Designation: F 1983 – 99

Standard Practice for Assessment of Compatibility of Absorbable/Resorbable Biomaterials for Implant Applications[1]

This standard is issued under the fixed designation F 1983; 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/resorbable biomaterials for implant applications. This practice applies only to resorbable/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 the 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 nonresorbable materials. In many cases, a chronic inflammatory response may be observed during the degradation phase, but the local histology should return to normal after degradation; therefore, the minimal tissue response usually equated with "biocompatibility" may require long implantations.

1.2 The time period for implant degradation will vary depending on chemical composition and implant size; therefore, the implantation times for examination of tissue response will be linked to the rate of resorption. No single implantation time is indicated in this practice.

1.3 These protocols assess the effects of the material on the animal tissue in which it is implanted. The experimental protocols do not fully assess systemic toxicity, carcinogenicity, teratogenicity, 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, all toxicological findings should be recorded. There are some aspects of systemic toxicity, including effects of degradation products on the target organs, that can be addressed with this practice, and these effects should be documented fully.

1.5 *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:*

F 561 Practice for Analysis of Implanted Medical Devices and Associated Tissues[2]

F 750 Practice for Evaluating Material Extracts by Systemic Injection in the Mouse[2]

F 763 Practice for Short-Term Screening of Implant Materials[2]

F 981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants With Respect to Effect of Materials on Muscle and Bone[2]

F 1408 Practice for Subcutaneous Screening Test for Implant Materials[2]

F 1903 Practice for Testing for Biological Responses to Particles[2]

F 1904 Practice for Testing the Biological Responses to Particles[2]

F 1905 Practice for Selecting Tests for Determining the Propensity of Materials to Cause Immunotoxicity[2]

F 1906 Practice for Evaluation of Immune Responses in Biocompatibility Testing Using ELISA Tests, Lymphocyte Proliferation, and Cell Migration[2]

3. Summary of Practice

3.1 Under strict aseptic conditions, specimens of the final implant form candidate material are implanted into the most relevant anatomical tissue site in small laboratory animals, preferably mice, rats, hamsters, or rabbits.

3.2 The use of larger animals, such as the dog, goat, or sheep may be justified based upon special considerations of the particular study. Choice of species also should consider the availability of historical data on biological responses of these animals to similar devices to aid in analysis and comparison of data obtained.

3.3 All animal studies must be done in a facility approved by a nationally recognized organization and in accordance with all appropriate regulations.

4. Significance and Use

4.1 This practice is a guideline for a screening test for the evaluation of the local tissue response to materials that may be

[1] This practice is under the jurisdiction of ASTM Committee F-04 on Medical and Surgical Material and Devices and is the direct responsibility of Subcommittee F04.16 on Biocompatibility Test Methods.

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[2] *Annual Book of ASTM Standards*, Vol 13.01.

selected for implantation into the human body and which are expected to undergo degradation by absorption or resorption within three years.

4.2 This practice is similar to that for studies on candidate materials that are not resorbable, such as those specified in Practices F 763, F 981, and F 1408; 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.

4.3 The material to be tested should be in the final finished form as for intended use, including sterilization. Material/body ratios should be relevant to that of intended device use. Material surface area or mass to body mass ratios of 1X, 10X, and 50X if applicable, are recommended.

4.4 Materials that are designed for use in devices with in situ polymerization shall be introduced in a manner such that in situ polymerization occurs. Testing of individual precursor components is not recommended.

5. Test Animals and Sites

5.1 Choice of test animal shall take into consideration the normal life span of the animal and the length of the implantation study. Small laboratory animals are preferred. The strain, sex, age, and origin of the animals used should be noted. If larger animals are used, justification for their use should be provided. The source of the animals, species/strain, weight, age (where known or approximate if not known), general health, and boarding conditions should be recorded. Animal use and care regulations must be followed.

5.2 The number of implant sites shall depend on the size of the implant and the animal. The distance between implants shall be sufficient so that separate tissue blocks are prepared easily for each implant and sufficient that the biological reactions do not overlap or interfere with each other. Implants may be placed bilaterally in soft tissue, including muscle. Bilateral implantation into bone should be considered carefully and justification given. In general, mice, rats, hamsters, and other similarly sized rodents should receive no more than one implant on each side. Larger animals, including rabbits, may receive up to five implants on each side. When the implant is composed of a collection of particles, pellets, etc., each collection is considered one implant site.

5.3 Before embarking on studies in large animals, it is recommended that a pilot study in rodents be undertaken to determine expected rate of degradation and the distribution and metabolism of the degradation products. When feasible, initial prediction may be done by radio-labeling the material and following the loss of radioactivity; however, radioactive specimens shall not be used for biocompatibility testing. Other methods of following the degradation are acceptable. The target organs of the metabolism and excretion of the products should be identified. It is recommended that acute systemic studies with material extracts according to Practice F 750 be completed prior to the initiation of the implantation study.

6. Implant Specimens

6.1 *Design of the Implant*—Specimens may be made from the final finished form candidate material in configurations specific for the animal study. As described in 4.3, the material/host ratio should be available and referrable to ultimate use in the human with material/body mass ratios of 1X, 10X, and 50X, if applicable, recommended. Relevant configurations of implant specimens, such as cylinders, flat cloth, amorphous gels, and polymerizable liquids may be used.

6.2 The use of positive and negative controls is not required in this practice; however, the implantation of the candidate material must be accompanied by the use of an implanted marker or other permanent method, such as a template, to mark the implant site to allow identification of the implant site at the various time periods. A sham surgical site, or a sham surgical animal, is necessary.

6.3 The material used shall be in its final finished form and sterilized as indicated for its ultimate use. It shall be handled for implantation in a manner analogous to that for intended final use, for example, special forceps, special cannulas or needles, special syringes, etc.

6.4 The candidate material shall be described thoroughly to facilitate development of a suitable implant application protocol. The absorption, distribution, metabolism, and excretion of the material and its degradation products should be described. The information shall include, but is not limited to, the following:

6.4.1 Expected method of degradation, for example, hydrolysis, enzymatic, phagocytosis, etc.

6.4.2 Expected nonresorbable degradation products, for example, fibrils, particles from composites.

6.4.3 Expected rate of degradation.

6.4.4 Expected target organ effects where known or expected, for example, eliminated in kidney, stored in liver, stored in spleen or lymph nodes.

6.5 For each time period, at least six rodents shall be used with either single or bilateral implants. For the larger animals, at least four animals shall be used per time period. It is recommended that additional animals be included in the initial protocol to accommodate any unexpected changes in degradation rates of the material.

7. Procedure

7.1 *Implantation*:

7.1.1 Implant the specimen under sterile conditions in anesthetized animals. Where possible, implant the specimen using a trochar method to avoid the need for an incision. If an incision is needed, insert the implant as far from the incision site as possible. Close the insertion site with a suitable suture material.

7.1.1.1 A sham site or sham animal with the identical implantation procedure, but not the test material, should be included in the protocol. If animals are to be used as part of systemic toxicity study, the sham must be a separate animal.

7.1.2 The implantation site must be marked in manner suitable for identification of the site at the designated time periods. The use of a permanent skin marker and a template marking the placement of the specimen and the sham site is recommended. Specimens that are radiopaque may have serial radiographs to identify the location. The implantation of a nonabsorbable marker material such as a monofilament, nonabsorbable suture attached to the specimen or embedded in the