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Biocompatibility Evaluation of Gas Pathways

Traditionally, toxicologists and biocompatibility experts considered the materials in breathing gas pathways of medical devices as external communicating devices and evaluated these materials according to the ISO 10993 series of international standards. Unfortunately, this approach leads to testing that provides questionable benefits and potential hazards being missed. Therefore, a new set of standards specifically geared towards the biocompatibility evaluation of breathing gas pathways in healthcare applications was released in March 2017. ISO 18562 is a four part standard aimed at providing the general framework required to adequately determine the acceptability of the vast array of medical devices that contain breathing gas pathways.

Evaluation of breathing gas pathways should fall under a larger risk management approach. The first step in this evaluation is identification of the potential hazards that are specifically associated with the gas stream coming from the device. While ISO 18562 is not prescriptive in evaluating these hazards, it does include some specific details that need to be considered when designing the test plan. For example, it provides guidelines for using the correct clinically relevant flow rates depending on the target patient population, sampling at adequate intervals throughout the testing depending on the duration of use of the device, and maintaining the correct temperature of the device during testing.

The first hazard specifically associated with the gas pathway of medical devices is emissions of particulate matter. There are two size ranges of particulates that need to be measured: $PM_{2.5}$ and PM_{10}. $PM_{2.5}$ includes all particles between 0.2 µm and 2.5 µm in size, while PM_{10} includes all particles between 2.5 µm and 10 µm. $PM_{2.5}$ particles pose a more dangerous hazard to patients because they can bypass the human body's natural defense mechanisms. Their size allows them to penetrate deeper into the patient's lungs, causing significant health risks. ISO 18562-2 requires that the total mass of $PM_{2.5}$ particles emitted not exceed 12 µg/m³ of gas. PM_{10} particles cannot penetrate as deep into the lungs, and thus pose fewer hazards. However, they can still be dangerous to patients. ISO 18562-2 requires that the total mass of PM_{10} particles emitted not exceed 150 µg/m³ of gas.

There are two methods for measuring particulate matter emitted from medical devices. The first is a filter collection method which involves measuring the difference in the mass of a filter before and after collection of particulate matter. Unfortunately, measuring particulate matter emitted from medical devices is not trivial as the amount of particulate matter emitted from a medical device is typically very small. Measuring the change in mass can sometimes require an extremely sensitive balance and can be disrupted by the slightest artifact. The second method for measurement of particulate matter emissions is a particle counter method. This method uses an analytical particle counter to measure and count each particle

emitted from the device. Particle counters employ a light scattering technique in which the gas stream from the medical device enters an isokinetic sampling probe and is directed past a laser. Detection of the light being redirected or absorbed allows for accurate measurements of particulates. Many particle counters only provide a count of the number of particles. Converting this count to a total mass is straightforward using a simple calculation and estimating the density of the particulates emitted based on the density of the materials used in the gas pathway.

Another major hazard associated with gas pathways of medical devices is volatile organic compounds (VOCs) that can be emitted in the gas stream. The VOCs are first collected onto a thermal desorption tube and then analyzed by gas chromatography mass spectrometry (GC/MS). Thermal desorption tubes are packed with mixtures of different carbon based absorbent materials that are designed to attract and trap VOCs. These tubes are then transferred to a GC/MS with a thermal desorption unit that heats the tubes, allowing the VOCs to desorb from the absorbent material and enter the GC/MS for analysis.

The final hazard specific to gas pathways of medical devices is leachables in condensate which becomes important for devices that deliver humidified gas. Leachables in condensate should be evaluated when the gas pathway can reach 100% saturation with water, condensation can form, and that condensate can reach the patient. There are three methods for collecting these leachable substances: (1) utilize clinical use conditions to cause the formation of condensation in the gas pathway, (2) circulate water through the gas pathway in conditions similar to clinical use, or (3) perform an aqueous extraction according to the principles established in ISO 10993-12. Once the leachables have been collected, the elemental impurities concentrations should be determined using pharmacopeial methods and organic impurities quantified and identified using GC/MS. Additionally, it may be advisable to utilize liquid chromatography mass spectrometry (LC/MS) to quantify and identify the nonvolatile organic impurities. Importantly, if the materials within the gas pathway of the device have previously been evaluated according to ISO 10993-12, then condensate does not need to be assessed as this is a similar evaluation.

Following the VOC emission and condensate testing, the chemical compounds identified must undergo a toxicological evaluation according to ISO 10993-17. Therefore, the actual dose of the identified compounds to the patients must be calculated considering parameters such as dilution from the amount of gas and the breathing volume of the target patient population. The toxicologists should pay extra attention to available inhalation toxicity data as this data will be the most relevant to breathing gas pathways. For any compounds found to pose a toxicological concern to patients, cytotoxicity and sensitization testing according to ISO 10993-5 and 10, respectively, will be required.

Once all of this information and data is collected, the acceptability of a breathing gas pathway device can be sufficiently determined. It is the consideration of all test data and toxicological information together that allows regulatory bodies to adequately determine the safety of a breathing device. Therefore, understanding the testing requirements of ISO 18562 will help to ensure a complete regulatory submission and save valuable resources when working to get a medical device to market.

References:

ISO 18562-1:2017, Biocompatibility evaluation of breathing gas pathways in healthcare applications -- Part 1: Evaluation and testing within a risk management process, International Organization for Standardization, 2017

ISO 18562-2:2017, Biocompatibility evaluation of breathing gas pathways in healthcare applications -- Part 2: Tests for emissions of particulate matter, International Organization for Standardization, 2017

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

ISO 18562-4:2017, Biocompatibility evaluation of breathing gas pathways in healthcare applications -- Part 4: Tests for leachables in condensate, International Organization for Standardization, 2017