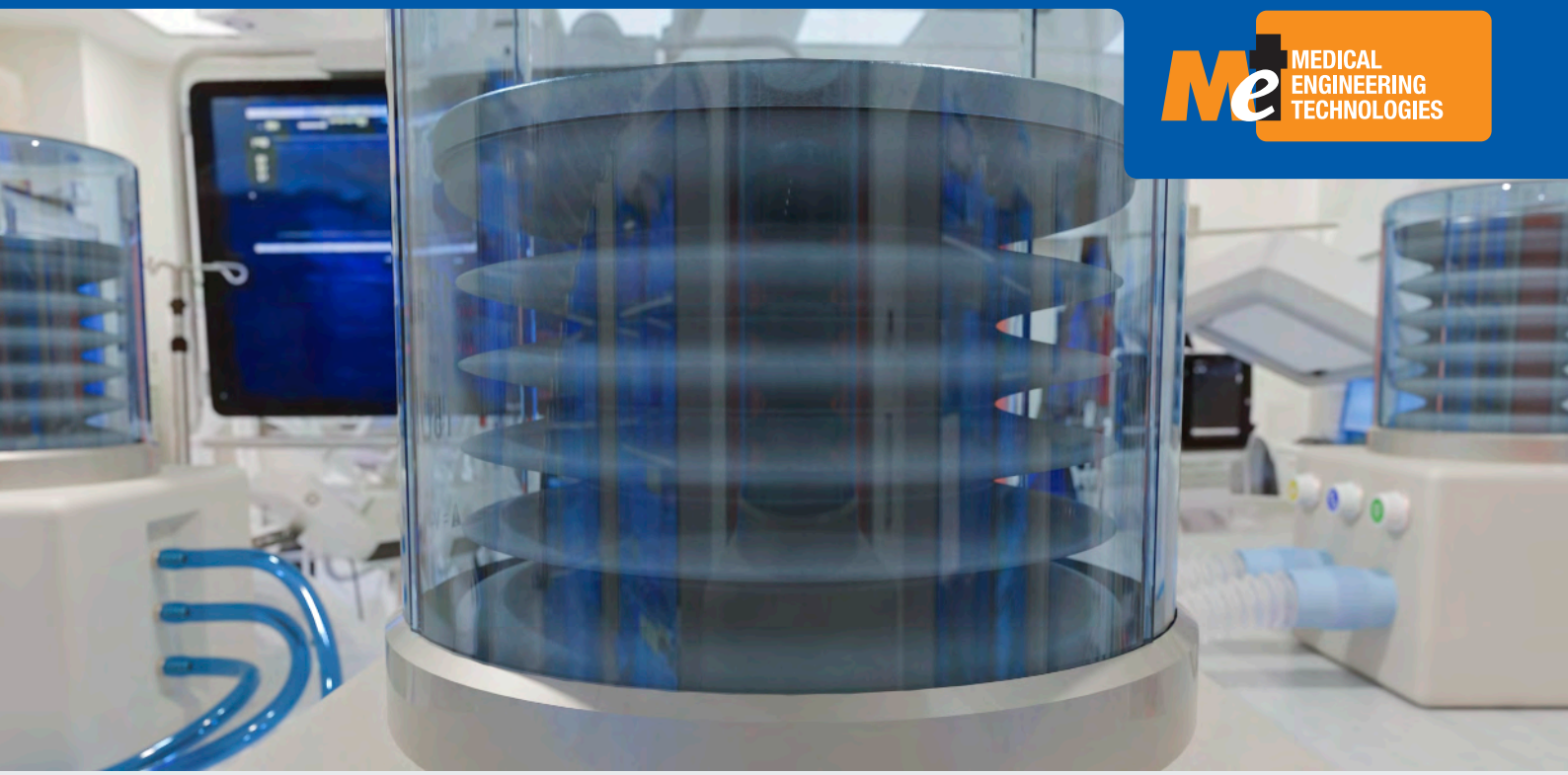

ISO 18562 – Biocompatibility evaluation of breathing gas pathways in healthcare applications

What have we learnt from three years of breathing component biocompatibility testing.

Published in 2017, ISO 18562 has become the reference standard for breathing component biocompatibility testing. It precedes the current version of ISO 10993-1, the general reference for medical device biocompatibility testing, which was published in 2018. ISO 10993 includes examples of breathing components (such as endotracheal tubes) and lists them as mucosal membrane contact. ISO 18562 very sensibly adds particulate and gas testing to ISO 10993.

ISO 18562 has four components: general principles, evaluation of particle emission, evaluation of volatile gas emission, and evaluation of liquid bourn leachables in condensate.

