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CURRENT REGULATORY LANDSCAPE FOR EO RESIDUE LEVELS IN MEDICAL DEVICES:

What Manufacturers Need To Know Now and What May Be on the Horizon

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One of many crucial steps a single-use medical device takes on its journey from concept to commercial product is sterilization. Ethylene oxide gas sterilization, in particular, is one of the most efficient and effective ways of deactivating bacteria and other potentially dangerous living microbes from medical devices; however, manufacturers must take care to control and minimize ethylene oxide residuals remaining in devices after sterilization has taken place. Ethylene oxide gas remains a popular choice for terminal sterilization because of its effectiveness and its suitability for use with plastic and other heat-sensitive device materials.

The gas itself is classified as a Category 1B carcinogen and a Category 1B mutagen per European Regulation Number 1272/2008 and is known to exhibit various biological effects, including tissue irritation, organ damage, mutagenicity, and carcinogenicity in both humans and animals; and reproductive side effects in animals.1 Despite these effects, sterilizing with ethylene oxide has "proven its worth in terms of microbiological effectiveness," and the benefit-risk ratio of an EO-sterilized device remains favorable.2

The goal for medical device manufacturers that use EO sterilization is to minimize patient exposures to EO residues (and EO derivatives) from their devices and ensure that the levels of residual EO, ethylene chlorohydrin (ECH), and ethylene glycol (EG) pose the least amount of risk possible to the patient during normal product use. Furthermore, testing for ethylene oxide residue on finished devices must be validated and the results documented by manufacturers per current regulations, particularly ISO 10993-7, to earn regulatory approval to market those devices.

Navigating 10993-7:2008

The standard ISO 10993-7, second edition, published in October 2008, is one with which manufacturers and marketers of single-use medical devices sterilized with ethylene oxide should be familiar. Referenced as ISO 10993-7:2008(E), developed by ISO Technical Committee 194, and titled Biological Evaluation of Medical Devices—Part 7: Ethylene Oxide Sterilization Residuals, this international standard serves for European nations, the United States, and other developed regions as the authoritative document guiding medical device makers in managing, testing, and validating ethylene oxide residuals. This standard specifies allowable limits for residual ethylene oxide and ethylene chlorohydrin (ECH) in individual EO-sterilized medical devices, procedures for the measurement of EO and ECH, and methods for determining compliance.

Medical device manufacturers seeking to interpret 10993-7 must pay particular attention to the requirements it sets forth on the following issues:

- Determination of EO-exposure category
- Concomitant EO exposure
- Topical contact
- Special situations
- Test method and validation
- Intended patient population

Products being sterilized by ethylene oxide

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Determination of EO-exposure category:

Section 4.2 of 10993-7, "Categorization of Devices," designates categories of EO-sterilized medical devices based on their duration of patient contact. These categories aid the manufacturer in establishing the maximum safe daily doses of EO and ECH that a device is allowed to deliver to patients.

Limited-exposure devices, or Category A devices, are those with cumulative single, multiple, or repeated use or contact up to 24 hours. Examples may include drapes, gowns, syringes, and needles; and the average daily dose of ethylene oxide delivered to the patient by these devices cannot exceed 4 mg, according to the standard.

Prolonged exposure devices, or Category B devices, are those with cumulative, single, multiple, or repeated long-term use or contact that is likely to exceed 24 hours, but not 30 days. These devices may include giving sets, adhesive wound care dressings, catheters (cumulative use), and wound-drainage systems; and the average daily dose of ethylene oxide delivered to the patient cannot exceed 2 mg/day. Additionally for this category, the maximum EO dose cannot surpass 4 mg in the first 24 hours or 60 mg in the first 30 days.

Permanent exposure devices, or Category C devices, are those with cumulative, single, multiple, or repeated long-term use or contact that will exceed 30 days. Some such devices are implants (e.g. stents, screws, and artificial joints); for these devices the average daily dose of EO to the patient cannot exceed 0.1 mg/day. In addition, the maximum EO dose cannot exceed 4 mg in the first 24 hours, 60 mg in the first 30 days, or 2.5 g in a lifetime.

Section 4.2 explains that if a device fits into more than one of these three duration categories, then the more rigorous testing and evaluation considerations will apply, to ensure potential patient exposure to ethylene oxide is minimized. For devices on which ECH residue is present, this section sets limits on patient exposure to that substance as well.

