Designation: F763 – 22

Standard Practice for Short-Term Intramuscular Screening of Implantable Medical Device Materials[1]

This standard is issued under the fixed designation F763; 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 guidelines for short-term testing or screening of candidate materials, both porous and dense, as to the local effects of the material that is implanted intramuscularly. This method may not be applicable for absorbable materials, depending on the absorption profile of the test material. The tissue reactions will be evaluated in comparison to those evoked by control materials that are accepted as clinical implant materials. This is a short-term (less than 30 days) screening procedure for determining acceptability of candidate materials.

1.2 This practice, along with other appropriate biological tests (including other appropriate ASTM tests), may be used in the biocompatibility assessment of the candidate materials for use in the fabrication of devices for clinical application.

1.3 This experimental protocol is not designed to provide a comprehensive assessment of the systemic toxicity, carcinogenicity, or mutagenicity of the material since other standards address these issues.

1.4 This practice is one of several developed for the assessment of the biocompatibility of materials. Practice F748 provides guidance for the selection of appropriate methods for testing materials for a specific application.

1.5 The values stated in SI units, including units officially accepted for use with SI, are to be regarded as standard. No other systems of measurement are included in this standard.

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]

F75 Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants (UNS R30075)

F86 Practice for Surface Preparation and Marking of Metallic Surgical Implants

F90 Specification for Wrought Cobalt-20Chromium-15Tungsten-10Nickel Alloy for Surgical Implant Applications (UNS R30605)

F136 Specification for Wrought Titanium-6Aluminum-4Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications (UNS R56401)

F138 Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants (UNS S31673)

F562 Specification for Wrought 35Cobalt-35Nickel-20Chromium-10Molybdenum Alloy for Surgical Implant Applications (UNS R30035)

F563 Specification for Wrought Cobalt-20Nickel-20Chromium-3.5Molybdenum-3.5Tungsten-5Iron Alloy for Surgical Implant Applications (UNS R30563) (Withdrawn 2005)[3]

F603 Specification for High-Purity Dense Aluminum Oxide for Medical Application

F648 Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants

F748 Practice for Selecting Generic Biological Test Methods for Materials and Devices

F981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of

[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] The last approved version of this historical standard is referenced on www.astm.org.

Materials on Muscle and Insertion into Bone

2.2 *ISO Standards:*[4]

ISO 10993-6:2016 Biological evaluation of medical devices—Part 6: Tests for local effects after implantation

3. Summary of Practice

3.1 Under aseptic conditions, test or control material is surgically implanted into a muscle or group of muscles of the anesthetized animal. The size of the implant should not impede the normal movement of the animal. After a period of time, the animals are euthanized and subjected to a necropsy with comprehensive histopathological assessments. The tissue reactions to implants of the candidate material during the subacute to acute time periods of healing are compared with tissue reactions to control materials that evoke a well-characterized response. The implants are not subjected to major stress while *in situ*.

4. Significance and Use

4.1 The use of *in vivo* implantation techniques for characterizing the biocompatibility of implantable materials to be utilized in various medical applications enables the assessment of such materials not achieved by other procedures. Physical characteristics (that is, form, density, hardness, surface finish) can influence the type and severity of the tissue response to the test materials.

4.2 This practice is intended as a short-term screening procedure for determining the acceptability of candidate materials. It may be utilized prior to using the long-term tests described in Practice F981. It is recommended that for some applications, additional tests, including long-term implantation studies, may be required to assess the final suitability of the candidate materials.

4.3 This practice may not be appropriate for all types of implant applications. The user is cautioned to consider the appropriateness of the method in view of the materials being tested, their potential applications, and the recommendations contained in Practice F748.

5. Test Preparation

5.1 Laboratory rabbits, rats, or other animals may be used as animal models. The following procedure is written for New Zealand White (NZW) rabbit (*Oryctolagus cuniculus*), a commonly used laboratory animal model, but the procedure can be adapted to other appropriate animal models.