The Standard

ISO 18562-1 Evaluation and testing within a risk management process

This section of the standard discusses the applied principals of testing and toxicological risk assessment. In the scope we are told that it applies to devices that deliver respired air or other materials into the respiratory tract. It also states that if there is contact between the outside of the device and the patient ISO 10993 should be considered. In keeping with ISO 10993-18 it emphasises that data may already be available and this should be included in the risk analysis. Here we are told that a representative device, which has been manufactured in the same way as the final product, can be tested (without subsequent changes). If risk analysis shows that it has the same toxicological hazard. The Biological Evaluation Plan should then be formulated to decide which testing (if any) is required. A re-evaluation is required if processing, materials, handling or purpose change.

Toxicological Risk Assessment

Clause 6 contains information on calculating the dosage of VOCs given to a patient during use. It has five categories which are related to breathing volumes:

1. Short term use – use the actual gas flow in calculations.
2. Neonate – default inspired volume 0.21m^3 per day (according to ISO 10562-1).
3. Infant – default inspired volume 2.0m^3 per day.
4. Paediatric – default inspired volume 5.0m^3 per day.
5. Adult – default inspired volume 20m3 per day.

These volumes can be used to calculate the inspired dose delivered from the µg per litre figure measured by the test laboratory.

This clause along with clause 7 looks into the toxicological risks posed by any VOCs and leachates found to be entering the patient. It is stated that materials should be assessed according to the individual toxicity data. If no inhalation toxicity data exists there is the possibility to use standard 'Thresholds of Toxicological Concern' according to patient mass and duration of contact.

If the volume of condensate entering a patient is unknown there is an allowance for a volume of 1ml per day to be used in the calculations.

Sample Numbers

The standard does not specify the number of samples that should be tested. In traditional biocompatibility testing ISO 10993-12 defines sample requirement by surface area (or mass) and it is not concerned with the number of products used. This applies to section four of ISO 18562, the leachables. However, there is no guidance for particles and gases.

It is relatively simple to test multiple samples of 'mass produced' components for short term use. For long term use ventilators the availability of samples can be very limited and the testing protracted (up to 30 days). To make matters worse samples may be bulky making testing multiple samples for VOCs expensive. For the full duration of sampling each test unit must be housed in its own temperature controlled test chamber to avoid cross contamination.

The use of representative samples is allowed. This can mean a preproduction sample for a complicated product such as a ventilator. Smaller components are generally tested in the final format and from their distribution packaging.

To date we have tested single use components at a sample size of 3 and as single sample of a ventilator. We expect there to be pressure for these numbers to rise.

ISO 18562-2 Evaluation of breathing gas pathways, particulate emission.

The standard gives a choice of test methods for capturing particles. This can be done gravimetrically by filtering the air on a 0.2 µm filter. All particles emitted over 24 hours, above this size will be counted. The second method is a particle counter which syphons off a small part of the airflow.

The test is normally carried out at the maximum recommended flow rate for the product. This is intended to dislodge particles, forming a worst-case test. There is scope for the use of an expansion chamber to help with the syphoning process.

Both methods have their strengths and weaknesses.

The filtration method lends itself well to longer term and higher flow monitoring as multiple filters can be used in parallel to increase the airflow. The weakness is in obtaining accurate measurements for tiny masses of particles. This method also captures all particles greater than 0.2 microns in size. The standard states that it gives methods for quantifying particle between 0.2 and 10 microns, but also infers that other sizes should be included in a risk analysis. So, whilst one 20 micron particle could outweigh many 0.2 micron particles registering its presence is helpful.

Because the particle counter method syphons off a fraction of the airflow it cannot be certain that a representative sample has been taken. Also, many laboratories previously stocked counters which have a minimum particle size of 0.25 microns and are hence these are incorrectly used. The counters are generally not designed for continuous use and careful selection is required to ensure that the full reading over 24 hours is obtained.

An expansion chamber can be added to the system if very high flow rates over a short time are required. This can be also used to simulate a cough or sudden inspiration.

For both methods measures must be taken to minimise and subtract the background particle count. The test should be conducted with an air supply filtered at 0.1 micron or less and it should be very dry.

ISO 18562-3 Evaluation of breathing gas pathways, VOC emissions.

Volatile Organic Compound emissions testing is normally carried at the device's minimum flow rate to allow time for diffusion of emitted vapours into the airflow. It is also often carried out at elevated temperature further increase volatisation. The VOCs are materials that become gases below 260°C.

The test is normally carried out at the minimum recommended flow rate for the product. This is intended to allow time for gases to diffuse into the airflow at the maximum concentration.

For short term devices measurements are made after; 30 minutes, 60 minutes and 24 hours.

