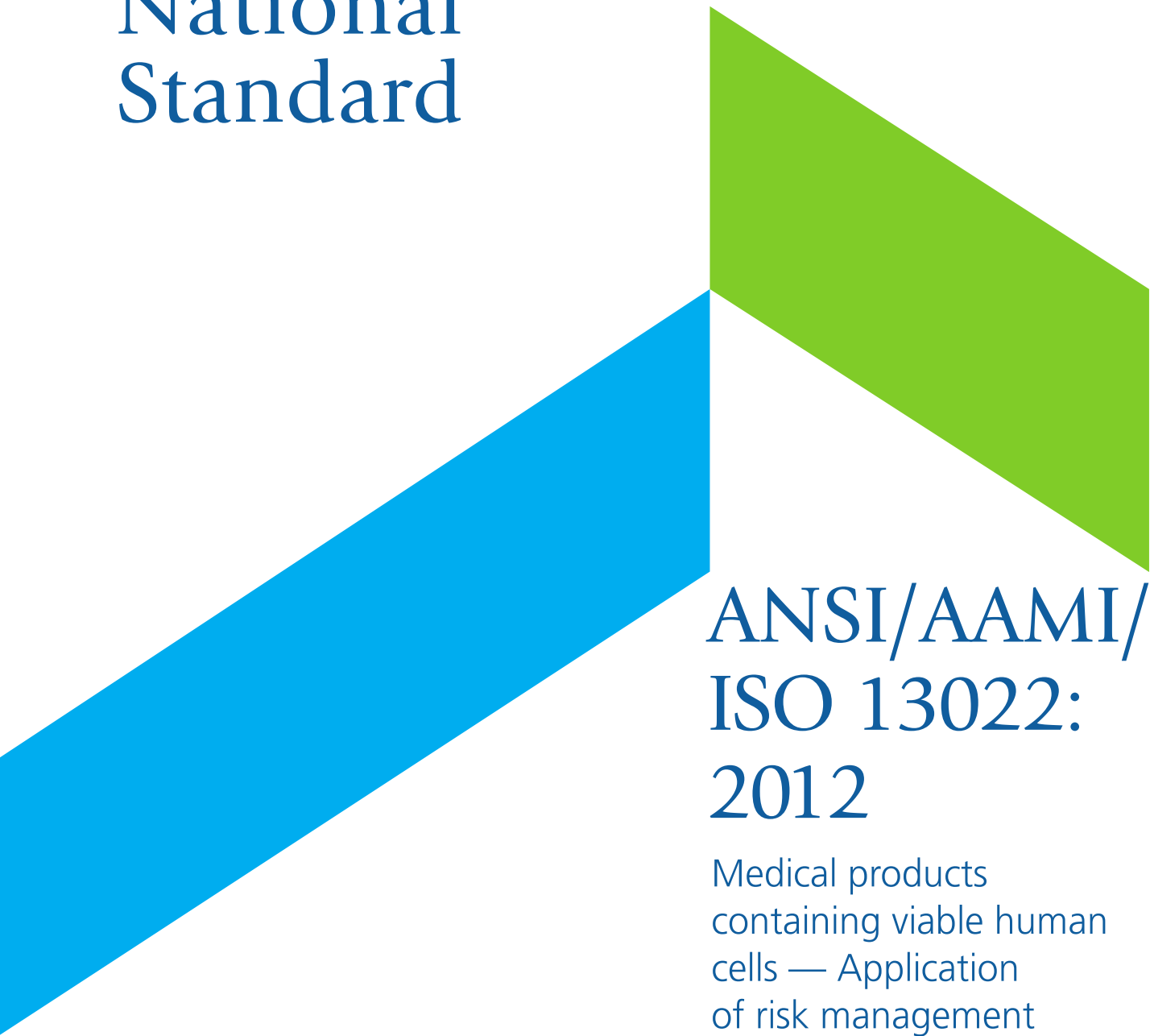


American National Standard



ANSI/AAMI/ ISO 13022: 2012

Medical products
containing viable human
cells — Application
of risk management
and requirements for
processing practices

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:

All AAMI standards and recommended practices are *voluntary* (unless, of course, they are adopted by government regulatory or procurement authorities). The application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document.

