American National Standard

ANSI/AAMI/ISO 10993-7:2008

Biological evaluation of medical devices— Part 7: Ethylene oxide sterilization residuals

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Objectives and uses of AAMI standards and recommended practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

A *recommended practice* provides guidelines for the use, care, and/or processing of a medical device or system. A recommended practice does not address device performance *per se*, but rather procedures and practices that will help ensure that a device is used safely and effectively and that its performance will be maintained.

Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a frame of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards healthcare professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

In determining whether an AAMI standard or recommended practice is relevant to the specific needs of a potential user of the document, several important concepts must be recognized:

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Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

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ANSI/AAMI/ISO 10993-7:2008(R)2012
(Combined revision of ANSI/AAMI/ISO 10993-7:1995/(R)2001,
AAMI TIR19:1998 and AAMI TIR19:1998:/A1:1999)

Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals

Approved 10 December 2008 by
Association for the Advancement of Medical Instrumentation

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Abstract: ANSI/AAMI/ISO 10993-7 specifies allowable limits for residual ethylene oxide (EO) and ethylene chlorohydrin (ECH) in individual EO-sterilized medical devices, procedures for the measurement of EO and ECH, and methods for determining compliance so that devices may be released. Additional background, including guidance and a flowchart showing how this document is applied, is also included in informative annexes. EO-sterilized devices that have no patient contact (e.g., in vitro diagnostic devices) are not covered by this standard.

Keywords: ethylene oxide, EO, allowable limits, biological evaluation, ethylene chlorohydrin

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Other normatively referenced International Standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

International designation	U.S. designation	Equivalency
IEC 60601-1:2005	ANSI/AAMI ES60601-1:2005	Major technical variations
IEC 60601-1-2:2007	ANSI/AAMI/IEC 60601-1-2:2007	Identical
IEC 60601-2-2:2006	ANSI/AAMI/IEC 60601-2-2:2006	Identical
IEC 60601-2-4:2002	ANSI/AAMI DF80:2003	Major technical variations
IEC 60601-2-19:1990 and A1:1996	ANSI/AAMI II36:2004	Major technical variations
IEC 60601-2-20:1990 and A1:1996	ANSI/AAMI II51:2004	Major technical variations
IEC 60601-2-21:1994 and Amendment 1:1996	ANSI/AAMI/IEC 60601-2-21 and Amendment 1:2000 (consolidated texts)	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:2004	Major technical variations
IEC 60601-2-47:2001	ANSI/AAMI EC38:2007	Major technical variations
IEC 60601-2-50:2001	ANSI/AAMI/IEC 60601-2-50:2006	Identical
IEC 80601-2-58:2008	ANSI/AAMI/IEC 80601-2-58:2008	Identical
IEC/TR 60878:2003	ANSI/AAMI/IEC TIR60878:2003	Identical
IEC/TR 62296:2003	ANSI/AAMI/IEC TIR62296:2003	Identical
IEC 62304:2006	ANSI/AAMI/IEC 62304:2006	Identical
IEC/TR 62348:2006	ANSI/AAMI/IEC TIR62348:2006	Identical
ISO 5840:2005	ANSI/AAMI/ISO 5840:2005	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001/(R)2004	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996/(R)2002	Identical
ISO 8637:2004	ANSI/AAMI RD16:2007	Major technical variations
ISO 8638:2004	ANSI/AAMI RD17:2007	Major technical variations
ISO 10993-1:2003	ANSI/AAMI/ISO 10993-1:2003	Identical
ISO 10993-2:2006	ANSI/AAMI/ISO 10993-2:2006	Identical
ISO 10993-3:2003	ANSI/AAMI/ISO 10993-3:2003	Identical
ISO 10993-4:2002 and A1:2006	ANSI/AAMI/ISO 10993-4:2002 and A1:2006	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:2007	ANSI/AAMI/ISO 10993-6:2007	Identical
ISO 10993-7:2008	ANSI/AAMI/ISO 10993-7:2008	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999/(R)2005	Identical
ISO 10993-10:2002 and Amendment 1:2006	ANSI/AAMI BE78:2002/(R)2008 ANSI/AAMI BE78:2002/A1:2006/(R)2008	Minor technical variations Identical
ISO 10993-11:2006	ANSI/AAMI/ISO 10993-11:2006	Identical
ISO 10993-12:2007	ANSI/AAMI/ISO 10993-12:2007	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999/(R)2004	Identical
ISO 10993-14:2001	ANSI/AAMI/ISO 10993-14:2001/(R)2006	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000/(R)2006	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997/(R)2003	Identical
ISO 10993-17:2002	ANSI/AAMI/ISO 10993-17:2002/(R)2008	Identical
ISO 10993-18:2005	ANSI/AAMI BE83:2006	Major technical variations
ISO/TS 10993-19:2006	ANSI/AAMI/ISO TIR10993-19:2006	Identical
ISO/TS 10993-20:2006	ANSI/AAMI/ISO TIR10993-20:2006	Identical
ISO 11135-1:2007	ANSI/AAMI/ISO 11135-1:2007	Identical

