas Pathways

US FDA recognises ISO 18562 series.

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The ISO 18562 series of standards “Biocompatibility evaluation of breathing gas pathways in healthcare applications” was published by ISO in 2017. The series includes four parts, which cover the current thinking on gas pathway requirements.

The ISO 18562 series is a “vertical” standard and includes pass criteria. It isn’t quite a “specific device” standard, but it does have a restricted range of applicability. The series was written by a Working Group of ISO/TC 121 Anaesthetic and respiratory equipment, SC 3 Lung ventilators and related equipment.

In contrast, the ISO 10993 series of biocompatibility standards is a “horizontal” standard. That is, it is a set of methods of how to establish biocompatibility, without pass criteria, applicable to a very broad spread of medical devices. The 10993 series is the responsibility of ISO/TC 194 Biological and clinical evaluation of medical devices. TC 194 provided a task force in liaison with TC 121/SC 3 to assist with the preparation of these new standards.

Well almost accepted...

On 7th June 2018 US FDA added the ISO 18562 standards to their list of Recognised Consensus Standards. As is sometimes the case, FDA did not recognise the standards in their entirety. The following is a brief description of the limits of FDA recognition, and some brief commentary on their rationale.

• **ISO 18562-1:2017** Biocompatibility evaluation of breathing gas pathways in healthcare applications - Evaluation and testing within a risk management process.

  **FDA Acceptance:** This standard is recognised in full except for Figure 2, “Perform evaluation for leachable substances, cytotoxicity and sensitization, as required. See ISO 18562-4. If required, perform tests.”  
  The FDA Rationale for exception is that Figure 2 contains test method and/or

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specification that is not scientifically acceptable. Figure 2 conflicts with existing (FDA) published final guidance. Ref.

**Commentary:** The title of Figure 2 is actually, “Flowchart of process to determine what tests are to be considered.” The last rectangle in the Figure 2 flowchart contains the text: “Perform evaluation for leachable substances, cytotoxicity and sensitisation, as required. See ISO 18562-4.” It would appear that the cause of this exception is actually in ISO 18562-4, rather than with ISO 18562-1. But as ISO 18562-1 references ISO 18562-4, the exception stands.

This part of the series was designed to be quite similar to ISO 10993-1, in that it is an overview document, that provides a systematic process, but retains the key idea of managing risks, rather than just passing certain criteria.


  **FDA Acceptance:** This standard is [recognised in full](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard_identification_no=36711).

  **Commentary:** The technical detail follows the long-established methods used by US EPA for the measurement of exposure of the general population to environmental particulates. There is however, considerable freedom for users to apply other measurement techniques.

  The acceptable limits for particulate matter are taken from the US EPA 40 § CFR Part 50.

- **ISO 18562-3:2017** *Biocompatibility evaluation of breathing gas pathways in healthcare applications - Tests for emissions of volatile organic compounds (VOCs)*

  **FDA Acceptance:** This standard is [recognised in full](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard_identification_no=36712).

  **Commentary:** The pass criteria are based on a risk assessment approach, using tolerable intakes and the threshold of toxicological concern (TTC) concept. All the toxicological data applied in the assessment are for the inhalation route of exposure.

- **ISO 18562-4:2017** *Biocompatibility evaluation of breathing gas pathways in healthcare applications - Tests for leachables in condensate.*

  **FDA Acceptance:** [FDA recognises parts of the standard](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=36713). The following parts are not recognised:

  - Subclause 5.2 Test Method, b) "Convert the concentration of each metal ion to a total dose/day by considering the total amount of liquid condensate that reaches the patient in a day as 1 ml."

  - Subclause 5.2 Test Method, c) "Convert the concentration of each substance to a total dose per patient per day by considering the total amount of condensate that reaches the patient per day as 1 ml. Confirm that the dose of each identified substance delivered to the patient in 1 ml of condensate or extract is less than the tolerable intake or threshold of toxicological concern derived from the method of ISO 18562-1:2017, Clause 7."

  - FDA rationale is the same for these two sections, in that they do not agree that the daily dose is 1 mL of condensate.

  - Subclause 5.2 Test Method, e) "Perform a sensitization test according to ISO 10993-10 on the condensate or extract. Select a method suitable for liquids."
FDA rationale for this exception is that they only recognise the Guinea Pig Maximisation Test for sensitisation as being appropriate for a mixture, e.g. extract of a medical device. Allowing other methods conflicts with FDA Guidance.