Each AAMI standard or recommended practice reflects the collective expertise of a committee of health care professionals and industrial representatives, whose work has been reviewed nationally (and sometimes internationally). As such, the consensus recommendations embodied in a standard or recommended practice are intended to respond to clinical needs and, ultimately, to help ensure patient safety. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important *reference* in responsible decision-making, but it should never *replace* responsible decision-making.

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.

INTERPRETATIONS OF AAMI STANDARDS AND RECOMMENDED PRACTICES

Requests for interpretations of AAMI standards and recommended practices must be made in writing, to the AAMI Vice President, Standards Policy and Programs. An official interpretation must be approved by letter ballot of the originating committee and subsequently reviewed and approved by the AAMI Standards Board. The interpretation will become official and representation of the Association only upon exhaustion of any appeals and upon publication of notice of interpretation in the "Standards Monitor" section of the *AAMI News*. The Association for the Advancement of Medical Instrumentation disclaims responsibility for any characterization or explanation of a standard or recommended practice which has not been developed and communicated in accordance with this procedure and which is not published, by appropriate notice, as an *official interpretation* in the *AAMI News*.

Medical products containing viable human cells— Application of risk management and requirements for processing practices

Approved 3 May 2012 by
Association for the Advancement of Medical Instrumentation

Approved 18 June 2012 by
American National Standards Institute, Inc.

Abstract: Specifies a procedure to identify the hazards and hazardous situations and to manage the risk associated with viable cellular component(s) of products regulated as medicinal products, biologics, medical devices and active implantable medical devices or combinations thereof. Covers viable human materials of autologous as well as allogeneic human origin.

Keywords: risk management, biological evaluation, tissue engineering, cellular, biologics

AAMI Standard

This Association for the Advancement of Medical Instrumentation (AAMI) standard implies a consensus of those substantially concerned with its scope and provisions. The existence of an AAMI standard does not in any respect preclude anyone, whether they have approved the standard or not, from manufacturing, marketing, purchasing, or using products, processes, or procedures not conforming to the standard. AAMI standards are subject to periodic review, and users are cautioned to obtain the latest editions.

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All AAMI standards, recommended practices, technical information reports, and other types of technical documents developed by AAMI are *voluntary*, and their application is solely within the discretion and professional judgment of the user of the document. Occasionally, voluntary technical documents are adopted by government regulatory agencies or procurement authorities, in which case the adopting agency is responsible for enforcement of its rules and regulations.

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Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. For each International Standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the International Standard. NOTE: Documents are sorted by international designation. The code in the US column, “(R)20xx” indicates the year the document was officially reaffirmed by AAMI. E.g., ANSI/AAMI/ISO 10993-4:2002/(R)2009 indicates that 10993-4, originally approved and published in 2002, was reaffirmed without change in 2009.