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International designation	U.S. designation	Equivalency
ISO/TS 11135-2:2008	ANSI/AAMI/ISO TIR11135-2:2008	Identical
ISO 11137-1:2006	ANSI/AAMI/ISO 11137-1:2006	Identical
ISO 11137-2:2006 (2006-08-01 corrected version)	ANSI/AAMI/ISO 11137-2:2006	Identical
ISO 11137-3:2006	ANSI/AAMI/ISO 11137-3:2006	Identical
ISO 11138-1: 2006	ANSI/AAMI/ISO 11138-1:2006	Identical
ISO 11138-2: 2006	ANSI/AAMI/ISO 11138-2:2006	Identical
ISO 11138-3: 2006	ANSI/AAMI/ISO 11138-3:2006	Identical
ISO 11138-4: 2006	ANSI/AAMI/ISO 11138-4:2006	Identical
ISO 11138-5: 2006	ANSI/AAMI/ISO 11138-5:2006	Identical
ISO/TS 11139:2006	ANSI/AAMI/ISO 11139:2006	Identical
ISO 11140-1:2005	ANSI/AAMI/ISO 11140-1:2005	Identical
ISO 11140-3:2007	ANSI/AAMI/ISO 11140-3:2007	Identical
ISO 11140-4:2007	ANSI/AAMI/ISO 11140-4:2007	Identical
ISO 11140-5:2007	ANSI/AAMI/ISO 11140-5:2007	Identical
ISO 11607-1:2006	ANSI/AAMI/ISO 11607-1:2006	Identical
ISO 11607-2:2006	ANSI/AAMI/ISO 11607-2:2006	Identical
ISO 11737-1: 2006	ANSI/AAMI/ISO 11737-1:2006	Identical
ISO 11737-2:1998	ANSI/AAMI/ISO 11737-2:1998	Identical
ISO 13408-1:2008	ANSI/AAMI/ISO 13408-1:2008	Identical
ISO 13408-2:2003	ANSI/AAMI/ISO 13408-2:2003	Identical
ISO 13408-3:2006	ANSI/AAMI/ISO 13408-3:2006	Identical
ISO 13408-4:2005	ANSI/AAMI/ISO 13408-4:2005	Identical
ISO 13408-5:2006	ANSI/AAMI/ISO 13408-5:2006	Identical
ISO 13408-6:2006	ANSI/AAMI/ISO 13408-6:2006	Identical
ISO 13485:2003	ANSI/AAMI/ISO 13485:2003	Identical
ISO 14155-1:2003	ANSI/AAMI/ISO 14155-1:2003/(R)2008	Identical
ISO 14155-2:2003	ANSI/AAMI/ISO 14155-2:2003/(R)2008	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998/(R)2008	Identical
ISO 14161:2000	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO/TR 14969:2004	ANSI/AAMI/ISO TIR14969:2004	Identical
ISO 14971:2007	ANSI/AAMI/ISO 14971:2007	Identical
ISO 15223-1:2007 and A1:2008	ANSI/AAMI/ISO 15223-1:2007 and A1:2008	Identical
ISO 15225:2000 and A1:2004	ANSI/AAMI/ISO 15225:2000/(R)2006 and A1:2004/(R)2006	Identical
ISO 15674:2001	ANSI/AAMI/ISO 15674:2001	Identical
ISO 15675:2001	ANSI/AAMI/ISO 15675:2001	Identical
ISO 15882:2008	ANSI/AAMI/ISO 15882:2008	Identical
ISO/TR 16142:2006	ANSI/AAMI/ISO TIR16142:2005	Identical
ISO 17664:2004	ANSI/AAMI ST81:2004	Major technical variations
ISO 17665-1:2006	ANSI/AAMI/ISO 17665-1:2006	Identical
ISO 18472:2006	ANSI/AAMI/ISO 18472:2006	Identical
ISO/TS 19218:2005	ANSI/AAMI/ISO 19218:2005	Identical
ISO 22442-1:2007	ANSI/AAMI/ISO 22442-1:2007	Identical
ISO 22442-2:2007	ANSI/AAMI/ISO 22442-2:2007	Identical
ISO 22442-3:2007	ANSI/AAMI/ISO 22442-3:2007	Identical
ISO 25539-1:2003 and A1:2005	ANSI/AAMI/ISO 25539-1:2003 and A1:2005	Identical
ISO 25539-2:2008	ANSI/AAMI/ISO 25539-2:2008	Identical
ISO 81060-1:2007	ANSI/AAMI/ISO 81060-1:2007	Identical

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Committee representation

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The adoption of ISO 10993-7 as a revision of ANSI/AAMI/ISO 10993-7:1995/(R)2001 was initiated by the AAMI Sterilization Residuals Working Group under the auspices of the AAMI Sterilization Standards Committee, and the AAMI Allowable Limits for Leachable Substances Working Group under the auspices of the AAMI Biological Evaluation of Medical Devices Committee. Both of these working groups function as U.S. Technical Advisory sub-Groups to the relevant work in the International Organization for Standardization (ISO). U.S. representatives played an active part in developing the ISO standard. Committee approval of the standard does not necessarily imply that all committee and working group members voted for its approval.

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Background of AAMI adoption of ISO 10993-7:2008

As indicated in the foreword to the main body of this document (page x), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard.

International Standard ISO 10993-7:2008 was developed as a revision to the 1995 edition by Working Group (WG) 11, *Allowable limits for leachable substances*, of Technical Committee ISO/TC 194, *Biological evaluation of medical devices*. This new edition was developed by evaluating the technical literature through 2006 and applying the methodology described in ISO 10993-17:2002, *Biological evaluation of medical devices – Part 17 Establishment of allowable limits for leachable substances*. Using this approach the expert committee established that the allowable limits for EO and ECH residuals for devices in the limited exposure category should be changed. The same review showed that the allowable limits for EO and ECH for the prolonged and permanent exposure categories should remain the same. The committee also determined that to meet the requirement to limit the potential acute irritation effects of EO and ECH a dual binding constraint of Tolerable Contact Limit (TCL) should be used and should be expressed in terms of amount of residue per unit surface area of device/patient interface.

Additionally, a new annex C, including a flowchart, has been added to provide guidance on the application of the standard, which is extensively based on AAMI TIR19:1998 and its 1999 amendment.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 194, administered by the Association for the Advancement of Medical Instrumentation on behalf of the American National Standards Institute. The U.S. made a considerable contribution to this International Standard.

AAMI encourages its committees to harmonize their work with international standards as much as possible. Upon review of ISO 10993-7, the AAMI Sterilization residuals Working Group and the AAMI Allowable limits for leachable substances Working Group decided to adopt 10993-7, verbatim, as a revision of ANSI/AAMI/ISO 10993-7:1995(R)2001.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication.

AAMI (and ANSI) have adopted other ISO standards. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI, which gives the corresponding U.S. designation and the level of equivalency with the ISO standard.

As used within the context of this standard, “shall” indicates requirements to be followed strictly in order to conform to the standard; “should” indicates that among several possibilities, one is recommended as particularly suitable, without mentioning or excluding others, that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action is undesirable but not prohibited; “may” is used to indicate that a course of action is permissible within the limits of the standard; “can” is used as a statement of possibility and capability; “must” is used only for those situations which cannot be otherwise, as in the example “Monday must follow Sunday.”

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

NOTE—Beginning with the ISO foreword on page x, this American National Standard is identical to ISO 10993-7:2008.

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 10993-7 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition (ISO 10993-7:1995) which has been technically revised.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *Part 1: Evaluation and testing within a risk management system*

— *Part 2: Animal welfare requirements*

— *Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

— *Part 4: Selection of tests for interactions with blood*

— *Part 5: Tests for in vitro cytotoxicity*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 9: Framework for identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and skin sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

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— *Part 13: Identification and quantification of degradation products from polymeric medical devices*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from metals and alloys*

— *Part 16: Toxicokinetic study design for degradation products and leachables*

— *Part 17: Establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials* [Technical Specification]

— *Part 20: Principles and methods for immunotoxicology testing of medical devices* [Technical Specification]

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Introduction

Requirements for the development, validation and routine control of an ethylene oxide sterilization process for medical devices are given in International Standards developed by ISO/TC 198. Certain requirements relating to medical devices for biological testing, selection of tests, and the allocation of devices to categories are dealt with in a variety of International Standards developed by ISO/TC 194. The specific requirement for ethylene oxide and other sterilization process residuals was referred to ISO/TC 194. Other International Standards delineate particular requirements for biological testing for specific products.

