Agence nationale de sécurité du médicament et des produits de santé

Decision of 10/09/2015 setting out the specific conditions for the placing on the market and distribution of certain medical devices sterilised using ethylene oxide.

Framework and implementation modalities

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1. What is the context of this health policy decision?

The CE marking under the Directive 93/42/EEC concerning medical devices (MD) implies conformity with the essential requirements of Annex 1 of the Directive. Compliance with the harmonised European standards under the Directive confers a presumption of conformity to the essential requirements. In this case, the ANSM considers that the harmonised standard NF EN ISO 10993-7 specifying the allowable limits of residues from sterilisation with ethylene oxide (EO) is flawed when applying to medical devices for the treatment of patients with a body mass different from 70 kg and for whom more than 5 MD sterilised with EO are used simultaneously.

Therefore, application of the standard alone is not sufficient to demonstrate compliance with the essential requirements related to the control of residues from EO sterilisation for MD used in the care of premature neonate, neonate and infant patients. Pending a modification of the standard on these aspects and in a more general context of reduction of population exposure to CMR substances[1], this decision should enable healthcare facilities to have information on EO residues and to choose the MD best suited to the care of premature neonate, neonate and infant patients.
Patient care and continuity of care remain the priority.

2. Does this decision prohibit placing medical devices sterilised with ethylene oxide on the market in France?

This health policy decision does not prohibit placing MD sterilised with ethylene oxide on the market in France. It aims to inform healthcare facilities of the quantities of ethylene oxide that may be delivered to patients during use of these MD. This information should help to guide purchasers when choosing the device used in premature neonates, neonates and infants.

Sterilisation by ethylene oxide is a well-known and widely used technique, especially for single-use medical devices. The affected devices are usually made from heat-sensitive materials or those that will not support irradiation or steam treatment. The use of this technique is not in question. However, the allowable limits of EO residues must be adapted in relation to the population on which the devices are used when it comes to premature neonates, neonates and infants. The information provided by the manufacturer allows the healthcare facility to make a choice, favouring the MD with the lowest EO residues.

3. Why is there a delay of 6 months for entry into force of this decision?

The period of 6 months between the publication of the decision and its entry into force should allow the manufacturer to implement the procedure by which the requested information will be provided to healthcare facilities. It is not a time for review or compliance of the sterilisation process with ethylene oxide.

[1] Substances carcinogenic, mutagenic or toxic to reproduction.

4. What are the medical devices involved in the decision?

The decision applies to medical devices under Directive 93/42/EEC, insofar as they are:

- used in healthcare facilities for the care of premature neonates, neonates and infants,
- sterilised with EO,
- in direct or indirect contact with the patient's body. During contact, they expose the patient to leachable sterilisation residues.

Example of affected devices: catheters, extension sets, syringes, nutrition bags.

5. What are the medical devices excluded from the decision?

Medical devices not part of the application of the decision are the following:

- Medical devices not sold in a sterile condition,
- Medical devices sterilised with EO in healthcare facilities,
- Medical devices sterilised by a method other than EO,
- *In vitro* diagnostic medical devices,
- Active implantable medical devices,
- Medical devices not purchased by a healthcare facility (private or public).
- Medical devices sold in pharmacies or supermarkets, those used by home care providers. Medico-social centers are not affected by this decision.

6. What is the patient population targeted by the decision?

The decision concerns medical devices purchased and used in healthcare facilities for the care of premature neonates (preterm), neonates (0-28 days) and infants (children under two years).

7. What about devices that are not intended by the manufacturer for a specific population and are used in adults in the same way as in premature neonates, neonates or infants?

For most products, medical device manufacturers do not specify for which patient populations in terms of age or body mass the MD can be used. Some of these MD are used in healthcare facilities for the care of premature neonates, neonates and infants. Information on the residual quantity of ethylene oxide to be sent to the healthcare facilities concerns these devices.

Ex: syringes, extension sets, stopcock manifolds.

8. Who transmits the information to healthcare facilities?

The decision asks the MD manufacturers concerned to transmit data concerning EO residues after sterilisation to healthcare facilities, via their distributors if applicable.
Indeed, only the manufacturer has access to this information, which is one piece of the data in the CE marking file.

9. Who is the recipient of the information?

The information is to be transmitted by the manufacturer in response to a request from the purchaser who selects the MD for healthcare facilities, through its calls for tenders or competitive bidding process.
For the same use, this information allows the purchaser to select the best device for limiting exposure to EO residues in premature neonate, neonate and infant patients.
The communication of the information to the purchaser, at his request, shall be enforced on April 9, 2016 at the latest: it is mandatory from this date, however, the manufacturer, if he wishes, can respond favourably to such requests before this date.