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 Technical Corrigendum 1 and 2	ANSI/AAMI ES60601-1:2005/(R)2012 and ANSI/AAMI ES60601-1:2005/A2:2010/(R)2012 ANSI/AAMI ES60601-1:2005/C1:2009/(R)2012 (amdt)	Major technical variations C1 Identical to Corrigendum 1 & 2
IEC 60601-1-11:2010	ANSI/AAMI HA60601-1-11:2011	Major technical variations
IEC 60601-1-2:2007	ANSI/AAMI/IEC 60601-1-2:2007/(R)2012	Identical
IEC 60601-2-2:2009	ANSI/AAMI/IEC 60601-2-2:2009	Identical
IEC 60601-2-4:2010	ANSI/AAMI/IEC 60601-2-4:2010	Identical
IEC 60601-2-16:2008	ANSI/AAMI/IEC 60601-2-16:2008	Identical
IEC 60601-2-19:2009	ANSI/AAMI/IEC 60601-2-19:2009	Identical
IEC 60601-2-20:2009	ANSI/AAMI/IEC 60601-2-20:2009	Identical
IEC 60601-2-21:2009	ANSI/AAMI/IEC 60601-2-21:2009	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:2004/(R)2009	Major technical variations
IEC 60601-2-25:2011	ANSI/AAMI/IEC 60601-2-25:2011	Identical
IEC 60601-2-27:2011	ANSI/AAMI/IEC 60601-2-27:2011	Identical
IEC 60601-2-47:2001	ANSI/AAMI EC38:2007	Major technical variations
IEC 60601-2-50:2009	ANSI/AAMI/IEC 60601-2-50:2009	Identical
IEC 80001-1:2010	ANSI/AAMI/IEC 80001-1:2010	Identical
IEC 80601-2-30:2009 and Technical Corrigendum 1	ANSI/AAMI/IEC 80601-2-30:2009 and ANSI/AAMI/IEC 80601-2-30:2009/C1:2009 (amdt) – consolidated text	Identical (with inclusion) C1 Identical to Corrigendum 1
IEC 80601-2-58:2008	ANSI/AAMI/IEC 80601-2-58:2008	Identical
IEC/TR 60878:2009	ANSI/AAMI/IEC TIR60878:2003	Identical
IEC/TR 61289:2011	ANSI/AAMI/IEC TIR61289:2011	Identical
IEC/TR 62296:2009	ANSI/AAMI/IEC TIR62296:2009	Identical
IEC 62304:2006	ANSI/AAMI/IEC 62304:2006	Identical
IEC/TR 62348:2006	ANSI/AAMI/IEC TIR62348:2006	Identical
IEC/TR 62354:2009	ANSI/AAMI/IEC TIR62354:2009	Identical
IEC 62366:2007	ANSI/AAMI/IEC 62366:2007	Identical
IEC/TR 80002-1:2009	ANSI/IEC/TR 80002-1:2009	Identical
ISO 5840:2005	ANSI/AAMI/ISO 5840:2005/(R)2010	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001/(R)2010	Identical
ISO 7199:2009 and Amendment 1:2012	ANSI/AAMI/ISO 7199:2009 and Amendment 1:2012	Identical
ISO 8637:2010	ANSI/AAMI/ISO 8637:2010	Identical
ISO 8638:2010	ANSI/AAMI/ISO 8638:2010	Identical
ISO 10993-1:2009	ANSI/AAMI/ISO 10993-1:2009	Identical
ISO 10993-2:2006	ANSI/AAMI/ISO 10993-2:2006/(R)2010	Identical
ISO 10993-3:2003	ANSI/AAMI/ISO 10993-3:2003/(R)2009	Identical
ISO 10993-4:2002 and Amendment 1:2006	ANSI/AAMI/ISO 10993-4:2002/(R)2009 and Amendment 1:2006/(R)2009	Identical
ISO 10993-5:2009	ANSI/AAMI/ISO 10993-5:2009	Identical
ISO 10993-6:2007	ANSI/AAMI/ISO 10993-6:2007/(R)2010	Identical
ISO 10993-7:2008	ANSI/AAMI/ISO 10993-7:2008/(R)2012	Identical
ISO 10993-9:2009	ANSI/AAMI/ISO 10993-9:2009	Identical
ISO 10993-10:2010	ANSI/AAMI/ISO 10993-10:2010	Identical
ISO 10993-11:2006	ANSI/AAMI/ISO 10993-11:2006/(R)2010	Identical
ISO 10993-12:2007	ANSI/AAMI/ISO 10993-12:2007	Identical
ISO 10993-13:2010	ANSI/AAMI/ISO 10993-13:2010	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 10993-16:2010	ANSI/AAMI/ISO 10993-16:2010	Identical
ISO 10993-17:2002	ANSI/AAMI/ISO 10993-17:2002/(R)2008	Identical
ISO 10993-18:2005	ANSI/AAMI BE83:2006/(R)2011	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