Concomitant EO exposure:

When multiple EO-sterilized devices are used together at one time, such as occurs with a kit containing tubing, connectors, and wound-care dressings, or when one EO-sterilized device is used multiple times per day, concomitant (similar to cumulative) ethylene oxide exposure factors warrant consideration. Manufacturers and testing labs must pay heed to concomitant EO exposure when determining acceptable limits of total EO residue per section 4.2 of 10993-7. Testers in particular need to understand from manufacturers how devices will be used on patients, and in what combination, to appropriately evaluate them for EO residue. The total dose of ethylene oxide received by a patient via EO-sterilized medical devices must not exceed the daily allowable limit for the total number of devices used; it is not sufficient to demonstrate that every individual device meets the specified daily EO limit, because the total amount of EO delivered might exceed the allowable limit when these devices are combined.

The solution is for all products used in combination to be pooled together to perform the EO-extraction test or to add the results of individual extractions together to obtain the total amount of EO that will be delivered to the patient.

Topical contact:

Because ethylene oxide is a skin irritant, EO-sterilized medical products that touch intact skin (such as drapes and hospital gowns) present an additional issue to manufacturers and testers when testing them for residual EO or ECH. The portions of these products that make direct contact with patient skin must be considered. For large products of this type, a representative portion of the item may be tested randomly with a known surface (substituting for human skin), and the results must be expressed in micrograms per square centimeter.

Per 10993-7:2008, the tolerable contact limit (TCL) for EO on such products is 10 micrograms per square centimeter, and for ECH, 5 milligrams per square centimeter. Or, as set forth in part 4.3.6 of the standard, drapes, in particular, "shall exhibit negligible irritation as specified in 10993:10."

Implants, too, may cause local irritation within tissues with which they make contact. The TCL, particularly for small implants, is sometimes more difficult to achieve than the "lifetime" category limits. As the surface area is minimal on small implants, the amount of residual EO shall not exceed 10 micrograms per square centimeter (5 milligrams per square centimeter for ECH), since the lifetime exposure limit for implants is set at 100 micrograms per device per day. XXX Examples of small implants include: orthopedic screws, intra uterine devices, and artificial heart valves.

Special situations:

Section 4.3.6 of 10993-7 specifies medical products for which the standard EO-residue limits do not apply, either because the low mass of the product can skew the results or because the product is so lifesaving and critical that the risk of increased EO residue is outweighed by the benefit the product confers to the patient. These products include intraocular lenses, blood-cell separators, blood oxygenators and separators, cardiopulmonary bypass devices, and drapes that are intended to contact only intact skin. Manufacturers of these products will need to earmark this particular section of the standard, as well as Annex F (which provides a rationale for the unique EO limits set for these special devices) and Annex C (which supplies guidance for the application of these limits).

Test method and validation:

As explained in section 4.4.6.1 of 10993-7, two basic extraction methods are used for determining EO residuals in medical products: simulated-use extraction (which is the default method) and exhaustive extraction (which is an alternate method). In choosing a method, manufacturers and testers need to consider the intended normal use of the product and how the product contacts the patient.

Analyst performing an EO residualanalysis test

Test method and validation: (continued)

In simulated-use extraction, water is used to mimic product use, and, per Annex K of 10993-7, testers should perform the extraction under conditions "that provide the greatest challenge to the intended use."3 For instance, blood-contacting and parenteral devices should be extracted with water by filling them completely or flushing the blood path or fluid path. While a catheter, for example, will be fully submerged for 24 hours at 37° C prior to extraction, a syringe, on the other hand, will be filled with water and extracted after one hour at room temperature.

Exhaustive extraction methods are intended to recover the entire residual content of a device. For EO-residue determination, these methods include thermal extraction followed by headspace gas analysis and solvent-extraction procedures followed by headspace gas analysis of the solvent extract, chromatography of the solvent extract, or preparation of the bromohydrin derivative of EO, which is determined using a more sensitive gas-chromatography detector.4

Additionally, the gas chromatography (GC) method must be validated per Annex B of 10993-7, which addresses linearity, precision, accuracy, limit of detection (LOD), limit of quantification (LOQ), and more. The range covered in the validation must be used as limits for the routine testing; that is, the results must be interpolated between LOQ and maximum validated limit and cannot be extrapolated due to inaccuracy. Finally, the potential interferences between the sample and the GC must be verified with a blank (a sample not exposed to EO) to properly evaluate the presence of a peak in the EO-integration window.

A device's probable contact with a patient is of utmost importance in how extraction is performed. A device that will contact the patient for more than 24 hours, for example, will not likely give an exhaustive amount of EO with a single extraction of 24 hours. Therefore, after 24 hours the water will be removed, the sample tested, and a new extraction on the same device performed for another 24-hour period. This pattern will continue "to exhaustion," meaning until the obtained results are below 10% of the value of the original result or close to the equipment quantification limit.

