

Ethylene oxide-sterilised medical devices in neonatology and paediatrics: Implementation of standard NF EN ISO 10993-7

Ethylene oxide is a widely used sterilising agent, especially for single-use medical devices. It has proven its worth in terms of microbiological effectiveness. The French National Agency of Medicines and Health Products Safety (ANSM) analysed, through a market surveillance operation, the quality of implementation of this sterilisation method for medical devices used on neonatal and paediatric wards. Divergence in observance of certain standards requirements was noted, especially concerning the allowable limits of ethylene oxide residuals for this population.

The ANSM is currently continuing to work to ensure a satisfying enforcement of the standards by industrialists, in order to provide the appropriate level of safety in the use of sterilised medical devices.

Background

According to the information provided by several neonatal wards in France, almost 85% of single-use sterile devices (especially tubes and catheters for medicinal or nutrition product administration) are sterilised using ethylene oxide.

This sterilisation technique has constraints, especially that of management of ethylene oxide (EO) residuals and its derivatives found in devices after sterilisation to which patients are likely to be exposed during use. EO is classified as a category 1B carcinogenic and mutagenic substance¹.

The requirements relating to EO sterilisation residuals in medical devices are covered by a standard (NF EN ISO 10993-7). This specifies the allowable EO residual limits from sterilisation and states that the manufacturer must ensure the level of exposure to these substances is as low as possible. Observance of the allowable residuals limits must in effect be considered as a minimum risk prevention objective.

The ANSM decided to study implementation of this standard in France by conducting a market surveillance operation between 2013 and 2014, on EO-sterilised enteral feeding tubes used in neonatology and paediatrics.

What was observed by the ANSM through the control of the manufacturers and what are the measures envisaged?

The results of the market surveillance operation² of EO-sterilised enteral feeding tubes in neonatology and in paediatrics carried out between 2013 and 2014 showed discrepancies in implementation of standard NF EN ISO 10993-7 on EO residuals. Most tube manufacturers did not take into account a neonate low birth weight or the concomitant use of other EO-sterilised devices in their calculation of the allowable residue limits. In the light of the results of the market surveillance operation, the ANSM therefore issued a reminder of current legislation to manufacturers and sterilisation companies in July 2014.

The Agency is currently continuing to work with manufacturers and plans to provide a framework for placing on the market of medical devices used in neonates and infants.

It also works with the International Standards Organisation in the draft standard ISO 10993-7 revision process. It specifies its requirements where sterilised devices are used on this population.

¹ According to European Regulation № 1272/2008 of 16/12/2008 (CLP regulation) relating to the classification, labelling and packaging of substances and mixtures and replacing European Directive 67/548/EEC.

² The market surveillance operation consisted of a survey of manufacturers and two successive tests of residues measurement.

The ethylene oxide sterilisation benefit/risk ratio remains favourable

It is reminded that the widely used ethylene oxide sterilisation technique has proven its worth in terms of microbiological effectiveness and that it cannot be replaced by other techniques in the short term. The risk relating to EO sterilisation residuals should be examined with regard to the benefit of use of a medical device which when sterilised ensures the appropriate level of microbiological safety for patients. The benefit/risk ratio of the device remains favourable. The Agency's work enters into a more comprehensive approach for the reduction of exposure to CMR³ substances, without the use of EO as sterilising agent being brought into question.

Further reading

- Medical devices sterilised with ethylene oxide and used in neonatology and paediatrics – Summary of Regulations (June 2014)
http://ansm.sante.fr/var/ansm_site/storage/original/application/a61b9de7675df4924563e026afafe48c.pdf

³ Carcinogenic, mutagenic or toxic to reproduction substance.

WARNING : this version is only a translation of the French decision to facilitate its comprehension and does not have any legal status.

Decision dated

Setting out the specific conditions for the placing on the market and distribution of certain medical devices sterilised using ethylene oxide.

