BIOCOMPATIBILITY OF MEDICINAL PRODUCT MEDICAL DEVICE COMBINATIONS FOR AIRWAY DELIVERY

In this article, Mark Turner, Managing Director of Medical Engineering Technologies, discusses biocompatibility testing for inhaled medical products, with particular reference to ISO 18562, and what MET has learned from three years of breathing component biocompatibility testing.

INTRODUCTION

Prefilled nebulisers, inhalers and nasal sprays are all drug delivery devices that may need to be assessed for biocompatibility as part of a combination product, under the specific standard developed for demonstrating toxicological safety of airway products – ISO 18562.[1] This ISO standard covers the biocompatibility evaluation of breathing gas pathways in healthcare applications.

The regulatory requirements for combination devices in Europe are given in Article 117[2] of the MDR. Regardless of which jurisdiction and filing approach is used, the US FDA will also be seeking evidence of biological safety.

Published in 2017, ISO 18562 has become the reference standard for breathing component biocompatibility testing. It precedes the current version of ISO 10993-1,[3] the general reference for medical device biocompatibility testing, published in 2018. ISO 10993 includes examples of breathing components 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-borne leachables in condensate.

ISO 18562-1 – EVALUATION AND TESTING WITHIN A RISK MANAGEMENT PROCESS

This section of the standard discusses the applied principles 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 then ISO 10993 should be considered. In keeping with ISO 10993-18,[4] 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, as long as there are no subsequent changes. If risk analysis shows that it has the same toxicological hazard, a biological evaluation plan should then be formulated to decide what testing (if any) is required. A re-evaluation is required if processing, materials, handling or purpose change.

Toxicological Risk Assessment

Section six of ISO 18562-1 contains information on calculating the dosage of volatile organic compounds (VOCs) given to a patient during use. It has five categories:

1. **Short-term use:** use the actual gas flow in calculations
2. **Neonate:** default inspired volume is 0.23 m^3 per day
3. **Infant:** default inspired volume is 2.0 m^3 per day
4. **Paediatric:** default inspired volume is 5.0 m^3 per day
5. **Adult:** default inspired volume is 20 m^3 per day.

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

This section, along with section seven, 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 their individual toxicity data. If no inhalation toxicity data exists there is the possibility to use standard thresholds of toxicological concern[5] according to patient

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mass and duration of contact. If the volume of condensate entering a patient is unknown, there is an allowance for a volume of 1 mL 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[6] defines a 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, which covers 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. This is likely to be the case for combination devices. For long-term use ventilators, the availability of samples can be very limited and the testing procedure protracted, taking 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 pre-production sample for a complicated product, such as a ventilator. Smaller components are generally tested in their final format and from their distribution packaging.

To date, MET has tested single-use components at a sample size of three and a ventilator with a sample size of one. It is expected that there will 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. The first is gravimetric filtering through a 0.2 µm filter, with all particles that are emitted over 24 hours and caught in the filter being counted. The second method is a particle counter, which siphons off a small part of the airflow.

The test is normally carried out at the maximum recommended flow rate for the product, which is intended to dislodge particles, forming a worst-case test. There is allowance 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 µm in size. The standard states that it gives methods for quantifying particles between 0.2 µm and 10 µm, but also implies that other sizes should be included in a risk analysis. So, whilst one 20 µm particle could outweigh many 0.2 µm particles, registering its presence is helpful. Subsequent microscopic inspection can gather information on particle sizes.

Because the particle-counter method siphons off a fraction of the airflow, it cannot be certain that a representative sample has been taken. Additionally, many laboratories previously stocked counters with a minimum particle size of 0.25 µm, which do not conform to the standard. 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 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 µm or less and should be very dry.

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ISO 18562-3 – EVALUATION OF BREATHING GAS PATHWAYS, VOC EMISSIONS

VOC emissions testing is normally carried out at the device's minimum flow rate to allow time for diffusion of emitted vapours into the airflow. Additionally, the test is often carried out at an elevated temperature to increase volatility. VOCs are materials that become gases below 260°C.

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 also 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 three days (to a maximum of 30 days) until the emission level falls below 40 µg per day.

There are several options for collecting the emitted VOCs. Primarily, the standard highlights thermal desorption (TD) systems, but includes alternatives such as activated carbon filters. Furthermore, ISO 16000-6[7] is referenced.

Similar to a laser-counting particle test, the thermal desorption system has the disadvantage that it samples only a small portion of the airflow, which 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. Gases are sampled externally to the device in the environmental standard and internally in the biocompatibility standard. Additionally, the standard test temperatures are different. For the breathing component, the test device 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 parts-per-billion levels or less. Once the chemical analysis data is available, it goes into a toxicological risk assessment.

The test system at MET 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

The 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 US for electrical equipment.

