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EO RESIDUE LEVELS IN MEDICAL DEVICES:

Best Practices for Demonstrating Compliance with ISO 10993-7:

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Sterilizing medical devices via ethylene oxide gas is an effective and common practice within the industry. EO gas is active at a relatively low temperature compared to other methods, such as steam, and it is compatible with plastics, polymers, and many products that are not compatible with other sterilization techniques, such as radiation. However, because of the potentially harmful effects of exposure to EO residue to patients, it is crucial to ensure the levels of EO residue meet the standards defined by ISO 10993-7:2008 by using validated testing methods. This paper will provide an overview of best practices for demonstrating compliance with that standard, and for demonstrating products sterilized via EO gas are safe for use.

How to assess and create product families

Given that many companies may have thousands of products in their portfolio, it is not feasible for a company to test every product that is sterilized via EO gas. Thus, products can be grouped into product families, and one or two master products for each family – those representing the worst-case potential in terms of patient exposure to EO residue – can be selected for testing. Product families may be grouped together according to a variety of criteria: the nature of their use, application, or contact with patients, whether they involve short-term, prolonged, or permanent exposure, or the type of materials they are made from. One useful reference document to consider is AAMI TIR:28, which explains how to group products and define a product family.

Once products have been grouped into families, master product(s) should be selected for each family. The master product should represent the worst-case scenario in terms of absorption/desorption properties and patient exposure for that family. For example, consider a family of catheters. The master product for that family should be the catheter that has the greatest surface area (say, the longest inner pathway) and/or involves the greatest mass of product material, thus presenting the greatest potential for exposure to EO residue. This would be the best unique candidate to represent the entire product family.

Range-finding tests sometimes are performed to identify the master product and verify that it carries the maximum potential for absorbing and releasing EO gas. The product is exposed to EO gas and the residue levels are tested, producing experimental data that supports its selection as the master product. ISO 10993-7 also requires that all rationale in the selection of the master product be properly documented.

Products being sterilized by ethylene oxide

How to design the sterilization cycle used to expose residue test samples

When testing for EO residue levels, it is crucial to ensure that each of the critical parameters in the sterilization process is set to the maximum levels, to ensure that the worst-case scenario of potential absorption and patient exposure is evaluated. Temperature and EO gas concentration should be set to their highest applicable levels; EO gas exposure levels should also be set to the maximum, by setting exposure time to its maximum tolerance and reducing the rate of EO injection and the level of EO removal. This is to ensure that the test covers the most extreme levels of EO gas exposure.

Consider a sterilization process that requires the EO gas to be injected into the sterilizer over a defined period. To ensure that the maximum possible EO exposure level is tested, the injection time would be set to target double the expected period. If the test normally involves a maximum dwell time – the length of time for which the product is exposed to the EO gas – with a time tolerance for the maximum exposure time, the dwell time would be set to that maximum to gather experimental data at the maximum limit. The removal of the EO gas would also be set to its maximum allowable time frame, mimicking the procedure used for gas admission. It is crucial to keep the parameters fixed, because replicate runs are necessary for the validation study.

Key elements of study

To construct the residue validation curve, a sterilized product is moved to a controlled, heated aeration stage and held at an elevated temperature, to allow the toxic EO to desorb from the product. The load is sterilized and placed into the heated aeration room. The product samples are taken from the sterilization load after a series of time points – a minimum of three time points is required – and are tested by gas chromatography, whereupon the levels of EO residue are analyzed. The rate of decay is plotted, and a dissipation curve is created. If the EO residue reaches the levels defined as safe by the standard, it's safe to release the product.

The experiment must be done in triplicate, with three separate products being exposed in three independent sterilization runs, and a minimum of three separate time points being challenged. The products are considered compliant to the ISO 10993-7 limits when they consistently fall below the residual limit with which they must comply (based on their exposure category). Extrapolation may be also used, using the prediction limit (Lp) under certain circumstances. It is preferable, however, to confirm the calculated extrapolation with experimental data points. The product should be tested at a time point where it is below safe levels, with safety being confirmed by at least one aeration time point that results in EO levels compliant with ISO 10993-7. Results should be properly documented, including any rationale used for product selection, definition of exposure category, extraction method used, and interpretation of results.

Design and optimization of the extraction method

The EO levels remaining in a product after sterilization are tested by extraction (typically, water is used as a solvent, due to the solubility of EO) with the appropriate extraction technique. The extraction method, time, and temperature will be dictated by product utilization (contact with the patient, contact duration, and utilization). To test and extract the product properly, it is necessary to know how the product will be used in the real world. The default method is simulated use (in such cases, it is necessary to know the contacting part of the device, the utilization time, and if it used within the body or only externally). Alternatively, for products involving longer exposure, it might be necessary to use exhaustive extraction to determine the whole amount of EO present in the product. The extract is then analyzed via gas chromatography, using a validated method (according to ISO 10993-7 annex B).