As noted in the introduction to ISO 11135-1:2007, when determining the suitability of ethylene oxide (EO) for sterilization of medical devices, it is important to ensure that the levels of residual EO, ethylene chlorohydrin (ECH) and ethylene glycol (EG) pose a minimal risk to the patient in normal product use. Therefore, it is important that the use of alternative materials and sterilization processes be considered during product design and development. EO is known to exhibit a number of biological effects. In the development of this part of ISO 10993, consideration was given to these effects, which include irritation, organ damage, mutagenicity and carcinogenicity in humans and animals, and reproductive effects in animals. Similar consideration was given to the harmful effects of ECH and EG. In practice, for most devices, exposure to EO and ECH is considerably lower than the maximum values specified in this part of ISO 10993.

Moreover, when the choice for EO sterilization has been made, irrespective of the provisions of this part of ISO 10993, exposure to EO residues should be minimized. Requirements herein are in addition to the biological evaluation and testing requirements for each individually designed medical device as indicated in ISO 10993-1. The biological evaluation and testing requirements, combined with the EO-sterilization process residue limits, form the justification that an EO-sterilized device is acceptable for use. Maximum allowable residues for ethylene chlorohydrin (ECH), when ECH has been found to be present in medical devices sterilized with EO, are also specified. Local effects (e.g., irritation) have been considered and are incorporated in the tolerable contact limit (TCL) as given in 4.3.5.2 and Annex G for EO, and in 4.3.5.3 and Annex H for ECH.

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Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals

1 Scope

This part of ISO 10993 specifies allowable limits for residual ethylene oxide (EO) and ethylene chlorohydrin (ECH) in individual EO-sterilized medical devices, procedures for the measurement of EO and ECH, and methods for determining compliance so that devices may be released. Additional background, including guidance and a flowchart showing how this document is applied, are also included in the informative annexes.

EO-sterilized devices that have no patient contact (e.g., *in vitro* diagnostic devices) are not covered by this part of ISO 10993.

NOTE This part of ISO 10993 does not specify limits for ethylene glycol (EG).

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

ISO 10993-3, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

ISO 10993-10, *Biological evaluation of medical devices — Part 10: Tests for irritation and delayed-type hypersensitivity*

ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-17:2002, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1, ISO 10993-17 and the following apply.

1) To be published. (Revision of ISO 10993-1:2003)

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3.1
simulated-use extraction
extraction to demonstrate compliance with the requirements of this part of ISO 10993, by evaluating residue levels available to the patient or user from devices during the routine use of a device with water extraction to simulate product use

3.2
exhaustive extraction
extraction until the amount of EO or ECH in a subsequent extraction is less than 10 % of that detected in the first extraction, or until there is no analytically significant increase in the cumulative residue levels detected

NOTE As it is not possible to demonstrate the exhaustive nature of residual recovery, the definition of exhaustive extraction adopted is as above.

4 Requirements

4.1 General

NOTE Information on the derivation of the limits in this part of ISO 10993 as well as other important background information and guidance relevant to the use of this document is contained in the informative annexes.

This clause specifies maximum allowable residues for ethylene oxide (EO) for each individual medical device sterilized with EO. As noted in the introduction to ISO 11135-1:2007, when determining the suitability of EO for sterilization of medical devices, it is important to ensure that the levels of residual EO, ethylene chlorohydrin (ECH) and ethylene glycol (EG) pose a minimal risk to the patient in normal product use. Moreover, when the choice for EO sterilization has been made, irrespective of the provisions of this standard, exposure to EO residues should be minimized. Maximum allowable residues for ECH, when ECH has been found to be present in medical devices sterilized with EO, are also specified. Local effects (e.g., irritation) have been considered and are incorporated in the tolerable contact limit (TCL) as discussed in 4.3.5.2 and Annex G for EO, and 4.3.5.3 and Annex H for ECH. No device limits are specified for EG because a risk assessment (Annex I) indicates that calculated allowable levels are higher than those likely to occur in a medical device. However, the potential exists for acute haemodynamic and haemolytic effects to occur following rapid intravenous administration of hyperosmolar compounds like EG. Ethylene oxide sterilization of medical devices would not be expected to produce hyperosmolar solutions. Methods for the determination of EO and ECH are given in 4.4.

The requirements in this part of ISO 10993 are in addition to the biological testing requirements set out in ISO 10993-1. For devices sterilized using ethylene oxide, attention shall be paid in particular to ISO 10993-3 and ISO 10993-10. All applicable requirements of ISO 10993-1 shall take into account the EO residual level at the time of release for each individually designed medical device.

Results of the biological assessment of the device may dictate more stringent limits than those specified in 4.3, which are designed to protect against systemic effects.

4.2 Categorization of devices

In establishing the maximum daily doses of EO and ECH that a medical device is allowed to deliver to patients, devices shall be categorized according to the duration of contact.

Devices shall be placed into one of three exposure categories in accordance with ISO 10993-1:—, 5.3:

a) limited exposure (A) – devices whose cumulative single, multiple or repeated use or contact is up to 24 h;

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b) prolonged exposure (B) – devices whose cumulative single, multiple, or repeated long-term use or contact is likely to exceed 24 h but not 30 d;

c) permanent contact (C) – devices whose cumulative single, multiple or repeated long-term use or contact exceeds 30 d.

If a material or device can be placed in more than one duration category, the more rigorous testing and/or evaluation considerations should apply. With multiple exposures, the decision into which category a device is placed should take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur.

NOTE As it is applied in this part of ISO 10993, "multiple use" is defined to mean repeated use of the same device type, e.g. dialyser cartridges.

4.3 Allowable limits

4.3.1 General

For each medical device, the maximum allowable doses of EO and ECH delivered to patients shall not exceed the values given below for the exposure category that the device has been placed into in accordance with 4.2.

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. These constraints place limitations on the amount of EO and ECH that can be delivered to the patient during these early time periods. 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, 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. The procedure that was used to establish the allowable limits is described in Annex G for EO, in Annex H for ECH, and the rationale for considering the establishment of allowable limits for EG is described in Annex I.

4.3.2 Permanent contact devices

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 mg in the first 24 h;

— 60 mg in the first 30 d;

— 2.5 g in a lifetime.

The average daily dose of ECH to patient shall not exceed 0.4 mg/d. In addition, the maximum ECH dose shall not exceed:

— 9 mg in the first 24 h;

— 60 mg in the first 30 d;

— 10 g in a lifetime.

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4.3.3 Prolonged exposure devices

The average daily dose of EO to patient shall not exceed 2 mg/d. In addition, the maximum EO dose shall not exceed:

— 4 mg in the first 24 h;

— 60 mg in the first 30 d.