The Director General of the French National Agency for Medicines and Health Products Safety (ANSM),

Having regard to amended Council Directive 93/42/EEC of 14 June 1993 relating to medical devices, and especially essential requirements 7.5 and 8.4 of its annex I;

Having regard to Regulation (EC) №1272/2008 on the classification, labelling and packaging of substances and mixtures, hereinafter referred to as the CLP (Classification, Labelling and Packaging) regulation, amending and repealing Directives 67/548/EEC and 1999/45/EC and amending Regulation (EC) № 1907/2006;

Having regard to the French code of public health (CSP) part five, especially articles L. 5211-1, L. 5311-1, L. 5312-1 and R.5211-22;

Having regard to the order of 15 March 2010 published in the OJFR of 16 March 2010, setting out the conditions for implementation of the essential requirements applicable to medical devices, in application of article R. 5211-24 of the CSP;

Having regard to standard NF EN ISO 10993-7 relating to residual ethylene oxide and ethylene chlorohydrin in ethylene oxide-sterilised medical devices, especially setting out the allowable limits for these substance residuals;

Having regard to standard NF EN ISO 10993-17 relating to establishment of allowable limits for leachable substances from medical devices;

Having regard to the letter of 2 July 2015 from the French authorities to the Committee for standardisation established in application of article 5 of aforementioned Directive 93/42/EEC;

Having regard to the information from the market surveillance operation on ethylene oxide-sterilised enteral feeding tubes used in neonatology and paediatrics, especially the responses to the survey of manufacturers and the results of tests carried out on tubes sampled after controlled aeration;

Having regard to the elements of response brought in 2014 by the manufacturers of the market surveillance operation on ethylene oxide-sterilised enteral feeding tubes used in neonatology and paediatrics;

Having regard to the recommendations published on the ANSM's website in July 2014, « Medical devices sterilised with ethylene oxide and used in neonatology and paediatrics – Summary of Regulations »;

Whereas in application of points 7.5 and 8.4 of section II, article 1 of the order of 15 March 2010 relating to the essential requirements, medical devices must be designed and manufactured so as to reduce risks resulting from leachable substances to a minimum level, special attention being paid to carcinogenic, mutagenic or toxic to reproduction substances in accordance with the classification in the annex to the aforementioned CLP regulation, and if they are provided sterile, they must be sterilised using the appropriate method;

Whereas in application of the above mentioned CLP regulation, ethylene oxide is a category 1B carcinogenic and category 1B mutagenic substance, and ethylene chlorohydrin, an ethylene oxide degradation product, causes acute toxicity;

Whereas standards NF EN ISO 10993-7 and NF EN ISO 10993-17 are harmonised standards under Directive 93/42/EEC; whereas in application of article R.5211-18 of the CSP, the compliance of these medical devices with these standards confers presumption of conformity with the applicable essential requirements;

Whereas, however, harmonised standards NF EN ISO 10993-7 and NF EN ISO 10993-17 have shortcomings with respect to their application to specific patient populations such as neonates, premature neonates and

infants; whereas these shortfalls were identified and reported to the Committee for standardisation in a letter on 2 July 2015; whereas presumption of conformity with the essential requirements cannot therefore be based on application of the said standards alone;

Whereas standard NF EN ISO 10993-7 states that calculation of the allowable limits takes into account:

- patient bodyweight,
- concomitant use of other ethylene oxide-sterilised medical devices;

Whereas firstly, the market surveillance operation by the ANSM on enteral feeding tubes used in neonatology and paediatrics showed:

- on one hand that certain manufacturers do not take into account neonatal and paediatric patient bodyweight for calculating the allowable residuals limits;
- on the other hand that no manufacturers have taken the clinical environment of neonatal or paediatric patients into account in the concomitant exposure factor for calculating allowable residuals limits;

Whereas compliance with standard NF EN ISO 10993-7 is not met and whereas the medical devices concerned are not, for this first reason, sterilised using an appropriate method;