Consider the example of a syringe. The outside of the syringe does not need to be tested; rather, the fluid pathway will be the target of testing, and the fluid pathway will be filled with the appropriate solvent (which, in most cases, can be water). The syringe will be extracted at room temperature for a period of 1 hour (the minimum time recommended in the ISO 10993-7).

However, if the product is a catheter that is used inside the body, the outside and inside must both be tested. The temperature of extraction must also simulate the product's intended use conditions. If the product is to be used internally, it must be tested at body temperature, and the period of extraction shall target 24 hours in order to establish the daily dose.

In terms of the time the product is used, the default is to use the 24-hour time period, as that would indicate the daily dose of EO exposure to patients. It is important to note that the acceptable remaining EO levels as defined by ISO 10993-7 are different depending on the amount of time for which a product is to be in contact with patients. Products that are for limited use – 24 hours or less – are Category A devices, for which the average daily dose of EO should be 4 mg or less. Products for prolonged use – from one day to one month – are Category B devices, for which the average daily dose of EO should be 2 mg or less, with the maximum EO dose in the first 24 hours set at 4 mg and the maximum for the first 30 days of use set at 60 mg. Products for permanent use – longer than one month – are Category C devices, for which the average daily dose should be 0.1 mg or less, with the maximum dose after the first 24 hours set at 4 mg, the maximum does for the first 30 days set at 60 mg in the first 30 days, and the maximum lifetime dose set at 2.5 g.

Analyst performing an EO residualanalysis test

Validation of analytical test method

Typically, the method must be validated in two ways: The equipment must be validated (use annex B of ISO 10993-7 for guidance), and the extraction efficiency must be validated. The extraction efficiency – whether all the EO remaining in the device has been tested – can be validated using different techniques. One would be repeated extraction, in which the device is extracted until less than 10 percent of the first extraction value is found. The other is thermal extraction, in which the product is heated until gas chromatography reveals that less than 10 percent of the first extraction value remains. The key is to validate the extraction procedure and ensure it is effective.

Concomitant exposure

Concomitant exposure can come into play in two different circumstances: when a device is used repeatedly and when multiple devices are used together. The key is to account for the total dose of EO residue that a patient might be exposed to. Consider a device that is intended to be used for 4 hours at a time but 8 times in a day. Rather than being evaluated as a limited-use product, it should be considered a product that is intended for prolonged use, since the combined hours of use total more than 24. The applicable limits of EO residue for that product must be divided by eight for each product. Consider also a product that is used with multiple products at once, such as a syringe. Rather than testing the syringe by itself, it must be tested in combination with the needle and any other pieces with which it is intended to be used, to ascertain the total dose of EO residue for patients.

Procedure for adoption of new products

When a new product is introduced to a company's portfolio, or when an existing product undergoes a change or modification in design, product material, packing material, or load configuration, it must be evaluated to determine if the EO residue levels are impacted to the degree that the new or modified product might become a new master product in the relevant product family. The goal is to first assess if re-testing is necessary, first by defining the exposure category of the new product and then comparing the new product on paper to the existing master product. In some cases, it might be possible to determine that, for instance, the new product is not as long or thick as the master product, and thus does not represent a new worst-case exposure potential to patients. A written rationale explaining why the new product will not replace the existing master product should be produced.

In other cases, such as when the material is changed or the load configuration is adjusted, the property of absorption and desorption might also change, potentially impacting the EO residue levels and thus necessitating the acquisition of experimental data. Even then, it might be possible to avoid repeating the whole study if the EO levels can be shown to be lower than those of the existing master product, and the EO levels of both are in compliance with ISO 10993-7. However, if the new or changed product is demonstrated to be a new potential master product, the aeration study must be repeated. In this case, the test method should be validated, and the dissipation curve must lead to the same outcome as before. All decisions and rationale should be documented along the way.

Even if a product isn't changed in design or load configuration, it is prudent to perform an annual spot-check to verify that the EO exposure levels still fall below the acceptable limits as specified by the ISO standard. Rather than performing an entire evaluation, again, a single element may be examined. The introduction of a new product can provide an opportune time to perform this spot-check.

Conclusion

EO gas sterilization is an effective method for sterilizing medical devices. However, the toxic nature of EO gas means it is essential to ensure products do not retain levels of EO that exceed the safe levels as specified by ISO 10993-7. Compliance with the standard can be demonstrated via the testing of master products accounting for worst-case exposure possibilities.