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Biological evaluation of medical devices —

Part 7: Ethylene oxide sterilization residuals

AMENDMENT 1: Applicability of allowable limits for neonates and infants

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This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*.

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Biological evaluation of medical devices —

Part 7:
Ethylene oxide sterilization residuals

AMENDMENT 1: Applicability of allowable limits for neonates and infants

Normative references

Replace the reference to ISO 10993-1:— (including the footnote) with the following:

> ISO 10993-1:2018, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

4.2, second paragraph

Replace the reference "ISO 10993-1:—, 5.3:" with "ISO 10993-1:2018, 5.3:".

4.2, a) to c)

Replace the text with the following:

a) Limited exposure (A) – medical devices whose cumulative sum of single, multiple or repeated duration of contact is up to 24 h.

b) Prolonged exposure (B) – medical devices whose cumulative sum of single, multiple or repeated contact time is likely to exceed 24 h but not exceed 30 d.

c) Permanent exposure (C) – medical devices whose cumulative sum of single, multiple or repeated contact time exceeds 30 d.

4.3.1, second paragraph

Replace the paragraph with the following:

> The limits for permanent contact and prolonged exposure devices are expressed as maximum average daily doses. These limits carry additional constraints for the first 24 h of the exposure period and, in the case of the permanent contact devices, for the first 30 days, whichever extraction method is used. These constraints place limitations on the amount of EO and ECH that can be delivered to the patient during these early time periods.

4.3.1, third paragraph

Add a new paragraph:

If data are available, consideration should be given for proportioning the limits downward if multiple devices with the residue of concern are used at one time, e.g. multi-device systems, convenience kits, or proportioning the limits upward when device use is only for a part of the exposure period of concern. These concomitant exposure factors (CEF) and proportional exposure factors (PEF) are given in ISO 10993-17. A default value of 0,2 for CEF have been given for 5 medical devices used and contributing to the patient residues daily exposure.

4.3.2, first paragraph

Replace the paragraph with the following:

In the case of a device used in an adult of body mass m_b = 70 kg, and with CEF = 0,2 and PEF = 1,0 (default factors), the average daily dose of EO to patient shall not exceed 0,1 mg/d. In addition, the maximum EO dose shall not exceed:

4.3.2, last paragraph

Replace the paragraph with the following:

When the device is intended to be used in special populations, the appropriate patient body mass shall be used for the derivation of the allowable limits. For example, if the device is intended to be used in premature neonates, neonates or children, the allowable limits shall be derived using the TI value of 0,02 mg/kg/day for EO and 0,029 mg/kg/day for ECH as established in G.6.4 and H.4.1.3, respectively. The appropriate default body mass used for each category of special patient population shall be justified and documented.

4.3.3, first paragraph

Replace the paragraph with the following:

In the case of a device used in an adult of body mass m_b = 70 kg, and with CEF = 0,2 and PEF = 1,0 (default factors), the average daily dose of EO to patient shall not exceed 2,0 mg/d. In addition, the maximum EO dose shall not exceed:

4.3.3, last paragraph

Replace the paragraph with the following:

When the device is intended to be used in special populations, the appropriate patient body mass shall be used for the derivation of the allowable limits. For example, if the device is intended to be used in premature neonates, neonates or children, the allowable limits shall be derived using the TI value of 0,3 mg/kg/day for EO and 0,27 mg/kg/day for ECH as established in G.6.3 and H.4.1.2, respectively. The appropriate default body mass used for each category of special patient population shall be justified and documented.

4.3.4

Replace the text with the following:

In the case of a device used in an adult of body mass m_b = 70 kg, and with CEF = 0,2 and PEF = 1,0 (default factors), the average daily dose of EO to patient shall not exceed 4 mg. The average daily dose of ECH to patient shall not exceed 9 mg.