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/(R)2010	Identical
ISO 11137-2:2012	ANSI/AAMI/ISO 11137-2:2012	Identical
ISO 11137-3:2006	ANSI/AAMI/ISO 11137-3:2006/(R)2010	Identical
ISO 11138-1:2006	ANSI/AAMI/ISO 11138-1:2006/(R)2010	Identical
ISO 11138-2:2006	ANSI/AAMI/ISO 11138-2:2006/(R)2010	Identical
ISO 11138-3:2006	ANSI/AAMI/ISO 11138-3:2006/(R)2010	Identical
ISO 11138-4:2006	ANSI/AAMI/ISO 11138-4:2006/(R)2010	Identical
ISO 11138-5:2006	ANSI/AAMI/ISO 11138-5:2006/(R)2010	Identical
ISO/TS 11139:2006	ANSI/AAMI/ISO 11139:2006	Identical
ISO 11140-1:2005	ANSI/AAMI/ISO 11140-1:2005/(R)2010	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/(R)2010	Identical
ISO 11607-2:2006	ANSI/AAMI/ISO 11607-2:2006/(R)2010	Identical
ISO 11663:2009	ANSI/AAMI/ISO 11633:2009	Identical
ISO 11737-1:2006	ANSI/AAMI/ISO 11737-1:2006	Identical
ISO 11737-2:2009	ANSI/AAMI/ISO 11737-2:2009	Identical
ISO/TS 12417:2011	ANSI/AAMI/ISO TIR12417:2011	Identical
ISO 13022:2012	ANSI/AAMI/ISO 13022:2012	Identical
ISO 13408-1:2008	ANSI/AAMI/ISO 13408-1:2008/(R)2011	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/(R)2009	Identical
ISO 13958:2009	ANSI/AAMI/ISO 13958:2009	Identical
ISO 13959:2009	ANSI/AAMI/ISO 13959:2009	Identical
ISO 14155:2011	ANSI/AAMI/ISO 14155:2011	Identical
ISO 14160:2011	ANSI/AAMI/ISO 14160:2011	Identical
ISO 14161:2009	ANSI/AAMI/ISO 14161:2009	Identical
ISO 14708-3:2008	ANSI/AAMI/ISO 14708-3:2008	Identical
ISO 14708-4:2008	ANSI/AAMI/ISO 14708-4:2008	Identical
ISO 14708-5:2010	ANSI/AAMI/ISO 14708-5:2010	Identical
ISO 14937:2009	ANSI/AAMI/ISO 14937:2009	Identical
ISO/TR 14969:2004	ANSI/AAMI/ISO TIR14969:2004	Identical
ISO 14971:2007	ANSI/AAMI/ISO 14971:2007/(R)2010	Identical
ISO 15223-1:2007 and A1:2008	ANSI/AAMI/ISO 15223-1:2007/(R)2012 and A1:2008/(R)2012	Identical
ISO 15223-2:2010	ANSI/AAMI/ISO 15223-2:2010	Identical
ISO 15225:2010	ANSI/AAMI/ISO 15225:2010	Identical
ISO 15674:2009	ANSI/AAMI/ISO 15674:2009	Identical
ISO 15675:2009	ANSI/AAMI/ISO 15675:2009	Identical
ISO 15882:2008	ANSI/AAMI/ISO 15882:2008	Identical
ISO 15883-1:2006	ANSI/AAMI ST15883-1:2009	Major technical variations
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 (with inclusions)
ISO/TS 17665-2:2009	ANSI/AAMI/ISO TIR17665-2:2009	Identical
ISO 18472:2006	ANSI/AAMI/ISO 18472:2006/(R)2010	Identical
ISO/TS 19218-1:2011	ANSI/AAMI/ISO TIR19218:2011	Identical
ISO 20857:2010	ANSI/AAMI/ISO 20857:2010	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/TR 22442-4:2010	ANSI/AAMI/ISO TIR22442-4:2010	Identical
ISO 23500:2011	ANSI/AAMI/ISO 23500:2011	Identical
ISO/TS 23810:2012	ANSI/AAMI/ISO TIR23810:2012	Identical
ISO 25539-1:2003 and A1:2005	ANSI/AAMI/ISO 25539-1:2003/(R)2009 and A1:2005/(R)2009	Identical
ISO 25539-2:2008	ANSI/AAMI/ISO 25539-2:2008	Identical
ISO 25539-3:2011	ANSI/AAMI/ISO 25539-3:2011	Identical
ISO 26722:2009	ANSI/AAMI/ISO 26722:2009	Identical
ISO 27185:2012	ANSI/AAMI/ISO 27185:2012	Identical
ISO 27186:2010	ANSI/AAMI/ISO 27186:2010	Identical
ISO 80369-1:2010	ANSI/AAMI/ISO 80369-1:2010	Identical
ISO 81060-1:2007	ANSI/AAMI/ISO 81060-1:2007	Identical
ISO 81060-2:2009	ANSI/AAMI/ISO 81060-2:2009	Identical