The results for 30 and 60 minutes are included to allow an assessment of the rate of decay in emission production.

For long term devices measurements are made after; 30 minutes, 60 minutes and 24 hours. Subsequent readings are taken according to the results, usually at 48 hours, and then approximately every 3 days (to a maximum of 30 days) until the emission level falls below 40µg per day.

There are several options for collecting the emitted VOCs. Primarily the standard highlights thermal desorption (TD) systems. Alternatives include activated carbon filters. ISO 16000-6 is referenced.

Similarly, to the particle counter method the thermal desorption system has the disadvantage that it samples only a small portion of the airflow. This decreases sensitivity. Gas mixing is likely to be complete so a lack of homogeneity should not be a problem in capture. Captured gases are subsequently released for analysis. In this phase of the test a lack of homogeneity can be a problem and quite complicated release and recapture mechanisms can be required to ensure that low boiling point gases are accurately measured.

Apart from the method of adsorbing the released gas for later analysis there is very little overlap between ISO 16000-6 and ISO 18562. The sampling of gas is external to the test item in the environmental standard and internal gases are sampled in the biocompatibility standard. Also the test temperatures are different. For the breathing component testing the device under test should be chambered at its maximum recommended temperature of use. This ensures that the worst case VOC release is assessed.

The absorbed gas is then desorbed and analysed by gas chromatography mass spectrometry (GC-MS). This technique is ultra sensitive and can detect ppb levels or less.

Once the chemical analysis data is available it goes on into a toxicological risk assessment.

The test system at Medical Engineering Technologies includes negative and positive controls.

The positive control consists of a mixture of 12 possible VOCs at known concentrations. The information from these controls is used to identify the system efficiencies, limit of detection (LOD) and limit of quantification (LOQ).

Inorganic Gases

Some environmental standards for respired air contain limits for the abundance of certain very low boiling point inorganic gases. Some of these gases can react with VOCs to produce irritants. Specifically, measurements of carbon dioxide, carbon monoxide and ozone concentrations are required in the USA.

ISO 18562-4 Biocompatibility evaluation of breathing gas pathway, Tests for leachables in condensate

Section 4 of the standard only comes into play if there is a liquid path from the gas pathway into the patient. This can occur if there is two way breathing and condensates from exhaled air can flow into the patient. The other circumstance is if water is introduced into the system through nebulisation or humidification. In these cases chemical and biological testing is required (ISO 18562 does not allow chemical analysis to replace the biological testing, in contrast to ISO 10993-1: 2020). The sample requirement follows ISO 10993-12 with aqueous only extract for the chemical analysis. It is possible that some nebulised drugs will be aliphatic. This circumstance is covered by the biological testing.

Chemical testing includes analysis for metals and organic compounds.

Obtaining samples for test is relatively easy for a face mask or filters. As with the other tests (VOCs and particles) it can become very complicated for large devices. A sampling strategy is required for many ventilators and diagnostic systems. Because it is the gas pathway that is under test, it

is highly desirable to extract from the inner surfaces of the device without cutting or disassembly. It is stated in the introduction to section 4 that for devices with significant patient contact (example tracheal tubes) the normal requirements of ISO 10993 should be followed.

Once the extracts are available chemical analysis is usually conducted for organic and inorganic materials. The inorganics (metals) are detected by ionisation followed by spectral or mass measurements in an electric field. The organic materials (most carbon based materials) are detected by chromatographic separation and mass spectroscopy analysis.

The chemical analysis is controlled and quantified with the use of negative controls (sample where the solvent has been through all the same processes but with no product present) and positive controls (negative samples 'spiked' with known amounts of suspected contaminants).

The biological testing encompasses cytotoxicity and sensitisation studies. These are carried out according to the standard GLP protocols.

Conclusion

There is a requirement for the biocompatibility assessment of a huge array of medical and drug delivery devices to go beyond ISO 10993 and include consideration of particles and volatile materials that can be inspired by a patient. This assessment can be carried out by examining existing data, but frequently requires testing of each specific product. Particle testing is relatively straight forward. The VOC testing can be complicated both in execution and analysis. The devices range from simple tubes to complicated diagnostic devices which a patient sits inside whilst breathing through a measurement system which introduces a variety of gases into the airflow. Other patient housing devices are also included such as incubators. The chemical testing is then very likely to identify a number of unexpected materials which need to be analysed by a toxicologist.

There is a variety of ways of expressing the data gathered and the toxicity. This can lead to confusion.

The requirements for leachate testing for fluid that can enter the respiratory system are better established but can still pose challenges.

There are currently no specific requirements for assessing the interaction between pharmaceuticals and their delivery device as far as ISO 18562 is concerned.

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