Annex A.2 Rationale for subclause d)

FDA rationale for this exception is related to the 2\textsuperscript{nd} sentence. (It is unclear why they have this objection.)

Annex A.2 Rationale for subclause e)

FDA rationale for this exception is ... (It is unclear why they have this objection.) (What “existing published final guidance?”)

**Commentary:** In my experience, the total amount of liquid condensate that reaches the patient in a day will have to be experimentally established. FDA’s preference for GPMT over all other sensitisation methods is well known.

FDA’s Technical Contact on ISO 18562 and breathing gas pathways is: Amy Levelle

FDA/OMPT/CDRH/ODE/DAGID/RPDB/ Ph: 301-796-6963 [amy.levelle@fda.hhs.gov](mailto:amy.levelle@fda.hhs.gov) Amy was one of several FDA participants in the ISO/TC 121/SC 3 working group which wrote this series of standards. So, FDA has no shortage of competence/expertise in these standards.

**What about outside US?**

ISO Standards are not written for the benefit of US FDA, but for the international community. Standards are generally written so they will have the maximum spread of international acceptance.

Every country is free to adopt standards as they see fit. The “authorities having jurisdiction” in various countries recognise/use/apply standards according to their own requirements.

**ISO 18562 or ISO 10993?**

ISO 10993 series covers a wide range of devices, categories according to the nature and duration of body contact. (see ISO 10993-1 Table A.1.) Gas pathway devices are a little hard to fit into this categorisation scheme. The correct interpretation of the evaluation requirements has always been a bit obscure. The creation of the ISO 18562 series is a way to directly address this problem, by removing any uncertainty.

A number of device manufacturers have been evaluating the biocompatibility of the breathing gas pathway devices using the ISO 10993 scheme, using the methods that were ultimately codified in ISO 18562. Such manufacturers were able to see how their devices fitted with ISO 10993, as well as how evaluation could be done. The problem was that it wasn’t quite so clear for a lot of the players in the market, either manufacturers of regulators.

*In a sense, ISO 18562 is a “worked example” of ISO 10993-1 in practice,* with a specific emphasis on ISO 10993-17 & ISO 10993-18. It uses the Chemical Characterisation ideas of ISO 10993-18 (and also Physical Characterisation in ISO/TS 10993-19) to quantify the daily dose of substances received by the patient. Then it uses the Toxicological Risk Assessment ideas of ISO 10993-17 to establish whether the risks from those substances are acceptable.

And in good keeping with a good “risk management process,” the outcome of the numerical pass criteria scheme is still open to the consideration of the benefit the patient receives from the device. As was often noted in the writing group, without exposure to the device, the patient can’t breathe. This is a compelling argument...

It’s also worth noting that there are some biological tests straight out of ISO 10993 invoked in ISO 18562. So, the two series are not designed to stand in isolation from each other.
The Challenges

Probably the most difficult part of implementing the use of the ISO 18562 series is in designing the experiments which will collect the data. The test methods noted in the standards do work, or can be made to work, but they may not be the best (most appropriate) method for the device.

Calculating the dose received by the patient, from the experimental data, is similarly challenging. Generally, multiple cases will have to be modelled to establish the worst-case dosage regime.

Some manufacturers and CROs are also likely to find the conduct of the toxicological risk assessments challenging, particularly if those assessments form part of a regulatory submission to FDA. Again, I have experience in presenting and defending such assessments in this context.

About the author:

James Morrison is a materials scientist and toxicologist with more than a decade in practice of biological evaluation of medical devices. James is the current Head of the Australian technical Delegation to ISO for development of biocompatibility standards and was closely involved in preparation of the ISO 18562 series. He has extensive practical experience in experimental design for evaluation of lung ventilators following the ISO 18562 practice. James has also been an active participant in drafting of ISO 10993 standards including the recent revision of ISO 10993-1 and the current drafting of Parts 17 and 18.

James is Senior Consultant – Biocompatibility and provides expert technical advice to clients on biological evaluation and risk assessment of medical devices. He is experienced in development of regulatory documentation and in dealing directly with regulators on these detailed technical subjects, including in face-to-face meetings with US FDA and other regulators.

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