5.2 *Animal Model and Implantation Sites:*

5.2.1 Choose healthy adult rabbits that weigh more than 2.5 kg and with paravertebral muscles that are sufficiently large to allow for implantation of the test or control specimens.

5.2.2 The paravertebral muscles are the commonly used anatomical site of implantation in NZW rabbits. In addition, the thigh muscle of rabbits may be used for implantation of smaller test articles. (The gluteal muscles of rats have been used as test sites by some investigators.)

5.2.3 *Preparation of Rabbits*—Animals should be examined prior to surgery to assess their health status to ensure that they are free from any disease or condition (for example, infections) that may interfere with the conduct of the study and study outcomes. On the day of the implantation or up to 20 h before implantation, clip the fur of the animals on both sides of the spinal column. Remove loose hair and scrub the area with appropriate disinfectant prior to surgery. Appropriate anesthesia and analgesia[5] for the specific veterinary patient and continuous monitoring in the peri-anesthetic period should be implemented.

5.3 *Selection of Control Materials:*

5.3.1 Selection of control material(s) should be based on their prior acceptable use in medical applications similar to those proposed for the candidate test material and is not restricted to those listed in 5.3.2.

5.3.2 Metallic control materials, which have been demonstrated to elicit minimal tissue reactions, are the metal alloys, such as in Specifications F75, F90, F136, F138, F562, or F563, or a ceramic, such as alumina (Specification F603). A suitable polymeric control material is found in polyethylene (Specification F648).

NOTE 1—Use of positive controls are not routinely recommended for implantation testing. They may be considered, for example, if there is a need to demonstrate the responsiveness of the test system to implantation challenges.

NOTE 2—A negative control is a well-characterized material with minimal or no known biological responses.

NOTE 3—Certain materials (for example, polymers) may elicit a greater tissue response than the negative control material. In addition, porous materials may not be available to be used as controls in implantation studies of a porous test material. In such cases, incorporation of and comparison to a similar marketed medical device material may be considered, if available.

5.3.3 If the appropriate control material is expected to elicit a tissue response greater than that normally observed with negative control polymer or the alloys cited above, samples of these latter materials may be implanted as controls on the surgical technique.

5.3.4 Implant studies should use test and control articles with similar size and geometry to avoid confounding the healing response. Alternatively, reliability of the comparison using dissimilar size and/or geometry between test and control articles should be justified.

6. Test Articles

6.1 *Fabrication*—Each implant shall be fabricated, finished, and its surface cleaned in a manner appropriate for its projected application in humans. Dense metal implants should be finished in accordance with Practice F86. The size, shape, and surface of test and control implants shall be as similar as is practically possible.

6.2 Implant size, shape, weight, and thickness of test articles may vary depending on the animal species and implant site. Discs (8 mm diameter), rods, and wedges (≤6 mm in length) may be appropriate for rats or rabbits. The edges of the

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

[5] Fish, R., Danneman, P. J., Brown, M., and Karas, A. (Eds.), *Anesthesia and Analgesia in Laboratory Animals*, Academic Press, 2011.

specimens should be as smooth as possible to avoid additional mechanical trauma upon implantation. The test article characteristics (for example, size, geometry, thickness) shall be described and justified.

6.3 *Implantation Period:*

6.3.1 The implantation of all test or control specimens into any one animal shall be done at the same surgical session.

6.3.2 The time points for implantation assessments should be justified. Implant evaluation should be performed at 7 days for assessment, and 14 to 30 days to capture initial and delayed responses to the test and control materials so that the range of healing and possible adverse tissue responses are evaluated. A minimum of three animals shall be used for each study group at each study time point, unless otherwise justified.

NOTE 4—During the first two weeks after implantation, the reaction due to the surgical procedure itself may be difficult to distinguish from the tissue reaction of the implant.

NOTE 5—Some investigators have found that extending the test to include a third group of animals maintained for 90 days to achieve a steady state can provide additional data on the short-term host responses to the implant material.