Committee representation

Association for the Advancement of Medical Instrumentation

Tissue Product Safety Committee

The adoption of ISO 13022:2012 as an American National Standard was initiated by the AAMI Tissue Product Safety Committee, which also functions as a U.S. Technical Advisory Group to the relevant work in the International Organization for Standardization (ISO) and the AAMI TSE Elimination Working Group.

At the time this document was published, the **AAMI Tissue Product Safety Committee** had the following members:

Cochairs: Richard W. Hutchinson, DVM PhD DABT, Johnson & Johnson
Scott G. McNamee, PhD, FDA/CDRH

Members: Steven B. Binion, PhD MBA, Becton Dickinson & Company
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Kimbrell Darnell, CR Bard
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NOTE--Participation by federal agency representatives in the development of this document does not constitute endorsement by the federal government or any of its agencies.

At the time this document was published, the **AAMI TSE Elimination Working Group** had the following members:

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NOTE--Participation by federal agency representatives in the development of this document does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI adoption of ISO 13022:2012

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.

ISO 13022:2012 was developed by ISO/TC 194/SC 1, Tissue product safety, to specify a procedure to identify the hazards and hazardous situations and to manage the risk associated with viable cellular component(s) of products regulated as medicinal products, biologics, medical devices and active implantable medical devices or combinations thereof.

U.S. participation in ISO/TC 194/SC 1 is organized through the U.S. Technical Advisory Group for ISO/TC 194/SC 1, administered by the Association for the Advancement of Medical Instrumentation (AAMI) on behalf of the American National Standards Institute (ANSI). U.S. experts made a considerable contribution to this standard.

AAMI encourages its committees to harmonize their work with international standards as much as possible. Upon review of ISO 13022:2012, the AAMI Tissue Product Safety Committee (U.S. TAG for ISO/TC 194/SC 1) and the AAMI TSE Elimination Working Group decided to adopt 13022, verbatim, as a new American National Standard.

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

AAMI (and ANSI) have adopted other ISO documents. 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 document, “shall” indicates requirements strictly to be followed to conform to the standard. “Should” indicates that among several possibilities, one is recommended as particularly suitable, without mentioning or excluding others, or 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 should be avoided but is not prohibited. “May” is used to indicate that a course of action is permissible within the limits of the recommended practice. “Can” is used as a statement of possibility and capability. Finally, “must” is used only to describe “unavoidable” situations, including those mandated by government regulation.

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, 4301 N. Fairfax Dr. Suite 301, Arlington, VA 22203-1633.

NOTE- Beginning with the ISO foreword on page x, this American National Standard is identical to ISO 13022:2012.

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 13022 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*, Subcommittee SC 1, *Tissue product safety*.

Introduction

Certain medical products utilize materials of human origin. Depending on national regulatory requirements, these products are addressed as medicinal substances, medical devices or biologics. Materials of human origin are used in the design and manufacture of medical products to provide performance characteristics that might be chosen for their advantages over non-human-based materials, particularly to improve regeneration of the patient's own tissues or organs, or to replace or to supplement organ function.

Medical products utilizing human materials comprise a heterogeneous group. Examples include cell suspensions, cell/matrix constructs or cells combined with complex medical devices such as dialysis equipment.

While the medical products utilizing human material are quite diverse, the hazards specifically related to all human materials are basically the same:

- a) the material can be contaminated with infectious agents [e.g. bacteria, molds, yeasts, viruses, Transmissible Spongiform Encephalopathy (TSE) infectious agents, parasites];
- b) the material can be contaminated with chemicals;
- c) the material can be unsuitable for the intended purpose due to unintended decomposition or degradation induced by inappropriate handling at any stage of the production process;
- d) the material can be hazardous for the patient due to tumorigenic potential;
- e) following application, unintended physiological and anatomical consequences can be hazardous, taking into account cell migration and release of biologically active substances;
- f) a failure of traceability;
- g) the material can cause harm for the patient by eliciting an immunogenic reaction.

