Designation: F 981 – 99 (Reapproved 2003)

Standard Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone[1]

This standard is issued under the fixed designation F 981; 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 a series of experimental protocols for biological assays of tissue reaction to nonabsorbable biomaterials for surgical implants. It assesses the effects of the material on animal tissue in which it is implanted. The experimental protocol is not designed to provide a comprehensive assessment of the systemic toxicity, immune response, carcinogenicity, teratogenicity, or mutagenicity of the material since other standards deal with these issues. It applies only to materials with projected applications in humans where the materials will reside in bone or soft tissue in excess of 30 days and will remain unabsorbed. It is recommended that short-term assays, according to Practice F 763, first be performed. Applications in other organ systems or tissues may be inappropriate and are therefore excluded. Control materials will consist of any one of the metal alloys in Specifications F 67, F 75, F 90, F 136, F 138, or F 562, high purity dense aluminum oxide as described in Specification F 603, ultra high molecular weight polyethylene as stated in Specification F 648 or USP polyethylene negative control.

1.2 This practice is a combination of Practice F 361 – 80 and Practice F 469 – 78. The purpose, basic procedure, and method of evaluation of each type of material are similar; therefore, they have been combined.

1.3 *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 and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:* [2]

F 67 Specification for Unalloyed Titanium for Surgical Implant Applications (UNS R50250, UNS R50400, UNS R50550, UNS R50700)

F 75 Specification for Cobalt-28Chromium-6Molybdenum Alloy Castings and Casting Alloy for Surgical Implants (UNS R30075)

F 86 Practice for Surface Preparation and Marking of Metallic Surgical Implants

F 90 Specification for Wrought Cobalt20-Chromium15-Tungsten10-Nickel Alloy for Surgical Implant Applications (UNS R30605)

F 136 Specification for Wrought Titanium-6Aluminum-4Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications (UNS R56401)

F 138 Specification for Wrought-18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants (UNS S31673)

F 361 Practice for Assessment of Compatibility of Metallic Materials for Surgical Implants with Respect to Effect of Materials on Tissue[3]

F 469 Practice for Assessment of Compatibility of Nonporous Polymeric Materials for Surgical Implants with Regard to Effect of Materials on Tissue[3]

F 562 Specification for Wrought Cobalt-35Nickel-20Chromium-10Molybdenum Alloy for Surgical Implant Applications (UNS R30035)

F 603 Specification for High-Purity Dense Aluminum Oxide for Surgical Implant Application

F 648 Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants

F 763 Practice for Short-Term Screening of Implant Materials

3. Summary of Practice

3.1 This practice describes the preparation of implants, the number of implants and test hosts, test sites, exposure schedule, implant sterilization techniques, and methods of implant retrieval and tissue examination of each test site. Histological criteria for evaluating tissue reaction are provided.

[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.

[3] Withdrawn.

4. Significance and Use

4.1 This practice covers a test protocol for comparing the local tissue response evoked by biomaterials, from which medical implantable devices might ultimately be fabricated, with the local tissue response elicited by control materials currently accepted for the fabrication of surgical devices. The materials may include metals (and metal alloys), dense aluminum oxide, and polyethylene that are standardized on the basis of acceptable long-term well-characterized long-term response. The controls consistently produce cellular reaction and wound healing to a degree that has been found to be acceptable to the host.

5. Test Hosts and Sites

5.1 Rats (acceptable strains such as Fischer 344), New Zealand White rabbits, and other small laboratory animals may be used as test hosts for soft tissue implant response. It is suggested that the rats be age and sex matched. Rabbits or larger animals may be used as test hosts for bone implants. When larger animals such as dogs, goats, or sheep are used, the decision should be based upon special considerations of the particular implant material or study.

5.2 The sacro-spinalis, paralumbar, gluteal muscles, and the femur or tibia can serve as the test site for implants. However, the same site must be used for test and material implants in all the animal species.

5.3 There shall be a minimum of four animals at each sacrifice interval for a total of twelve animals per study. If larger animals are used, in which a greater number of implants can be placed, there shall be at least two animals sacrificed at each time period.

6. Implant Specimens

6.1 *Fabrication*— Each implant shall be made in a cylindrical shape with hemispherical ends (see 6.3 and 6.4 for sizes). If the ends are not hemispherical, this shall be reported. Each implant shall be fabricated, finished, and its surface cleaned in a manner appropriate for its projected application in human subjects in accordance with Practice F 86. If the specimens are porous, the method of preparation of the porous specimens shall be representative of the contemplated human implant application and shall yield a specimen with characteristic pore size, pore volume, and pore interconnection diameter. The choice between using solid core specimens with porous coatings and specimens that are porous throughout shall be a decision of the investigator and shall be reported.

6.2 Reference metallic specimens shall be fabricated in accordance with 6.1 from materials such as the metal alloys in Specifications F 67, F 75, F 90, F 138, or F 562, ceramic in Specification F 603, or polymers such as in Specification F 648 polyethylene or USP Negative Control Plastic. If the test materials are porous, consideration should be given to using porous specimens for reference specimens. Alternatively, nonporous reference specimens may be used.

6.3 *Suggested Sizes and Shapes of Implants for Insertion in Muscle*:

6.3.1 The implants shall be cylindrical in shape and may range from 1 mm to 6 mm in diameter and from 10 mm to 20 mm in length depending upon the relative size of the species under study.

6.3.2 The dimensions used shall be reported in accordance with 8.1.

6.3.3 Depending upon the particular device application, other sample shapes may be used. For instance, an investigator might wish to test the biocompatibility of a new material for screws in the form of a screw. If an alternative specimen shape is used, this should be reported in accordance with 8.1.

6.4 *Sizes and Shapes of Implants for Insertion in Bone*:

6.4.1 Implant diameters for use in bone shall be approximately equal to the cortex thickness. Implant lengths shall allow them to reside in one cortex and the medulla without excessive protrusion beyond the periosteum.

6.4.2 The dimensions used shall be reported in accordance with 8.1.

6.5 *Number of Test and Control Implants*:

6.5.1 In each rat, due to size, there may be two implants; one each test and control material implant.

6.5.2 In each rabbit, due to size, there may be six implants; four test materials and two control material implants.

6.5.3 In larger animals, there may be twelve implants; eight test materials and four control material implants.

6.5.4 In rabbits or larger animals, there shall be tested at least sixteen test material implants and eight control material implants at each time period.

6.6 *Conditioning*:

6.6.1 Remove all surface contaminants with appropriate solvents and rinse all test and control implants in distilled water prior to sterilization. It is recommended that the implant materials be processed and cleaned in the same way the final product will be.

6.6.2 Clean, package, and sterilize all implants in the same way as used for human implantation.

6.6.3 After final preparation and sterilization, handle the test and control implants with great care to ensure that they are not scratched, damaged, or contaminated in any way prior to insertion.

6.6.4 Report all details of conditioning in accordance with 8.1.

6.7 *Implantation Period*—Insert all implants into each animal at the same surgical session for implantation periods of 12, 26, and 52 weeks.

7. Procedure

7.1 *Implantation (Muscle)*:

7.1.1 Place material implants in the paravertebral muscles in such a manner that they are directly in contact with muscle tissue.

7.1.2 Introduce material implants in larger animals by the technique of making an implantation site in the muscle by using a hemostat to separate the muscle fibers. Then insert the implant using plastic-tipped forceps or any tool that is nonabrasive to avoid damage to the implant.