The average daily dose of ECH to patient shall not exceed 2 mg/d. In addition, the maximum ECH dose shall not exceed:

— 9 mg in the first 24 h;

— 60 mg in the first 30 d.

4.3.4 Limited exposure devices

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.

4.3.5 Tolerable contact limits for surface contacting devices and implants

4.3.5.1 Overview

The tolerable contact limit (TCL) is expressed in units of micrograms per square centimeter for EO and milligrams per square centimeter for ECH. The unit of square centimeter represents the surface area of the patient-device interface.

NOTE The intent of this subclause is to prevent localized irritation due to EO or ECH released from the device.

4.3.5.2 Tolerable contact limit for EO

Either the EO TCL for surface contacting devices and implants shall not exceed 10 µg/cm^2 or it shall exhibit negligible irritation as specified in ISO 10993-10.

4.3.5.3 Tolerable contact limit for ECH for surface contacting devices

Either the ECH TCL for surface contacting devices and implants shall not exceed 5 mg/cm^2 or it shall exhibit negligible irritation as specified in ISO 10993-10.

4.3.6 Special situations

For multi-device systems the limits shall apply to each individual patient-contact device.

Residue of EO in intraocular lenses shall not exceed 0.5 µg EO per lens per day, or 1.25 µg per lens. Prorate limits for other intraocular devices are set on the basis of the mass of the device, with the mass of an intraocular lens taken as 20 mg. The acceptability of ECH levels in intraocular devices made from viscoelastic materials that contain chlorine may need to be evaluated, as the level of ECH that results in ocular toxicity is about four times greater than the corresponding EO level.

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For blood cell separators used in patient and donor blood collection, the maximum allowable dose of EO is 10 mg and the maximum allowable dose of ECH shall not exceed 22 mg.

For blood oxygenators and blood separators, the maximum allowable dose of EO to patient is 60 mg and the maximum allowable dose of ECH shall not exceed 45 mg.

For devices used in cardiopulmonary bypass procedures, the maximum allowable limits shall be 20 mg for EO and 9 mg for ECH.

For extracorporeal blood purification devices, the EO and ECH limits specified shall be 4.6 mg/device, but the allowable EO dose for a lifetime may be exceeded.

For drapes that are intended to contact only intact skin, the maximum allowable limits shall be the TCL of 10 μg/cm^2 for EO and 5 mg/cm^2 for ECH, or the drapes shall exhibit negligible irritation as specified in ISO 10993-10.

NOTE The rationale for specifying EO limits for certain devices that are at variance with the general requirements appears in Annex F.

A flowchart providing guidance for the application of this part of ISO 10993 to the determination of EO residuals in medical devices is presented in Annex C.

4.4 Determination of EO and ECH residuals

4.4.1 General

4.4.1.1 Procedure

The procedure for determining compliance with 4.3 consists of extracting the residue from samples, determining the amount of residue, determining the contact surface of the device, and analyzing and interpreting the data.

DANGER — Analysts and others who obtain samples should perform all work involving the use of the chemicals and solvents required for these methods in a fume cupboard whilst wearing appropriate protective clothing, and should review the Material Safety Data information for each chemical prior to such use. Healthcare workers using EO-sterilized medical devices shall take appropriate precautions to protect against exposure to residues, which may be required by local occupational health and safety regulations.

4.4.1.2 Ethylene oxide

This is a flammable gas that is irritating to body surfaces and highly reactive. It is mutagenic under many conditions, has fetotoxic and teratogenic properties, can adversely effect testicular function and can produce injury to many organ systems in the body. In cancer studies in animals, inhalation exposure produced several types of neoplastic changes including leukaemia, brain tumours and mammary tumours while ingestion or subcutaneous administration produced tumours only at the site of contact. One investigator has reported higher cancer and mortality rates in some subpopulations of exposed workers. However, the results of several studies in workers have shown even weaker associations. See References [177], [178] and [181]. In 1994 the International Agency for Research on Cancer (IARC) reclassified EO as a human carcinogen (class 1) based mainly on its mechanism of action. See Reference [75].

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4.4.1.3 Ethylene chlorohydrin

This is a flammable liquid that is irritating to body surfaces, acutely toxic and readily absorbed through the skin in toxic amounts. It has weak mutagenic potential, has some potential to produce fetotoxic and teratogenic changes and can produce injury to several organ systems in the body including lungs, kidneys, central nervous system and cardiovascular system. It was negative in cancer bioassays in animals.

4.4.2 Determination of residue

A valid method of extraction and measurement shall be used to determine the amount of EO and, where necessary, ECH delivered to the patient.

If ECH is not detected based on the results of analyses performed using the methods given in either K.4.2 or K.4.7, no further monitoring for ECH is required.

NOTE Many gas chromatography (GC) methods that use a capillary column instead of a packed column will produce EO, ECH and EG results during a single sample run.

The guiding principle in selecting appropriate extraction methods (4.4.6) for the quantitative determination of EO and, where necessary, ECH is the evaluation of the dose to the patient in order to show compliance with the requirements set out in 4.3.

Where residues are shown to be within the requirements for products tested by exhaustive extraction, there is no need to further challenge the device by simulated-use extraction, provided all applicable limits in 4.3 are met. When exhaustive extraction is used, particular attention shall be paid to the limits expressed for the first 24 h and for the first 30 days in 4.3.

Many analytical methods for these EO-sterilization residuals have been described and are reviewed in the Bibliography. However, the enormous diversity of materials and methods of construction of sterile medical devices may, in certain cases, still present problems in determining residual EO and ECH levels using the methods given in the Bibliography. Therefore, any method that has been shown to be analytically sound (i.e. demonstrated accuracy, precision, linearity, sensitivity, and selectivity) may be used, provided that it has been validated. Annex A contains general validation requirements for gas chromatographic methods.

4.4.3 Product sampling and sample “blank”

4.4.3.1 Product sampling

Samples to be used for residual analysis shall be selected in such a manner as to be truly representative of the product. When selecting samples, attention shall be given to the many factors described in Annex D. Since many of these factors influence not only the initial levels of residuals in device components but also the rate of residue dissipation, they shall also be considered when test samples are drawn from a processed load and sent to the laboratory for analysis. Removal of the product samples from the processed load soon after a sterilization cycle is completed and shipment to a laboratory far from the sterilization site or storage in the laboratory for later analysis can jeopardize correlations of residual levels on the samples with those on the rest of the load. Moreover, if samples cannot be drawn from the load and handled so that the effect on aeration conditions for the sample will be negligible, an experiment to establish the relationship between the sample aeration and load aeration at various seasons of the year shall be carried out.

