Agence nationale de sécurité du médicament et des produits de santé

Medical devices sterilized with ethylene oxide and used in neonatology and pediatrics

Summary of Regulations

June 2014

ansm.sante.fr

Medical devices sterilized with ethylene oxide and used in neonatology and paediatrics

Summary of Regulations

During its market surveillance duties, the French National Agency for Medicines and Health Products Safety (Agence nationale de sécurité du médicament et des produits de santé – ANSM) found that market operators applied the standard for the control of residues of ethylene oxide, used as a sterilizing agent for medical devices (MD), in a very heterogeneous manner. The ANSM would therefore like to issue an update by disseminating the present document for the attention of manufacturers and providers of sterilization.

1. Ethylene oxide, sterilizing agent

Among the various available techniques, sterilization by ethylene oxide gas (EO) is widely used in particular for single-use medical devices.
Although this technique has proven microbiological efficacy, it has the constraint that residuals of ethylene oxide and its derivatives are still present in MD after sterilization, and must therefore be controlled. A controlled desorption phase is done systematically to help the residues elimination.
Ethylene oxide is classified as a category 1B carcinogen and 1B mutagen, according to the European Regulation No. 1272/2008 on classification, labelling and packaging of substances and mixtures («CLP» regulation). Hence, manufacturers have the complete responsibility to implement and provide proof of the validation of the sterilization process both for its microbiological efficacy and for the satisfactory control of residuals of EO and its derivatives.

2. Directive 93/42/CEE and EO sterilization

CE marking according to Directive 93/42/EEC amended, concerning medical devices, requires compliance with the Essential Requirements of Annex I and in particular requirement 7.5, which specifies that « *devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction, in accordance with Annex I to Council Directive 67/548/EEC*[1] […] ». This directive was repealed and replaced by the CLP regulation above-mentioned.

⇨ Therefore, sterilization and the risks related to substances released by the DM after sterilization must be studied during the design of the device.
Various sterilization methods are available and during the development of an MD, the choice of materials and other aspects of the design must give priority to the use of a method of sterilization not presenting the risk of exposing patients to genotoxic carcinogens such as ethylene oxide.

⇨ The stricto sensu respect of Essential Requirement 7.5 must lead the manufacturer to reduce to the minimum the levels of residuals of EO and its derivatives.

The standard EN ISO 10993-7[2] « Ethylene oxide sterilization residuals » specifies the provisions to implement to control EO sterilization residuals. This standard is a European harmonized standard and allows presumption of conformity with the above-mentioned Essential Requirement 7.5.
A manufacturer claiming the application of this standard should strictly adhere to its content, so the MD that is produces can be presumed conform to Essential Requirement 7.5.

[1] Council Directive 67/548/EEC of 27 June 1967 concerning the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.
[2] EN ISO 10993-7: Biological evaluation of medical devices - Part 7: ethylene oxide sterilization residuals.

3. EN ISO 10993-7 implementation

When, during the design phase, the manufacturer has determined that it is obliged to use EO as a sterilizing agent and when it claims the use of the harmonized standard EN ISO 10993-7, the application of this standard shall be documented in the technical documentation and risk analysis file.

The harmonized standard EN ISO 10993-7 is notably designed to specify the allowable limits for residues of EO and ethylene chlorohydrin (ECH) derived from the sterilization. The foreword of this standard also recalls that the calculated levels given by the standard EN ISO 10993-7 are maximum values, and manufacturers must make every effort to ensure that the DM sterilized with EO have, when used, the residual rate of EO and its derivatives the lowest possible.

As part of this recall of the regulation, it should be, without prejudice to the provisions of Directive 93/42/EEC mentioned above, attached particular importance to the following points of the standard EN ISO 10993 -7:

⇨ In the design phase:

- «*Use of alternative materials and sterilization methods should have been considered during product development and design with the aim of minimizing exposure to residues. The rationale and basis for this decision should be documented*» (see §C.2.1 of the standard).

- When the choice for EO sterilization has been made, «*exposure to EO residues should be minimized*» (see §4.1 of the standard).

The manufacturer documents the choice of EO as a sterilizing agent and endeavours to clarify the reasons obliging it to make this choice. In addition, measures taken during design (choice of materials, design of DM, etc.) to reduce residuals are also described.

⇨ During the validation phase of the sterilization process

Standard EN ISO 10993-7 provides a means for calculating the allowable limits of EO (and derivatives) per MD, according to the contact duration, the patient's body weight and the simultaneous use of several MD liable to expose patients to EO sterilization residuals.

The manufacturer takes into account the body weight of the target patient (§4.3.1 of the standard). Particular attention shall be paid to the case of infants or preterm infants by using a weight hypothesis corresponding to this population.

As regards the use of multiple MD sterilized with ethylene oxide, the standard provides for a default reduction factor of 0.2 corresponding to the simultaneous use of 5 MD.

The manufacturer takes into account the foreseeable environmental conditions of use of its MD and lowers the allowable limits in consequence. Clinical situations in neonatal medicine or intensive care frequently lead to the use of a large number of MD. Hypotheses must therefore be formulated and validated accordingly.

The standard also allows to take into account the desorption occurring during storage or quarantine (in §5.3). This desorption must therefore be documented and demonstrated under worst case conditions in order to determine the minimum time required after sterilization for the products to reach a level equal to or below the defined residual limits.

There has finally to be pointed out that the reduction of EO residues, and the search for alternatives to the sterilization process should be continued throughout the life of the DM and taking into account the state of the art.