When the device is intended to be used in special populations, the appropriate patient body mass shall be used for the derivation of the allowable limits. For example, if the device is intended to be used in premature neonates, neonates or children, the allowable limits shall be derived using the TI value of 0,3 mg/kg/day for EO and 0,64 mg/kg/day for ECH as established in G.6.2 and H.4.1.1, respectively. The appropriate default body mass used for each category of special patient population shall be justified and documented.

B.2.1, second paragraph

Add the following sentence to the end of the paragraph:

Guidance on analytical method validation is available in numerous guidelines including ICH Q2 (R2) (see Bibliography).

B.2.1, third paragraph

Delete the second and third sentence of this paragraph.

C.1, second paragraph

Replace the text of the second sentence with the following:

Maximum allowable limits for ethylene chlorohydrin residues where ECH has been found to be present in medical devices sterilized with EO are also specified in the case of a device used in an adult of body mass m_b = 70 kg, and with CEF = 0,2 and PEF = 1,0 (default factors).

C.1, Table C.1

Replace the heading with the following:

Summary of allowable limits in adults for EO and ECH (limits per device). See also Figure C.1.

C.2.6

Replace the text of the first paragraph with the following:

For permanent exposure medical devices (those contacting the patient for longer than 30 d to a lifetime), exhaustive extraction is preferred. If another procedure is used this should be justified and documented.

C.2.7

Replace the second paragraph by the following:

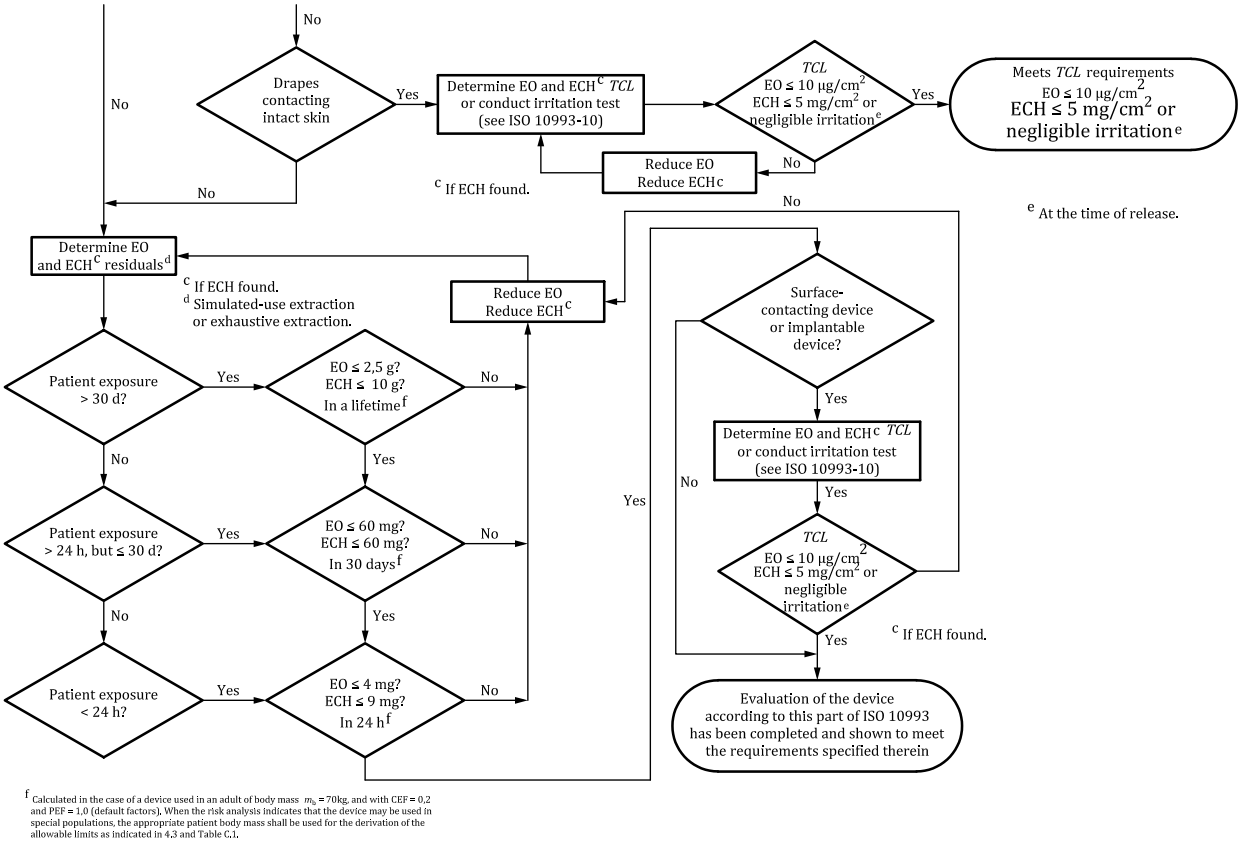
a) If the measured EO and ECH are not more than 60 mg, go to C.2.7 b). Otherwise, use appropriate temperatures (either 37 °C or 25 °C) and times (based on anticipated use time) with water as the extracting medium to simulate product use (see C.3). If the measured EO and ECH dose, where ECH has been found, is not more than 60 mg, go to C.2.7 b). Otherwise, reduce EO and/or ECH.