Precautions shall be taken to minimize or control the effects of laboratory conditions on the rate of aeration for test samples that have been removed from a product load (see D.1.5). In addition, operator and analyst safety shall be ensured. Samples should remain with the product load until the day of

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analysis or until test samples are retrieved and immediately frozen. The time between removal of samples from a controlled aeration area and the beginning of extraction should be held to a minimum. Samples shall be sealed, shipped and stored frozen when analysis is delayed. Samples shall be shipped on dry ice on overnight delivery. Dry ice shall remain in the shipping container throughout the shipment and be present when the package is opened in the laboratory. Test samples may also be taken directly from the product load at the desired aeration interval and immediately placed into a headspace vial, which is sealed and then shipped to the laboratory for analysis. As an alternative, samples may be extracted and the extraction fluid shipped to the analytical laboratory for analysis. If the extraction fluid is water, then shipment shall be done such that the fluid is kept at ice-cold temperatures (< 10 °C) until arrival. Testing should be carried out to measure hydrolysis of EO to EG.

Samples to be analyzed shall be placed in a fume cupboard and removed from the packaging. Samples shall be prepared according to any applicable pre-use instructions in the product labeling. Extractions shall be started as soon as possible after the device has been removed from the packaging or pre-use preparations have been completed.

4.4.3.2 Sample “blank”

To ensure that no other sample matrix components with the same retention time as any of the residues being determined are present, a “blank” sample shall be evaluated for the possible presence of such interferences by the extraction of a non-sterilized sample using the identical procedure being applied to the EO-sterilized samples. In the event of materials being extracted from such a “blank” with conflicting or overlapping retention times in the GC analysis, chromatographic conditions shall be modified to separate the interfering peak from the analyte peak, or an alternative analytical procedure shall be used.

4.4.4 Sample/fluid ratios

The volume of fluid used to extract residues from devices, or representative sections of them, shall be sufficient to maximize extraction efficiency while maintaining detection sensitivity. The nature and size of the device sample therefore determines what constitutes the optimal fluid volume for extraction. Therefore, to maximize analytical sensitivity, a minimum amount of extraction fluid should be used depending on the extraction method required and size of the sample. Devices composed of highly absorbent materials or those from which residues are extracted by filling may require sample/extraction fluid ratios reflecting increased fluid volume. In any case, sample/extraction fluid ratios shall not undermine detection sensitivity.

4.4.5 Extraction time and conditions

The aim of product extraction is to indicate the worst-case amount that could be delivered to the patient in actual use of the device: on a daily basis for limited exposure items; on a daily and up to monthly basis for prolonged exposure items; on a daily, monthly, and up to a lifetime basis for permanent contact items. As indicated in Annexes E and F, exhaustive extraction as described below can be a useful alternative for permanent contact devices, provided that shorter-term constraints are ensured.

4.4.6 Product extraction

4.4.6.1 Overview

There are two basic extraction methods used for the determination of EO-sterilization residuals in medical devices: simulated-use extraction, which is the reference method; exhaustive extraction, which represents an acceptable alternative in certain situations. The choice of extraction method shall be based on the intended use of the device. Examples of suggested extraction methods are shown in Annex K.

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The extraction method chosen shall represent the intended use of the product with the greatest challenge to the patient and not solely expeditious analysis or to minimize the apparent concentration of residuals.

Extraction temperatures and times shall be determined based on the nature of the patient's exposure and the patient's duration of contact with the device as described in 4.2 and 4.3. See ISO 10993-12 for extraction temperatures.

The analyst is cautioned that for certain devices, simulated-use extraction may result in relatively large elution volumes. Should this occur it might significantly increase the limit of detection for the residual material to the point where a determination of compliance with this part of ISO 10993 is compromised.

Small devices shall be extracted in a suitable container. When a device is too large to be extracted in its entirety, it may be necessary to extract several representative portions of the device components in order to ensure confidence in the data derived.

These representative portions may be selected in one of two ways. If several varied materials are used, the proportion of each component, as compared with the total sample mass, should parallel the ratio of that component to the total mass of the device being tested. An alternative method would be to select one of the components for testing, subsequent to an evaluation demonstrating that it represented the worst case with regard to residual content. The method chosen shall be validated.

4.4.6.2 Simulated-use extraction (reference method)

Simulated-use aqueous extraction is the reference method in that it is the only method that produces results directly comparable to the limits specified in 4.3. These limits are expressed in terms of delivered dose of EO and ECH to patients.

Since it is necessary to evaluate the residue levels available to the patient, or other end user, from devices in routine use, extraction methods that simulate use are required. Simulated-use extraction shall be carried out under conditions that provide the greatest challenge to the intended use.

For example, many blood-contacting and parenteral devices can be extracted with water by filling or flushing the blood or fluid path (whichever is appropriate). Samples shall be extracted for a time equivalent to or exceeding the maximum time for single use, and at temperatures that provide the greatest realistic simulated challenge.

To determine the dose of EO and, where necessary, ECH delivered to the patient or user over the course of normal product use, simulated-use aqueous extraction procedures are used.

NOTE The amounts of EO (or ECH) extracted by simulating normal product use are not necessarily similar to the total product residual content.

Water (see [92]) is commonly used for the recovery of residual EO, ECH (and EG if there is any concern about hydrolysis of EO) in simulated-use extractions. Water is used for elution of EO residuals from the sample rather than to dissolve the sample material itself. If the intent is to simulate product use by filling the device, the device should be filled so as to eliminate any air pockets: extract devices that are wholly or partially in contact with the body during use at 37 °C (body temperature); extract devices having no immediate body contact during use (e.g., hypodermic syringes) at 25 °C (room temperature). See also ISO 10993-12. If the assay is not performed immediately, the extract should be decanted from the sample and sealed in a poly-(tetrafluoroethylene) (PTFE)-lined, septum-capped vial. The headspace in the vial of any standard solution or extract shall be less than 10 % of the total volume. The extract can be stored in the refrigerator for several days (see Annex F) but, where water extraction is used, caution shall be taken, as EO may convert to EG or ECH (or both) during the extraction period as well as during storage of the

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extract (see [35]). The analyst shall evaluate the possibility of this conversion to EG and/or ECH at the analysis site when extracting the sample with water.

4.4.6.3 Exhaustive extraction (acceptable alternative method)

4.4.6.3.1 Overview

Exhaustive extraction represents an acceptable alternative and can provide useful information. It produces results that would tend to represent a dose greater than or equal to one the patient may receive. Because such an extraction precludes measurement of dose as a function of time, it does not ensure that the mass of residue is not delivered to the patient on the first day or during the first month of exposure. However, when all applicable limits in 4.3 are met and residues are shown to be within the requirements for products tested by exhaustive extraction, there is no need to further challenge the device by simulated-use extraction. When exhaustive extraction is used, particular attention shall be paid to the limits expressed for the first 24 h and for the first 30 d in 4.3.