10. What is the information to be transmitted?

The decision asks the MD manufacturers concerned to transmit data concerning EO residues after sterilisation to healthcare facilities, via their distributors if applicable. Insofar as the manufacturer applies and claims the standard NF EN ISO 10993-7, it defines the sterilisation residue limits during the sterilisation validation process (in particular depending on duration of use or patient contact). These values constitute the criteria, among others, for product release for placement on the market. The information to be transmitted is one of these limit values defined by the manufacturer and corresponds to the maximum amount of residue delivered to the patient during the first 24 hours of use, or the term of use if the MD is used for less than 24 hours.
The decision therefore requires the transmission of data present in the manufacturer's CE marking file.

11. What exposure category is concerned?

When establishing EO sterilisation residue limits, the standard NF EN ISO 10993-7 defines three categories of exposure according to the time the device remains in contact with the patient :

i. Up to 24 hours, limited contact,
ii. More than 24 hours and up to 30 days, prolonged contact,
iii. More than 30 days, permanent contact.

Devices from the three categories of exposure are affected by the decision.

12. What is the data to be transmitted for a "prolonged contact" or "permanent contact" device category?

For devices with prolonged contact or permanent contact, the information to be transmitted is the maximum amount of EO delivered to the patient, which should not be exceeded in the first 24 hours of the exposure period (µg per device). This EO limit per device on the first 24 hours of the exposure period is defined by the manufacturer using the standard NF EN ISO 10993-7 and is one of the criteria that allows the manufacturer to release its product in terms sterilisation residues.

13. What is the data to be transmitted for a “limited contact" device category?

For devices with limited contact, used for 24 hours or less, the information to be transmitted is the maximum amount of EO delivered to the patient, which should not be exceeded during the exposure period, meaning the length of use intended by the manufacturer (µg per device).
This EO limit per device on the exposure period is defined by the manufacturer using the standard NF EN ISO 10993-7 and is one of the criteria that allows the manufacturer to release its product in terms of sterilisation residues.

14. Should the manufacturer transmit the residue assay results lot by lot?

Regardless of the method chosen by the manufacturer to release its products in terms of EO residues (determination of residues of each lot or dissipation curves), it defines an EO limit per device on the first 24 hours of the exposure period or on the length of use if the MD is used less than 24 hours.
The manufacturer is not required to provide the results of assays on each lot but on the residue limit per device in the first 24 hours of the exposure period, or the period of use if the MD is used less 24 hours. This limit is one of the criteria that serves to release the product in terms of EO sterilisation residues (see questions 12 and 13).

15. What method of residue extraction should the manufacturer use?

The residue limits set by the manufacturer based on the NF EN ISO 10993-7 standard are independent of the extraction method it uses to collect residues from sterilisation and may expose the patient during use. The standard provides two methods (exhaustive extraction or extraction by simulation-used). With this decision, the ANSM does not require the use of either of these methods and does not describe the corresponding procedure.

16. Should the purchaser choose the device with the least residue?

Without hindering the care of premature neonates, neonates and infants, it is expected that the purchaser will select products whose residues are among the lowest.
To date, some manufacturers have set residue limits corresponding to a 70 kg adult, that is, of the order of several mg of EO delivered to the patient in the first 24 hours of the exposure period, while the range of this limit for a neonate is in the hundred µg.

17. Are the special situations stipulated by the NF EN ISO 10993-7 standard affected by the decision?

The NF EN ISO 10993-7 standard provides several special situations where the limits it sets are specific:

1. Intraocular lenses,
2. Blood cell separators (apheresis),
3. Blood oxygenators,
4. Cardiopulmonary bypass devices,
5. Blood purification devices (hemodialysers),
6. Drapes contacting with intact skin.

Except for the drapes provided to be in contact with intact skin where the requirements of the NF EN ISO 10993-7 standard is limited to the verification of the absence of local irritation due to residues, other special situations stipulated by the standard are also affected by the decision.

18. Does the decision apply to drapes intended to be in contact with intact skin?

The decision does not apply to drapes intended to be in contact with intact skin. In this case, the requirements of the NF EN ISO 10993-7 standard are limited to the verification of the absence of local irritation due to sterilisation residue (see also question 17).