To address the hazards related to contamination, degradation, unintended modification and/or mix-up of viable human cells and products, this International Standard was developed for the application of risk management on the manufacture of medical products utilizing viable human material.

The hazards mentioned above have been related to the relevant manufacturing steps. The essential aspects to be covered by this International Standard are as follows:

- terminology and definitions;
- donor selection and testing, addressing both living and deceased donors;
- human material procurement;
- human material handling (including production);
- human material packaging, storage and transport;
- human material labeling;

- risk related to handling of the product during application;
- consideration of risks and benefits in relation to intended use.

This International Standard will assist manufacturers of products based on viable human materials that produce medicinal substances, medical devices or biologics.

Medical products containing viable human cells — Application of risk management and requirements for processing practices

1 Scope

This International Standard specifies requirements and guidance for processing practices and managing risk associated with viable cellular components of products regulated as medicinal products, biologics, medical devices and active implantable medical devices, or combinations thereof. It covers viable human materials of autologous as well as allogeneic human origin, obtained from living or deceased donors.

For manufacturers of medical products containing viable cells of human origin, this International Standard specifies procedures to be used in processing and handling, as well as those to be used in identifying the hazards and hazardous situations associated with such cells, in order to estimate and evaluate the resulting risks, to control these risks, and to monitor the effectiveness of that control. Furthermore, this International Standard outlines the decision process for the residual risk acceptability, taking into account the balance of residual risk and expected medical benefit as compared to available alternatives.

This International Standard provides requirements and guidance on risk management related to the hazards typical of medical products manufactured utilizing viable human materials, such as:

- a) contamination by bacteria, molds, yeasts or parasites;
- b) contamination by viruses;
- c) contamination by agents causing Transmissible Spongiform Encephalopathies (TSE);
- d) contaminating material responsible for undesired pyrogenic, immunological or toxicological reactions;
- e) decomposition of the product and degradation products caused by inadequate handling;
- f) hazards related to the tumorigenic potential of the cell types used;
- g) complications resulting from unintended physiological and anatomical consequences (this includes unintended migration of cells, unwanted release of biologically active substances such as hormones and cytokines, and unintended interactions between cellular and non-cellular components of the product);
- h) failure of traceability;
- i) complications resulting from the material eliciting an unintended immunogenic reaction.

For the evaluation of contamination with other unclassified pathogenic entities, similar principles might be applicable.

Hazards related to genetic modification are outside the scope of this International Standard and are addressed elsewhere.

NOTE 1 A definition of “genetically modified” can be found in ASTM F2312.

NOTE 2 This International Standard does not specify a quality management system for the control of all stages of production of medical products as described above.

If additional national or regional criteria beyond what is defined in this International Standard exist in the country where the medical product will be used, they are also applicable.

NOTE 3 Regional requirements can be more stringent than requirements referenced in this International Standard, especially with regard to donor eligibility criteria.

This International Standard is not applicable to:

- non-viable materials of human origin;
- viable cells of non-human origin;
- blood and its components used for transfusion, germ cells, organs and bone marrow used for transplantation, and other tissues that do not meet the definition of “medical product”;
- *in vitro* diagnostic devices.

NOTE 4 For guidance on the application of this International Standard, see Annex A.

2 Normative references

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

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 22442-1, *Medical devices utilizing animal tissues and their derivatives — Application of risk management*

ASTM F2312, *Standard Terminology Relating to Tissue Engineered Medical Products*

BSI PAS 84, *Regenerative Medicine — Glossary, June 2008*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 13485, ISO 14971, ISO 22442-1, ASTM F2312, BSI PAS 84 and the following apply.