Exhaustive extraction methods are intended to recover the entire residual content of a device. For EO determination, extraction procedures used include thermal extraction followed by headspace gas analysis, solvent extraction procedures, with either 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 GC detector such as an electron capture detector.

4.4.6.3.2 Residual ethylene oxide

A variety of extraction fluids has been used for the exhaustive recovery of residual EO. Thermal desorption followed by headspace gas analysis, as described in K.4.3, is an example of a procedure that does not use an extraction fluid. When conducted as described, headspace methods are considered exhaustive since they are designed to recover all of the residual EO from the sample. However, headspace methods may not be feasible or preferred for intact testing of large or complex devices. The analyst shall exercise caution in the execution of headspace methods when evaluating residue levels in polymer materials such as poly-(methylmethacrylate) to ensure total recovery of EO.

For solvent extraction procedures, selection of a suitable extraction fluid depends on the material composition of the device and its components. To facilitate complete recovery of EO from the sample, fluids that dissolve the sample material are generally preferred in an exhaustive extraction, provided that interfering substances are not also put into solution by the procedure. Solvent extraction procedures that are combined with headspace gas analysis are described in K.4.4 and such procedures may be able to separate EO from co-extracted interfering chemicals from the sample matrix. Several extraction fluids have been evaluated through interlaboratory comparison testing, see References [112], [113] and [114].

Prudent analytical procedure dictates that, in the initial analysis of a given material, more than one extraction procedure shall be used to validate quantitative recovery whenever an exhaustive extraction is to be performed. For devices containing a relatively small amount of residual EO, the commonly used methods may not be capable of extracting these small amounts, even after relatively long extraction times.

4.4.6.3.3 Residual ethylene chlorohydrin

Water is typically used to extract residual ECH from medical devices using methods similar to those described for determining residual EO.

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4.4.7 Data analysis and interpretation

4.4.7.1 Calculation of amount of residue extracted

The concentration of residue observed in the extracts, C_e, is converted to the amount delivered to a patient, in milligrams, M_d, as follows.

Residue extracted by simulated use may be calculated as follows:

$$M_d = \sum_{1}^{n} (C_{en} \times V_{en}) \quad (1)$$

Residue extracted by exhaustive extraction may be calculated as follows:

$$M_d = \sum_{1}^{n} (C_{en} \times V_{en}) \times \frac{m_d}{m_s} \quad (2)$$

where

M_d is the extract residue, in milligrams;

n is the number of extractions;

C_e is the amount of EO in milligrams per milliliter of extract as derived from the standard curve;

V_e is the extract volume, in milliliters;

m_d is the entire device mass, in grams;

m_s is the mass of sample, in grams.

NOTE This applies only if a portion of the device is extracted.

4.4.7.2 Calculation of average delivered dose, M_{add}, for comparison to allowable limits in 4.3

For permanent contact devices, the average delivered dose, M_{add}, in milligrams per day, is as follows:

$$M_{add} = \frac{M_d}{25{,}000} \quad (3)$$

where

25,000 is the number of days per lifetime;

M_d is the extract residue, in milligrams.

Permanent contact devices shall also meet the prolonged exposure and limited exposure limits as calculated below.

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For prolonged exposure devices

$$M_{\text{add}} = \frac{M_{\text{d}}}{30} \tag{4}$$

where

30 is the number of days per month;

M_{d} is the extract residue, in milligrams.

Prolonged exposure devices shall also meet the limited exposure limits as calculated below.

For limited exposure devices:

$$M_{\text{add}} = M_{\text{d}} \tag{5}$$

5 Product release

5.1 General

A product is in compliance with this part of ISO 10993 when it meets the requirements for EO and, if applicable, ECH. If sufficient experimental data on residue diffusion kinetics are available, it may be possible to group devices for quality assurance testing based on similarity of materials, manufacturing processes and use (see Annex D).

For release of batches of EO-sterilized product, one of the two methods in 5.2 and 5.3 respectively shall be used.

5.2 Release of products without dissipation curve data

When dissipation curve data are not available on a product, the product may be released if it is in compliance with this part of ISO 10993 and the data were obtained from testing carried out according to appropriate procedures delineated in Annex K and meet the requirements for EO and, if applicable, ECH set out in 4.3.

5.3 Procedure for product release using residue dissipation curves

Dissipation curves are used to estimate the post-sterilization time required for products, or families of similar products, to reach residue limits, principally for EO, in compliance with 4.3. Products shall be released to the marketplace according to predetermined post-sterilization times and conditions defined by experimental dissipation curves so that the target EO residue levels for the device, as set out in 4.3, are ensured. The product aeration concerns documented in Annex D are to be considered by pooling data from sterilization loads taken from aeration or quarantine storage at different times of the year if aeration temperatures differ. Re-sterilization of product and the presence of other EO-sterilized medical devices in adjacent areas shall also be considered when obtaining experimental data to generate such dissipation curves.

Release of products manufactured and sterilized under controlled conditions, as described in ISO 11135-1, may be carried out if data are pooled from a minimum of three sterilization lots run at different times. Dissipation of EO from most materials and devices follows first-order kinetics, i.e. (ln[EO])α (time after sterilization). A plot of the natural logarithm of the experimentally determined EO

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concentration against time after sterilization is linear. Release shall then be based on the time after sterilization when the mean regression line intersects the maximum allowable residue. This approach may be used for products which are not sterilized in sufficient quantity (numbers of sterilization runs) for the procedure described below to be applied, or may be used while the dissipation curve data described is being collected. Various alternative methods can be used; for example, if dissipation curves are established whereby samples are tested after the residual limits have been met, interpolation of the dissipation curve can be used to establish the release of the product after sterilization.

Regression analysis of pooled data from sufficient time points for at least three lots of the same product to establish the nature of the dissipation curve will enable product to be released at the calculated upper 95 % prediction limit, L_p, for the allowed residue limit for the product. Time-concentration curves for devices made from combinations of dissimilar materials may not fit this simple pattern over the entire range and may need to be handled differently.

Formulae for calculating the prediction limit, L_p:

$$x_o = \frac{y_o - a}{b} \tag{6}$$

$$L_p = x_o + t_\alpha \times \sqrt{\frac{(S_\alpha)^2}{b^2} \times \left[1 + \frac{1}{n} + \frac{(y_o - y_\mu)^2}{b^2 \times \sum (x_i - x_\mu)^2}\right]} \tag{7}$$

where

x_o is the calculated average value of the release time corresponding to the EO limit;

y_o is the logarithmic value of the EO limit;

a is the intercept of the linear regression line obtained from the plot ln[EO]α time;

b is the slope of the regression line;

L_p is the prediction limit for a single individual of the product;

t_α is the student t value at significance α with $n - 2$ degrees of freedom;

$(S_\alpha)^2$ is the residual variance of the regression line;

y_μ is the average of logarithmic EO values;

n is the number of values;

x_i is the individual time after sterilization at which measurements are made;

x_μ is the average of the times after sterilization;

$\Sigma (x_i - x_\mu)^2$ is the sum of squares for x (time).

