Designation: F1983 – 23

Standard Practice for Assessment of Selected Tissue Effects of Absorbable Biomaterials for Implant Applications[1]

This standard is issued under the fixed designation F1983; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This practice provides experimental protocols for biological assays of tissue reactions to absorbable biomaterials for implant applications. This practice applies only to absorbable materials with projected clinical applications in which the materials will reside in bone or soft tissue longer than 30 days and less than three years. Other standards with designated implantation times are available to address shorter time periods. Careful consideration should be given to the appropriateness of this practice for slowly degrading materials that will remain for longer than three years. It is anticipated that the tissue response to degrading biomaterials will be different from the response to nonabsorbable materials. In many cases, a chronic inflammatory response may be observed during the degradation phase, but the local histology should return to normal after absorption; therefore, the minimal tissue response usually equated with biocompatibility may require long implantations.

1.2 The time period for implant absorption can depend on variables of chemical composition, implant size, implant location, and animal models. Therefore, the selected time points for assessing tissue effects may be selected based on the rate of absorption.

1.3 These protocols assess the effects of the material on the animal tissue in which it is implanted. They do not fully assess systemic toxicity, carcinogenicity, reproductive and development toxicity, or mutagenicity of the material. Other standards are available to address these issues.

1.4 To maximize use of the animals in the study protocol, some aspects of systemic toxicity, including effects of degradation products on different organs and tissues downstream of or surrounding the target site, can be addressed with this practice.

1.5 Because animal models are not identical to human biology, this practice cannot account for all potential biological hazards, for example the effect of the oligosaccharide a-Gal (Gala 1,3-Galb1-4GlcNAc-R), known as the "a-Gal" epitope present in xenogeneic materials on humans. See ISO 22442.

1.6 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.7 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

F561 Practice for Retrieval and Analysis of Medical Devices, and Associated Tissues and Fluids

F763 Practice for Short-Term Intramuscular Screening of Implantable Medical Device Materials

F981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Insertion into Bone

F1408 Practice for Subcutaneous Screening Test for Implant Materials

F1635 Test Method for ***in vitro*** Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants

F1903 Practice for Testing for Cellular Responses to Particles ***in vitro***

F1904 Practice for Testing the Biological Responses to Particles ***in vivo***

F2902 Guide for Assessment of Absorbable Polymeric Implants

F3268 Guide for ***in vitro*** Degradation Testing of Absorbable Metals

[1] This practice is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.16 on Biocompatibility Test Methods.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

2.2 *ISO Standards:*[3]

ISO 10993-6 Biological evaluation of medical devices—Part 6: Tests for local effects after implantation

ISO 10993-9 Biological evaluation of medical devices—Part 9: Framework for identification and quantification of potential degradation products

ISO 10993-11 Biological evaluation of medical devices—Part 11: Tests for systemic toxicity

ISO 10993-18 Biological evaluation of medical devices—Part 18: Chemical characterization of medical device materials within a risk management process

ISO/TS 10993-19 Biological evaluation of medical devices—Part 19: Physico-chemical, morphological and topographical characterization of materials

ISO 13781 Implants for surgery—Homopolymers, copolymers and blends on poly(lactide)—In vitro degradation testing

ISO/TS 17137 Cardiovascular implants and extracorporeal systems—Cardiovascular absorbable implants

ISO 22442 Medical devices utilizing animal tissues and their derivatives

ISO/TS 37137-1 Biological evaluation of absorbable medical devices—Part 1: General requirements

3. Terminology

3.1 *Definitions:*

3.1.1 *final finished form*—a device or device component that includes all manufacturing processes for the "to be marketed" device including packaging and sterilization, if applicable.[4]

4. Summary of Practice

4.1 Under strict aseptic conditions, sterile test articles (for example, final device) are implanted into a relevant animal model and at a clinically relevant anatomical tissue site. However, for screening candidate materials, testing in a clinically relevant animal model and anatomical tissue site may not be necessary. Small laboratory animals such as mice, rats, hamsters, or rabbits are preferred. In addition, the use of larger animals, such as the dog, goat, pig, or sheep may be justified based upon special considerations of the particular study. Choice of the animal model should also consider the availability of historical data on biological responses of these animals to similar devices to aid in analysis and comparison of the data obtained.

4.2 All animal studies shall be done in a facility in accordance with all appropriate regulations.

5. Significance and Use

5.1 This practice is a guideline for a screening test of candidate materials or assessment of local tissue response to absorbable medical devices which are expected to undergo complete absorption within three years.

5.2 This practice is similar to those for studies on candidate materials or medical devices that are not absorbable, such as those specified in Practices F763, F981, and F1408; however, analysis of the host response must take into account the effect of degradation and degradation products on the inflammatory response at the local tissue site and on subsequent healing of the implantation site, as well as the potential for adverse distal tissue effects.

5.3 For testing of absorbable medical devices, the test article for implantation should be in the final finished form as for intended use, including packaging and sterilization (if applicable). Configurations specific to the animal study may be needed. The test article's surface-area-to-body mass or mass-to-body mass ratios within the animal model should be established by calculating based on surface-area-to-body mass or mass-to-body mass ratios in humans during the device's intended clinical use. Worst-case clinical dose should be considered in the study design. For implantation studies incorporating evaluation of both local tissue responses and systemic toxicity, exaggerated material surface area or mass-to-body mass ratios (for example, a 2X to 10X safety factor to assess implant safety for regulatory submissions) compared to clinical use (for example, largest device size, maximum number of devices) should be considered, unless otherwise justified. For example, implantation of exaggerated doses may not be feasible in the selected animal model. For some devices, additional animal group(s) for exaggerated conditions should be considered if dose response information is needed. Additionally, for some devices, exaggerated dose at a specific implantation site can also be used to evaluate local tissue responses.

5.4 Materials that are designed for use in devices with *in situ* polymerization shall be introduced in a manner such that *in situ* polymerization occurs. Additional testing of individual precursor components or partially polymerized materials may be needed in some cases (for example, if testing of the final implant indicates an adverse response or incomplete polymerization).

6. Animal Model

6.1 The choice of animal model shall take into consideration the normal life span of the animal, the clinical use conditions, device absorption kinetics, and the length of the implantation study, and shall be justified. The strain, sex, age, weight, origin, and general health of the animals used should be recorded. Institutional and government animal use and care policies and regulations shall be followed.[5,6,7,8,9]

[3] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

[4] FDA Biocompatibility Guidance, "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process'" (https://www.fda.gov/media/85865/download).

[5] Animal Welfare Act, 7 U.S.C. § 2131 et seq., as amended. 2013.

[6] Animal Welfare Regulations, 9 CFR Chapter 1, Subchapter A, Parts 1, 2, and 3. 2004.

[7] Health Research Extension Act of 1985, Public Law 99-158 November 20, 1985.

[8] Office of Laboratory Animal Welfare, National Institutes of Health. Public Health Service Policy on Humane Care and Use of Laboratory Animals, Bethesda, MD, 2015.

[9] National Research Council, Guide for the Care and Use of Laboratory Animals: Eighth Edition. Washington, DC, The National Academies Press; 2011.