3.1

medical device

instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes of:

- a) diagnosis, prevention, monitoring, treatment or alleviation of disease;
- b) diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
- c) investigation, replacement, modification, or support of the anatomy or of a physiological process;
- d) supporting or sustaining life;
- e) control of conception;
- f) disinfection of medical devices;
- g) providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body;

and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

NOTE 1 This definition has been developed by the Global Harmonization Task Force (GHTF).

NOTE 2 Products which could be considered to be medical devices in some jurisdictions but for which there is not yet a harmonized approach are:

- a) aids for disabled/handicapped people;
- b) devices for the treatment/diagnosis of diseases and injuries in animals;
- c) accessories for medical devices (see NOTE 3);
- d) disinfection substances;
- e) devices incorporating animal and human tissues which can meet the requirements of the above definition but are subject to different controls.

NOTE 3 Accessories intended specifically by manufacturers to be used together with a “parent” medical device to enable that medical device to achieve its intended purpose, should be subject to this International Standard.

NOTE 4 The term “medical devices” covers non-active and active medical devices as well as active implantable medical devices.

NOTE 5 Adapted from ISO 14971:2007, definition 2.9.

3.2

active implantable medical device

active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure

NOTE 1 An active medical device relies for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity.

NOTE 2 Adapted from ISO 13485:2003, definition 3.1.

3.3

medicinal product

substance or combination of substances presented as having properties for treating or preventing disease in human beings, or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis

NOTE See Reference [34].

3.4

medical product

medicinal product, biologic, medical device, or a combination of these

3.5

cell-based medical product

medical product that includes viable human cells of autologous as well as allogeneic human origin, obtained from living or deceased donors, having undergone a manufacturing process

NOTE Cell-based medical products may be combined with non-cellular components.

3.6

biologics

biologicals

cell therapy product of autologous or allogeneic origin in which the cells have been propagated, expanded, selected, pharmacologically treated or otherwise altered in biological characteristics *ex vivo* to be administered to humans and which is applicable to the prevention, treatment, cure, diagnosis or mitigation of disease or injuries

NOTE 1 See Reference [57].

NOTE 2 Clarification of the FDA concerning the definition of biologic can be found at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm>

3.7

donor

human source, whether living or deceased, of human cells or tissues

NOTE In the case of an autologous donation, the living donor is the patient.

3.8

procurement

recovery process by which tissue or cells are obtained from a donor

3.9

residues

substances or materials remaining after production processes such as cell debris, degradation products from a scaffold, chemicals, growth factors, or solvents

3.10

inactivation

process by which the ability to cause infection or pathogenic reaction by a transmissible agent is reduced

NOTE 1 The effectiveness of the process for inactivation of viruses and TSE agents is expressed mathematically in terms of a reduction factor (see ISO 22442-3:2007, Annex F).

NOTE 2 Inactivation aims to prevent infection by, and replication of, transmissible agents.

[ISO 22442-1:2007, definition 3.5]

3.11

manufacture

any or all of the steps in the procurement, screening, testing, processing, storage, labeling, packaging or distribution of any human cellular or tissue-based medical product, including the screening and testing of the cell or tissue donor

3.12

manufacturer

natural or legal person with responsibility for the design, manufacture, packaging and labeling of a cell-based medical product before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party

3.13

storage

maintaining the cell-based medical product under appropriate controlled conditions until the time of future processing or distribution

3.14

transport

transferring the cell-based medical product under appropriately controlled conditions

3.15

risk

combination of the probability of occurrence of harm and the severity of that harm

[ISO/IEC Guide 51:1999, definition 3.2]

3.16

harm

physical injury or damage to the health of people, or damage to property or the environment

[ISO/IEC Guide 51:1999, definition 3.3]

3.17

hazard

potential source of harm

NOTE 1 See ICH Q9.

NOTE 2 Adapted from ISO/IEC Guide 51:1999, definition 3.5.

3.18

residual risk

risk remaining after risk control measures have been taken

NOTE 1 Adapted from ISO/IEC Guide 51:1999, definition 3.9.

NOTE 2 ISO/IEC Guide 51:1999, definition 3.9 uses the term “protective measures” rather than “risk control measures”. In the context of this International Standard, “protective measures” are only one option for controlling risk as described in this International Standard.