All data obtained for release of medical devices in compliance with this part of ISO 10993 shall be obtained from experiments and data analyses carried out following valid standard operating procedures.

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When sterilization process parameters listed in Annex D are changed, an audit shall be made of the product residue. When this audit shows an increase in the level of residual EO, new residue dissipation curves shall be obtained to ensure product acceptability. When this audit shows a decrease in the level of residual EO, consideration should be given to the generation of new dissipation curves.

NOTE Verification of dissipation curves is typically done during routine sterilization revalidation in accordance with ISO 11135-1.

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Annex A
(normative)

Evaluation of gas chromatograms

A.1 General

This annex discusses the minimum requirements for the analytical procedures employed for EO and ECH measurements. These requirements apply for both packed and capillary GC column systems.

A.2 Background

These requirements are discussed in reference books on GC and should be reviewed by analysts before their use of any of the procedures. Also recommended is a review of the articles concerning detection limits, see References [15], [35] and [74].

A.3 Symbols

The symbols in Table A.1 are used in Figures A.1 and A.2.

Table A.1 — Symbols

Symbol	Description
f	distance from peak maximum to leading edge of peak
k'	capacity factor
R	resolution
T	tailing factor
t	retention time of the relevant residue peak (EO or ECH)
t_a	retention time for a non-retained component, such as air, which is not retarded in its passage through the column
t_1, t_2	retention time of chromatographic peaks 1 and 2, where t_1 is EO (or ECH) and t_2 is an immediately adjacent peak
W_1, W_2	respective widths extrapolated to the baseline for peaks 1 and 2 in the same units as the retention time
$W_{0.05}$	peak width at 5 % of height

A.4 Minimum requirements

A.4.1 For these procedures, it is recommended that the following minimum requirements be met for these parameters (see Figures A.1 and A.2).

Resolution, R, calculated as follows

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$$R = 2\frac{(t_2 - t_1)}{(W_2 + W_1)} \quad \text{(A.1)}$$

shall be ⩾ 2.0 for peak area or peak height quantitation.

Alternatively, the following equation may be useful to calculate the capacity factor, k', which shall be greater than 1,5 for well-resolved peaks:

$$k' = \frac{t}{t_a} - 1 \quad \text{(A.2)}$$

Tailing, T, given by the following equation, shall be less than or equal to 1.8 for the EO and ECH peaks:

$$T = \frac{W_{0.05}}{2f} \quad \text{(A.3)}$$

A.4.2 Relative deviation of the standard curve (RSD) should not exceed 5 % for EO and ECH for the range of standards used, see References [13] and [14].

$$\text{RSD} = \left(\frac{\sigma}{\lambda}\right) \times 100 \quad \text{(A.4)}$$

$$\sigma^2 = \frac{\left(\frac{\Sigma_y^2 - \Sigma^2}{n}\right) - S \times \left(\Sigma_{xy} - \frac{\Sigma \times \Sigma_y}{n}\right)}{n - 2} \quad \text{(A.5)}$$

$$\lambda = \frac{\Sigma_y}{n} \quad \text{(A.6)}$$

where

n is the total number of samples evaluated;

y is the chromatographic peak area or peak height;

λ is the mean;

x is the concentration of the standard;

σ is the standard deviation;

σ^2 is the variance;

S is the slope of the least squares regression line for the standard curve.

These criteria are calculated for triplicate analyses of at least three standards prepared to cover the expected linear dynamic range of each of the standard curves used in the analysis of EO and ECH.

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A.5 Chromatographic baseline

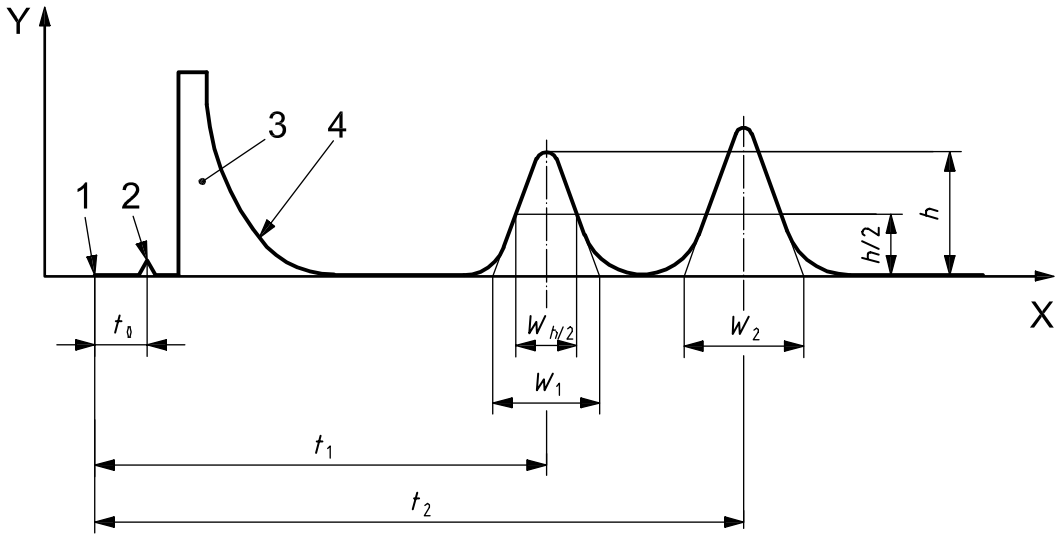
In addition, it is recommended that the chromatographic baseline return to within 5 % of the initial baseline between chromatographic runs.

A.6 Resources

The following sources of information are suggested when corrective changes in these analytical procedures are indicated:

— the manufacturer's manual for the gas chromatograph used;

— the various textbooks on GC.



Key

X time
Y detection response
1 injection
2 air peak
3 solvent peak
4 solvent tail

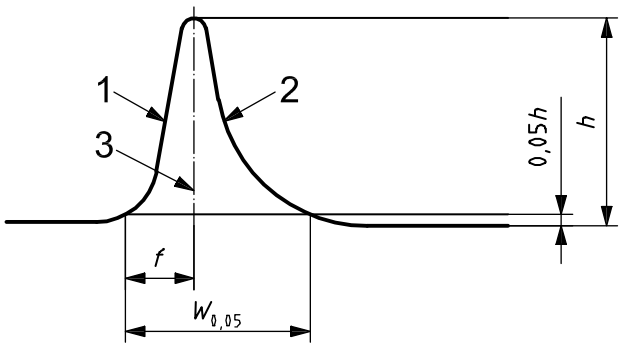
Figure A.1 — Chromatographic separation of two substances

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Key

1 peak front
2 peak tail
3 peak maximum

Figure A.2 — Asymmetrical chromatographic peak

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Annex B
(informative)

Gas chromatographic determination for EO and ECH

B.1 Chromatographic procedures

B.1.1 Preparation of standards

Analysts should establish the stability of the standards they use to calibrate the chromatographic procedure(s) used and ensure that standards are not used past their established expiry point.