ISO 18562-4 – BIOCOMPATIBILITY EVALUATION OF BREATHING GAS PATHWAY, TESTS FOR LEACHABLES IN CONDENSATE

Section four of the standard only comes into play if there is a liquid path from the gas pathway to the patient. This can occur if device use involves two-way breathing and condensates from exhaled air can flow into the patient, or 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.

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Obtaining samples for test is relatively easy for a nebuliser or vaporiser. However, 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 desirable to extract samples from the inner surfaces of the device without cutting or disassembling it. It is stated in the introduction to section four that devices with significant patient contact, such as tracheal tubes, should follow the normal requirements of ISO 10993.

Once the extracts are available, chemical analysis is usually conducted for organic and inorganic materials. The inorganic materials (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, a sample where pure solvent has been through all the same processes with no product present, and positive controls, negative samples spiked with known amounts of suspected contaminants.

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

CONCLUSION

There is a requirement for the biocompatibility assessment of a huge array of medical and drug delivery devices (both combination products and co-packaged devices) to go beyond ISO 10993 and include consideration of particles and volatile materials delivered to a patient. This assessment can be carried out by examining existing data, but frequently requires testing of each specific product.

Particle testing is relatively straightforward, but the VOC testing can be complicated in both execution and analysis. The devices range in question from inhalers to larger inspiratory systems. Chemical testing is then very likely to identify a number of unexpected materials from these items which need to be analysed by a toxicologist, and there is a variety of ways of expressing the gathered data and toxicity evaluation, which 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. However, there are currently no specific requirements for the interaction between the pharmaceuticals and their delivery device as far as ISO 18562 is concerned.

ABOUT THE COMPANY

Medical Engineering Technologies (MET) has successfully delivered design validation testing to medical device and pharmaceutical companies in 20 countries across Africa, Asia, Australasia, Europe and North America. MET knowledgeably, reliably and effectively delivers medical device and

packaging testing. Services include protocol development, laboratory testing and data analysis. The laboratory is equipped for performance testing, chemical analyses and sterile barrier verification and – with accreditation to ISO 17025 – customers can have complete confidence in the quality and accuracy of results.

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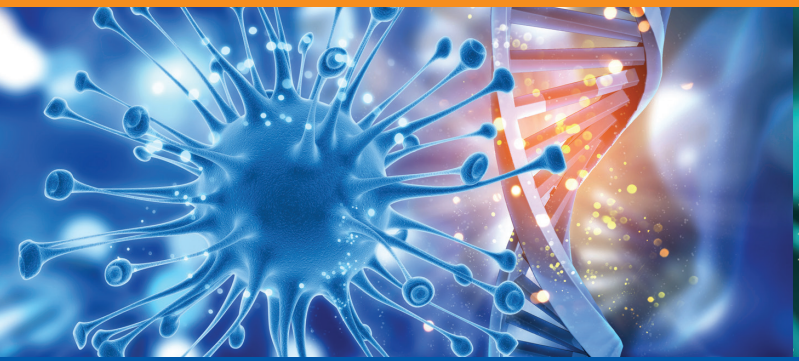
ABOUT THE AUTHOR

Mark Turner is Managing Director of Medical Engineering Technologies, which provides a wide range of services to engineers and project managers in the medical device industry. Mr Turner founded MET in 1997 after 12 years of project management and device design with Smiths Medical. He has also worked as a perfusionist in the cardiac unit of King's College Hospital (London, UK), providing experience of the application of medical devices first-hand. He received a BSc in Chemistry (with Biochemistry) from the University of Wales (UK) in 1983 and has also studied astronomy, business administration, cosmology and opto-electronics.

- CCIT
- ISO 8009
- ISO 11040
- ISO 11608
- Glide Force
- Connectivity
- Trigger Force
- Needle Testing
- Dose Accuracy
- Human Factors
- Break Loose Force
- Performance Testing
- Transit /Altitude Testing
- Design Validation Testing
- On Body Delivery Systems
- Extractables and Leachables



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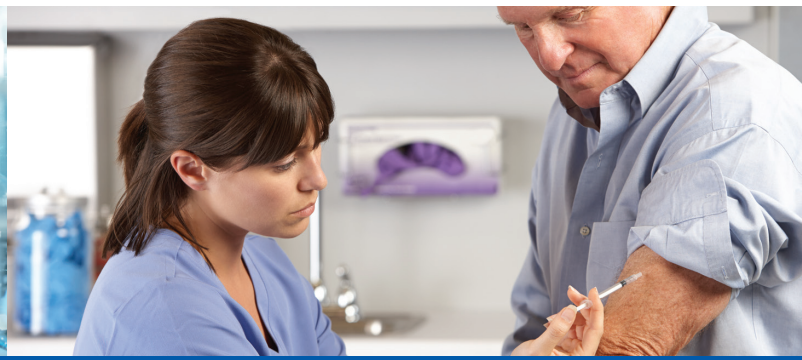

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