3.19

risk analysis

systematic use of available information to identify hazards and to estimate the risk

[ISO/IEC Guide 51:1999, definition 3.10]

3.20

risk assessment

overall process comprising a risk analysis and a risk evaluation

[ISO/IEC Guide 51:1999, definition 3.12]

3.21

risk control

process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels

[ISO 14971:2007, definition 2.19]

3.22

risk estimation

process used to assign values to the probability of occurrence of harm and the severity of that harm

[ISO 14971:2007, definition 2.20]

3.23

risk evaluation

process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

[ISO 14971:2007, definition 2.21]

3.24

risk management

systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring risk

[ISO 14971:2007, definition 2.22]

3.25

risk management file

set of records and other documents that are produced by risk management

[ISO 14971:2007, definition 2.23]

3.26

safety

freedom from unacceptable risk

[ISO/IEC Guide 51:1999, definition 3.1]

3.27

severity

measure of the possible consequences of a hazard

[ISO 14971:2007, definition 2.25]

4 Risk management process

4.1 General

Considerations on risk management shall take into account two components:

- a) the probability of occurrence of harm to the patient or user of the product;
- b) the consequences of that harm, i.e. how severe it might be.

Risk management is of particular importance to the cellular component of medical products including viable human cells or tissues because of the inherent hazards of this group of products and the variety of stakeholders, including medical practitioners, organizations providing health care, governments, industry, patients and members of the public. Additionally, these stakeholders might be affected by the availability of this type of medical product (the cellular component of a medical product is of particular importance because this raw material can be more rare than other components of a medical product). Therefore lack of availability for the patient is to be considered.

The manufacturer shall make judgments relating to the safety of a cell-based medical product, including the acceptability of risks, taking into consideration the generally accepted state of the art, to determine the suitability of a medical product to be placed on the market for its intended use. This International Standard specifies a process through which the manufacturer of a cell-based medical product can identify hazards associated with the cellular component of the product, estimate and evaluate the risks associated with these hazards, control these risks, and monitor the effectiveness of that control.

The manufacturer shall justify the use of human material (including the choice and source of cell type and/or tissues) based on the residual risk acceptability, considering the balance of residual risk and expected medical benefit, as compared to available alternatives. When considering the risks and benefits of the product, the impact of the surgical procedure required for its administration is to be considered.

The requirements of ICH Q9^[20] and Good Manufacturing Practice apply for the medicinal substances part of the product.

The requirements of ISO 14971 and ISO 13485 apply for the medical devices part of the product.

4.2 Hazards associated with the cellular component

4.2.1 General

The manufacturer shall establish, document and maintain throughout the life-cycle of the product a systematic process for identifying hazards associated with the cellular component of a cell-based medical product, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls. This process shall include the following elements:

- a) risk analysis;
- b) risk evaluation;
- c) risk control;
- d) consideration of production and post-production information.

Appropriate parts of the risk management process shall be implemented in the documented product realization process throughout the life-cycle of the product.

NOTE A documented quality management system process can be used by the manufacturer to deal with safety in a systematic manner, in particular to enable the early identification of hazards and hazardous situations in complex cell-based medical products.

Compliance shall be determined by inspection of appropriate documents such as risk management files. Inspection is performed and documented by authorized personnel.

4.2.2 Responsibilities

The manufacturer shall have an organizational structure and operational procedures appropriate to their activities. There shall be an organizational chart which clearly defines accountability and reporting relationships.

The manufacturer shall ensure the availability of adequate resources and of qualified personnel for the manufacture of the product and the risk management activities.

The manufacturer shall:

- a) define and document the policy for determining criteria for risk acceptability. This policy shall ensure that criteria are based upon applicable national or regional regulations and relevant International Standards, and consider available information such as the generally accepted state of the art and known stakeholder concerns;
- b) review the suitability of the risk management process at planned intervals to ensure continuing effectiveness of the risk management process and document any decisions and actions taken. This review can be part of the quality management system review.

4.2.3 Documentation

4.2.3.1 Risk management activities shall be documented. A suitable means can be a risk management file which includes the risk management plan.