B.1.2 General

The following paragraphs outline the procedure for preparation of GC standards. Two alternatives are commonly available:

a) use of prepared standards from commercial sources;

b) preparation of standards either volumetrically, by diluting known volumes of EO gas or gravimetrically, by diluting a known mass of liquid EO. In all cases, prepare a standard curve of peak height or peak area response versus EO concentration.

NOTE Peak area response compiled by the software of computer-controlled GC instrumentation is more precise than measuring peak height in determining EO concentrations.

Examples of procedures used for the preparation of EO and ECH standards are provided in Annex J.

B.2 Criteria for validating gas chromatographic methods

B.2.1 General overview

Many methods are suitable for quantitatively analyzing extracts for ethylene oxide. A number of procedures for exhaustive extraction followed by GC for the determination of EO have been described. There are probably just as many unpublished methods for determining residual ethylene oxide. Because of the diversity in medical devices, published methods may not be suitable for all devices. Therefore, any method that has been shown to be analytically sound and meets the performance criteria described in this part of ISO 10993 can be used.

Analytically sound means that the method demonstrates sufficient accuracy, precision, selectivity, linearity, ruggedness and sensitivity to determine the specified level of EO in a device which is intended to be analyzed in relation to the residue limits shown in 4.3 and is applicable to the device which is intended to be analyzed.

A number of analytical methods for assessing levels of EO and ECH residues have been reviewed from the literature (see Bibliography). For a more detailed discussion of each method, the original literature should be consulted. The following are recommended criteria for validating a method.

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B.2.2 Accuracy

Accuracy is a measure of the closeness of test results obtained by the test method, to the true value. Accuracy is expressed in terms of recovery, the measured value expressed as a percentage of the accepted or true value. It requires the comparison of the test method measurement with a known value. The known value can be prepared from an analyte of known purity or from spiked samples.

Spiked samples as the means of determining accuracy can be reported as percent recovery of a known added amount of analyte in the sample. However, for EO, this method for determining accuracy is extremely difficult to carry out because of the volatility of this compound. As an alternative, the use of commercially available certified standards is recommended. Thus, the measure of accuracy becomes the mean measured results divided by the accepted true value together with the confidence interval. In either case, the percent recovery can be calculated as

$$R = \frac{R_0 \times 100}{a \text{ or } t_V} \tag{B.1}$$

where

R is the recovery in percent;

R_0 is the result obtained;

a or t_V is the accepted or true value.

Accuracy should be assessed using a minimum of nine determinations over a minimum of three concentration levels covering the specified range (i.e. three replicates each at three different concentrations).

B.2.3 Precision

B.2.3.1 Overview

Precision is the measure of how close the data values are to each other for a number of measurements under the same analytical conditions. Precision contains three components: repeatability, intermediate precision and reproducibility.

B.2.3.2 Repeatability

Repeatability can be assessed using a minimum of nine determinations covering the specified range of standards used (i.e., three replicates each at three different concentrations). Data generated from method accuracy as in B.2.2 above can be used for repeatability assessment.

Repeatability can be calculated as the relative standard deviation (coefficient of variation) of the peak area as specified in Equation (A.4).

The % RSD for EO and ECH should not exceed 5 % for the range of the standards used. The % RSD is calculated as described in A.4.2.

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B.2.3.3 Intermediate precision

Intermediate precision can be assessed by establishing the effects of random events on the precision of the analytical procedure. Examples of random effects include days, analysts, equipment, etc. It is not necessary to study these events individually. The use of an experimental design (matrix) is encouraged.

As a minimum, data generated as described in B.2.2, accuracy, for two separate events is recommended to indicate the intermediate precision of the test method. The standard deviation, relative standard deviation (coefficient of variation), and confidence interval should be reported.

B.2.3.4 Ruggedness/reproducibility

The ruggedness of an analytical method is the degree of reproducibility of test results obtained by analysis of the same samples under a variety of conditions, such as different laboratories, different analysts, different instruments, different lots of reagent, different elapsed assay times, different assay temperatures, different days, etc. Ruggedness is normally expressed as the lack of influence on the test results of operational and environmental variables of the analytical method. Ruggedness is a measure of reproducibility of the test results under the variation in conditions normally expected from laboratory to laboratory and from analyst to analyst.

Since the method of validation would be performed in an individual laboratory to introduce a new column or new method, this part of the validation can be done by a combination of different analysts, different days, different instruments, etc. Reproducibility is not normally expected if intermediate precision is accomplished. The interlaboratory studies are not important in this part.

B.2.4 Linearity

Linearity is a measure of the correlation between the method response and the concentration of the analyte. Linearity should be established across the range of standards used. Regression analysis of the standard concentration versus peak area or peak height should be performed using a minimum of five concentrations.

The analyst should determine the linearity of the calibration data, along with the reproducibility of the slope and intercept. The minimum correlation coefficient for the standard curve should be 0.95.

B.2.5 Method detection limit (MDL)

B.2.5.1 Overview

The method detection limit is the smallest amount that can be detected with a reasonable confidence. The detection limit can be determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.

There are many ways to determine the method detection limit. Approaches other than those listed below may be acceptable.

B.2.5.2 MDL based on signal-to-noise

Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and establishing the minimum concentration at which the analyte can be reliably detected. A signal-to-noise ratio of 3:1 is generally accepted.

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B.2.5.3 MDL based on the standard deviation of the response

To determine the method detection limit, make a known standard of the analyte of interest near the estimated MDL and determine the standard deviation for seven injections of the standard.

$$\text{MDL} = s \times t \tag{B.2}$$

where

s is the standard deviation of injections;

t is the student t value at $n - 1$ degrees of freedom at the 99 % confidence level.

B.2.6 Quantitation limit (QL)

B.2.6.1 Overview

The quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.

There are many ways to determine quantitation limit. Approaches other than those listed below may be acceptable.

B.2.6.2 QL based on signal-to-noise

Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and establishing the minimum concentration at which the analyte can be reliably quantified. A signal-to-noise ratio of 10:1 is generally accepted.

B.2.6.3 QL based on the standard deviation of the response

The quantitation limit can be expressed as

$$\text{QL} = 5 \times \text{MDL} \tag{B.3}$$

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