b) If the measured EO and ECH are not more than 4 mg and 9 mg, respectively, go to C.2.9. Otherwise, use appropriate temperatures (either 37 °C or 25 °C) for 24 h with water as the extracting medium

to simulate product use (see C.3). If the measured EO and ECH doses from simulated use are not more than 4 mg or 9 mg respectively, go to C.2.9. Otherwise, reduce EO and/or ECH.

C.3.6, Figure C.3

Replace Figure C.3 with the following figure, which includes footnote f:



[f] Calculated in the case of a device used in an adult of body mass m_b = 70 kg, and with CEF = 0,2 and PEF = 1,0 (default factors). When the risk analysis indicates that the device may be used in special populations, the appropriate patient body mass shall be used for the derivation of the allowable limits as indicated in 4.3 and Table C.1.

Bibliography

[1] ISO 11135:2007

Replace the above reference with the following one:

[1] ISO 11135:2014, *Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices*

[2] AAMI EO VRSU 3/81

Replace the above reference with the following one:

[2] Association for the Advancement of Medical Instrumentation, *Good Hospital Practice: Ethylene Oxide Gas — Ventilation Recommendations and Safe Use*, Arlington, VA, 1987

[14] AAMI ST30 1989

Delete this reference and renumber the subsequent references.

[15] ASTM E691-05

Replace the above reference with the following one:

[14] ASTM E691-18, Standard practice for conducting an interlaboratory study to determine the precision of a test method

[17] ATSDR (1997)

Replace the above reference with the following one:

[16] ATSDR. Toxicological profile for ethylene glycol and propylene glycol. Atlanta, GA, 2010

Add the following references at the end of the Bibliography:

[207] Validation of analytical procedures: Text and methodology Q2 (R1), ICH Harmonised Tripartite Guideline, November 2005

[208] Harmonized Guidelines for Single Laboratory Validation Methods of Analysis (IUPAC Technical Report). Pure Appl. Chem., Vol. 74, No. 5, pp. 835.855, 2002

[209] AOAC Guidelines for Single Laboratory Validation of Chemical Methods for Dietary Supplements and Botanicals (December 12, 2002)

[210] Guidance for industry - Analytical Procedures and Methods Validation for Drugs and Biologics, US. Department of Health and Human Services, FDA, July 2015

[211] Harmonisation of strategies for the validation of quantitative analytical procedures A SFSTP proposal Part I. J. Pharm. Biomed. Anal. 2004, 36 pp. 579–586

[212] Eurachem, The Fitness for Purpose of Analytical Methods, A Laboratory Guide to Method Validation and Related Topics. Second Edition, 2014

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