Whereas secondly, standard NF EN ISO 10993-7 is based on standard NF EN ISO 10993-17 and that the latter specifically states:

- on one hand the hypothesis of 3.5 kg for a neonate; whereas to this effect standard NF EN ISO 10993-17 is incomplete, as it does not take patients managed in neonatal reanimation and intensive care wards into account, especially premature neonates, the bodyweight of which is under 3.5 kg or even 1 kg for extreme low weights;
- on the other hand, whereas the default concomitant exposure factor, in the absence of information, is 0.2, which corresponds to the concomitant use of 5 ethylene oxide-sterilised devices; whereas to this effect standard NF EN ISO 10993-17 is not sufficiently explicit for calculating the concomitant exposure factor, as the number of ethylene oxide-sterilised medical devices used in neonatal reanimation and intensive care wards often exceeds 5;

Whereas, to this effect, the concomitant exposure factor must be lowered in proportion to the number of ethylene oxide-sterilised devices used concomitantly;

Whereas, in any event, compliance with the applicable essential requirements could not be met solely by observing the aforementioned standards, due to the incomplete nature of the latter;

Whereas compliance with the applicable essential requirements, for ethylene oxide-sterilised medical devices used in neonates, premature neonates and infants is not therefore demonstrated, and whereas the manufacturers have not therefore, for this second reason, sterilised the said devices according to the appropriate method;

Whereas, in the light of the above, manufacturers must adapt their medical device ethylene oxide sterilisation process, in view of their use in neonates, premature neonates and infants especially;

Whereas nevertheless, in order to ensure continuity of care for the aforementioned patients, a transition phase will be necessary to enable manufacturers to adapt, if needed, their ethylene oxide sterilisation process;

Whereas it is also necessary for the user health care establishment to have information on the residual quantities of carcinogenic substances for these devices, to enable it to select devices that minimize exposure during contact with the neonate, premature neonate or infant as far as possible;

Whereas the allowable limits set out by the manufacturer also depend on the time during which the patient is in contact with the device; whereas to this effect standard NF EN ISO 10993-7 provides for three categories of exposure according to contact time: less than 24 h, less than 30 days and more than 30 days; whereas also for a device in a given exposure category, the limits of the categories of lower duration must also be met; whereas as a result, all devices have a maximum limit for residues leached over the first 24 hours;

Whereas the information forwarded to the user health care establishment must be used to compare medical devices, regardless of their exposure category, the said data are the maximum quantities of ethylene oxide

residuals leached over the first 24 h of the exposure period; If the device is used less than 24h, the allowable limit is the maximum quantity leached over the duration of use defined by the manufacturer;

Whereas certain devices used in neonates, premature neonates and infants are not specifically intended by the manufacturer for this population and whereas information on the quantities of ethylene oxide residuals must also be available for the user health care establishment;

Whereas, in application of the above, it is appropriate to oblige manufacturers to provide distributors and user health care establishments with information relating to residual ethylene oxide;

Decides

Article 1 – The manufacturer placing on the market an ethylene oxide-sterilised medical device having a contact with patient, shall provide distributors and health care establishments using them in neonates, premature neonates and infants, the residual ethylene oxide value that it has defined as allowable limit and that it can guarantee at the placing on the market of the device;

Among the allowable limits set out by the manufacturer, target residual ethylene oxide is the maximum quantity of residuals leached over the first 24 h of the exposure period (μg per device). If the device is used less than 24h, the allowable limit is the maximum leached over the period of use;

Article 2 – The provisions of article 1 shall be enforced 6 months after the date of publication of this decision in the Official Journal of the French Republic at the latest.

Article 3 – The Diagnostic Medical Devices and Medical Devices Equipments Director, the Therapeutic Medical Devices and Cosmetics Director and the Inspection Director shall each enforce this decision, which will be published in the Official Journal of the French Republic.

Date