Manufacturers should note that while the sterilization company can provide advice and guidance regarding extraction methods based on the information it has about the product, ultimately, the final decision of which method to use rests with the manufacturer.

Intended patient population:

Potential changes to EO residue limits are on the horizon as urged by ANSM. While ISO 10993-7:2008 remains the primary and authoritative source for EO-residue testing and validation, its working group began a timeline for its revision in October of 2016. It is possible, if not likely, that this next revision will take into account the opinions and recommendations of France's Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) regarding EO residue limits for devices used on neonates and other persons weighing less than 70 kg.

Intended patient population: (continued)

In public documents released between June 2014 and October 2015, ANSM put forth its contention that the "harmonized standards NF EN ISO 10993-7 and NF EN ISO 10993-17 [Biological Evaluation of Medical Devices—Part 17: Establishment of Allowable Limits for Leachable Substances] have shortcomings with respect to their application to specific patient populations such as neonates, premature neonates, and infants," and "conformity with the essential requirements cannot therefore be based on application of the said standards alone."5 ANSM states that it reached this conclusion after performing a market surveillance of EO-sterilized enteral feeding tubes in neonatology and pediatrics during 2013 and 2014. The agency found "discrepancies in implementation of standard NF EN ISO 10993-7 on EO residuals," it stated in a July 2015 Information Update on the subject. "Most tube manufacturers did not take into account a neonate's low birth weight or the concomitant use of other EO-sterilized devices in their calculation of the allowable residue limits."6

The agency published in October 2015 its Decision of 1%9/2015: setting out the specific conditions for the placing on the market and distribution of certain medical devices sterilized using ethylene oxide, which is a Q&A document updating medical-device manufacturers and other interested parties on its decisions regarding EO residuals on devices used on neonates.7 The document specifies that EO-residual information for medical devices "is to be transmitted by the manufacturer in response to a request from the purchaser who selects the [medical device] for healthcare facilities, through its calls for tenders or competitive bidding process," and that the communication of this information shall be enforced beginning April 9, 2016. "It is mandatory from this date," the agency states.

Of further interest, the agency mentions in this document that it "also works with the International Standards Organization on the draft standard ISO 10993-7 revision process. It specifies its requirements where sterilized devices are used on this population." It seems reasonable to assume that the next revision of 10993-7 will incorporate additional information for manufacturers of EO-sterilized devices for their neonate, premature neonate, and infant patients.

Ethylene Oxide in the Medical-Device Supply Chain: A Word about Fugitive Emissions

For EO-sterilized products in transit from the sterilizing facility to the customer, a regulatory and ethical obligation exists for protecting personnel from residual EO gas that may escape from product packaging. This obligation is borne primarily by employers at warehouses, lorry fleet companies, and other places where finished EO-sterilized devices are handled en route to hospitals and healthcare centers. Whilst it is the responsibility of the device manufacturer to label the products as being treated with ethlene oxide and to comply with EO residue limits as laid out in 10993-7, it is the responsibility of those along the product transit pathway to monitor fugitive EO emissions and take steps to safeguard workers.

Ethylene Oxide in the Medical-Device Supply Chain: A Word about Fugitive Emissions (continued)

Most European nations and the United States have established a workplace EO-exposure limit of 1.0 ppm. Exposure is measured with technology that includes "passive" monitoring badges, "active" monitoring badges, airspace monitoring, and even worker blood tests; and it is minimized via ventilation and, in some cases, employee respirators.

Germany, however, has published legislation in its Joint Ministerial Gazette (GMBI) that reduces the acceptable concentration limit to 0.1 ppm—a considerable decrease.8 The 1.0-ppm limit deemed acceptable in many other countries is defined by the German government as merely "tolerable," not "acceptable." So far, Germany appears to stand alone in its pursuit of a 0.1-ppm EO goal, but medical device manufacturers and handlers throughout the supply chain are advised to seek updated education on this issue as it evolves.

Ethylene Oxide Sterilization: Reaping the Benefits While Reducing the Risk to Human Health

Despite the volumes of regulation and discussion devoted to residual ethylene oxide and fugitive EO emissions, sterilization with this gas remains an excellent choice for critical, single-use medical devices to deactivate potentially dangerous microbes. As ANSM itself has stated, the benefits of EO sterilization outweigh the drawbacks. Manufacturers, sterilizers, and finished-product handlers are urged to keep themselves informed of regulatory discussions and standards updates on these issues, with the ultimate goal being the safeguarding of human health.