7. Procedure

7.1 *Implantation:*

7.1.1 The recommended method for delivering the test article to the implantation site is by hypodermic needle or tube and trocar. For larger diameter test articles, an incision of appropriate size will be required to permit passage of the larger diameter tube. If this technique is not practical, other implantation techniques judged appropriate may be used. These should be reported as in 8.1. The implantation shall be done using aseptic procedures.

7.1.2 *Preparation of Test Articles*—The test articles should be fabricated as described in 6.1 and prepared for implantation following the procedure in either 7.1.2.1 or 7.1.2.2.

7.1.2.1 Sterilize each test article as appropriate for final application and, using aseptic technique, insert it into a sterile needle or tube; or,

7.1.2.2 Insert the test article into a needle or tube, protect the ends with an appropriate cover, and sterilize the assemblies in an appropriate manner.

NOTE 6—Allow for proper degassing if sterilizing agents such as ethylene oxide are used.

NOTE 7—If the materials to be tested are harder than the materials from which the handling instruments are made, there is a risk of surface contamination of the test articles by abrasion from the instruments which can affect the results (for example, ceramic test specimens implanted with metal instruments). If accessory devices are needed to handle the test articles, soft textile or plastic should be used between the implants and the instruments. Care must be taken to ensure that any accessories used to manipulate the test articles are not left in the implantation site or surrounding tissues.

7.1.3 The animals should be anesthetized following standard veterinary practices that are appropriate for the animal species used for testing, to prevent muscle movement such as twitching and to follow animal welfare and use practices.

7.1.4 Careful incision can be made on each side of the back through the skin and parallel to the lumbar region of the vertebral column. Four articles of the sample can be implanted through the incision into the dorso-lumbar paravertebral muscles on one side of the spine of each rabbit, about 2.5 cm from the mid-line and parallel to the spinal column, and about 2.5 cm apart from each other. In a similar fashion, four articles of the control material should be implanted in the corresponding muscle on the opposite side of the spine of each animal. If other animal models are considered, the number of implanted articles per animal and the distance between the implanted articles shall be justified.

7.1.5 When using a sterile needle for insertion, a sterile stylet should be inserted into the needle to hold the test specimen in the tissue while withdrawing the needle. With trocar implantation, the test specimen should be inserted after withdrawing the central point and a stylet should be used to hold the sample while withdrawing the cannula.

7.1.6 If excessive bleeding is observed after implantation of a test article, a duplicate test article should be placed at another site on the test article side. The incision should be closed after implantation is complete, if applicable. If excessive bleeding is observed during or after implantation, a justification shall be provided for the cause of the excessive bleeding.

7.1.7 Regardless of the animal model chosen, the number of animals to be tested should permit the implantation of twelve test articles and twelve controls for each assessment time point to allow assessment of a minimum of ten tests articles and ten controls for each time period (see 7.2.4).

7.2 *Postoperative Care:*

7.2.1 All animal studies must be done in a facility approved by a nationally recognized organization and in accordance with all appropriate animal welfare and use regulations. Appropriate analgesic regimens should be administered in the animals postoperatively.

7.2.2 Each animal should be carefully observed during the study period and any abnormal findings shall be reported.

7.2.3 If an animal dies prior to the expected assessment time point, perform a necropsy to determine the cause of death. The results of the necropsy shall be included in the test report regardless of whether the cause of death is related/unrelated to the procedure or test material.

7.2.4 A successful test is one in which ten test articles and ten controls for each test period of three animals are available for histologic evaluation.

7.2.5 Should infection or injury of the test and/or control implant site invalidate the results, the infected/injured animal(s) should be replaced with new test/control animals, if necessary, and a justification shall be provided to include whether the timing of the replacement and the cause of injury/infection would impact data analysis.

7.3 *Euthanasia and Implant Retrieval:*

7.3.1 Study animals should be euthanized at the intervals suggested in 6.3.2.

7.3.2 During and after necropsy, record any gross abnormalities of color or consistency observed in the tissue surrounding the implant. Documentation of these findings using photography (photo documentation) is highly recommended.

7.4 *Gross Evaluation, Acute Test (7 days), and Subacute Test (30 days):*