19. How should this decision be applied in the case of sets or care kits?

The NF EN ISO 10993-7 standard provides for the case of multi-device systems, for which it states that the EO limits defined by the manufacturer apply to each individual patient-contact device. In this case, the information to be transmitted corresponds to the sum of the limits associated with each device having a contact with the patient present in the kit. The interest for the healthcare facility purchaser is to be able to use this data as one criterion among many in MD selection.

20. Does this decision apply in the case of fitting accessories in a care set?

To the extent that the accessory meets the conditions specified in question 4 of this document, the decision also applies in this case.

21. When is the information to be transmitted to the healthcare facility?

Manufacturers routinely communicate information on EO residues in response to calls for tenders/consultations from healthcare facilities.
Following further validation of the sterilisation procedure, if the information given in the tender is changed, the manufacturer reports the change to the healthcare facility and communicates the new value in the first order of the products concerned.

22. What is the support information?

The decision does not impose support information and leaves it up to the manufacturer to use its own appropriate means allowing the healthcare facility to receive the information requested for the devices they use.
Ex: Labelling or package insert or element of a data sheet during consultations for calls for tender.

23. Why are only healthcare facilities concerned with this decision?

This decision targets the population of premature neonates, neonates and infants receiving major care, requiring special attention in a complex clinical setting. These patients, for whom the use of EO-sterilised devices is very frequent, are mainly managed in healthcare facilities.

24. What is meant by product release?

Release is the manufacturing stage at which it is shown that the manufacturing and sterilisation procedures applied to the devices, follow the predefined and validated conditions. In the case of EO-sterilised medical devices, among the release criteria defined by the manufacturer, some relate to the levels of ethylene oxide sterilisation residuals. Once release is granted, the products can be placed on the market and the manufacturer ensures and communicates these residue levels to healthcare facilities.

25. What are the allowable limits?

The NF EN ISO 10993-7 standard defines the allowable limit as the largest amount of EO deemed acceptable as a result of exposure from a medical device.
The standard defines a number of limits according to the duration of exposure and, for all MD, the standard specifies a dose that should not be exceeded within the first 24 hours of exposure (use). This value was chosen by the ANSM as a reference to be transmitted to healthcare facilities as part of this decision.

Additional information:
For each of its medical devices, the manufacturer determines the dose delivered to the patient during use and this dose should not exceed the allowable limits calculated by the manufacturer using the standard:
For a medical device with limited exposure (1 day or less), the allowable limit is expressed in average daily dose and should not be exceeded.
For a medical device with prolonged exposure (more than 1 day and up to 30 days), the allowable limits that must not be exceeded include the average daily dose (µg/d), the maximum dose over the first 24 hours (µg) and the maximum dose over 30 days (µg).
For a medical device with permanent exposure (more than 30 days), the allowable limits that must not be exceeded include the average daily dose (µg/d), the maximum dose over the first 24 hours (µg), the maximum dose over 30 days (µg), and the dose over a lifetime (µg).

26. What should be done if a manufacturer doesn't transmit the information requested?

In this case it is advised to choose a different MD whose manufacturer has provided the information regarding the EO residue levels with preference to those among who have the lowest rates.
Troubles in obtaining this information can be sent to the ANSM at: dmdpt@ansm.sante.fr

27. What patient body weight should be taken into account? What is the concomitance factor?

The assumptions of patient body weight and concomitance to calculate the allowable EO limits fall under the responsibility of the manufacturer. In any case, the assumptions used take into account actual use of the device.

28. What are the implementation modalities of this decision and transmitted by the DGOS to healthcare facilities?

On November 16, 2015, the general directorate for healthcare provision (DGOS) has circulated to healthcare facilities the directive N° DGS/PP3/DGOS/PF2/2015/311 *du 16 octobre 2015 relative aux conditions particulières de mise sur le marché et de distribution des dispositifs médicaux stérilisés à l'oxyde d'éthylène utilisés chez les nouveau-nés, nouveau-nés prématurés et les nourrissons*.
This directive informs the health facilities of the decision ANSM dated on September 10, 2015, setting out the specific conditions for the placing on the market and distribution of medical devices sterilised using ethylene oxide used in newborns, premature newborns and infants, and the measures to be implemented within this framework.
The implementation modalities shall be enforced on April 9, 2016 at the latest: manufacturers are required to transmit the information from this date, however, the purchaser can now request this information in the event the manufacturer is already able to provide them.

29. How to request additional information?

Requests for additional information may be sent to the following address: dmdpt@ansm.sante.fr