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Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices[1]

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1. Scope

1.1 This practice recommends generic biological test methods for materials and devices according to end-use applications. While chemical testing for extractable additives and residual monomers or residues from processing aids is necessary for most implant materials, such testing is not included as part of this standard practice. The reader is cautioned that the area of materials biocompatibility testing is a rapidly evolving field, and improved methods are evolving rapidly, so this standard is by necessity only a guideline. A thorough knowledge of current techniques and research is critical to a complete evaluation of new materials.

1.2 These test protocols are intended to apply to materials and medical devices for human application. Biological evaluation of materials and devices, and related subjects such as pyrogen testing, batch testing of production lots, and so on, are also discussed. Tests include those performed on materials, end products, and extracts. Rationale and comments on current state of the art are included for all test procedures described.

1.3 The biocompatibility of materials used in single or multicomponent medical devices for human use depends to a large degree on the particular nature of the end-use application. Biological reactions that are detrimental to the success of a material in one device application may have little or no bearing on the successful use of the material for a different application. It is, therefore, not possible to specify a set of biocompatibility test methods which will be necessary and sufficient to establish biocompatibility for all materials and applications.

1.4 The ethical use of research animals places the obligation on the individual investigator to determine the most efficient methods for performing the necessary testing without undue use of animals. Where adequate prior data exists to substantiate certain types of safety information, these guidelines should not be interpreted to mean that testing should be unnecessarily repeated.

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:*

E 1262 Guide for Performance of the Chinese Hamster Ovary Cell/Hypoxanthine Guanine Phosphoribosyl Transferase Gene Mutation Assay[2]

E 1280 Guide for Performance of the Mouse Lymphoma Assay for Mammalian Cell Mutagenicity[2]

F 619 Standard Practice for Extraction of Medical Plastics[3]

F 719 Practice for Testing Biomaterials in Rabbits for Primary Skin Irritation[3]

F 720 Practice for Testing Guinea Pigs for Contact Allergens: Guinea Pig Maximization Test[3]

F 749 Practice for Evaluating Material Extracts by Intracutaneous Injection in the Rabbit[2]

F 750 Practic for Evaluating Material Extracts by Systemic Injection in the Mouse[3]

F 756 Practice for Assessment of the Hemolytic Properties of Materials[3]

F 763 Practice for Short-Term Screening of Implant Materials[3]

F 813 Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices[3]

F 895 Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity[3]

F 981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone[3]

F 1027 Practice for Tissue and Cell Compatibility of Orofacial Prosthetic Materials and Devices[3]

F 1408 Practice for Subcutaneous Screening Test for Implant Materials[3]

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

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[2] *Annual Book of ASTM Standards*, Vol 11.04.

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

F 1439 Guide for Performance of Lifetime Bioassay for the Tumorigenic Potential of Implant Materials[3]

2.2 *Other Referenced Documents:*

ISO/AAMI/ANSI 10993-1 Biological Testing of Medical and Dental Materials and Devices - Part 1: Guidance on Selection of Tests[4]

EN 30993–1 Biological Testing of Medical and Dental Materials and Devices - Part 1: Guidance on Selection of Tests[4]

General Program Memorandum #G95-1 FDA[5]

Immunotoxicity Testing Guidance-FDA[5]

3. Summary of Practice

3.1 A matrix listing biological test methods versus materials (devices) and their applications is included in Table 1. The expected duration of use of the device is also considered. Intra-operative is less than 24 h, short-term is up to and including 30 days, chronic is greater than 30 days. The position of row and column intersection is marked to indicate whether the test is recommended for a material or device for the specific application indicated. The terms relating to device or material type and application are addressed in Section 5. Discussion of applicability, current state of the art, and rationale for individual test methods also appears in that section.

4. Significance and Use

4.1 The objective of this practice is to recommend sufficient biological testing to establish a reasonable level of confidence concerning the biological response to a material or device, while at the same time avoiding unnecessary testing.

4.2 This document is intended to provide guidance to the materials investigator in selecting the proper procedures to be carried out for the screening of new or modified materials. Because each material and each implant situation involves its own unique circumstances, these recommendations should be modified as necessary and do not constitute the only testing that will be required for a material nor should these guidelines be interpreted as minimum requirements for any particular situation. While an attempt has been made to provide recommendation for different implant circumstances, some of the recommended testing may not be necessary or reasonable for a specific material or application.

5. Classification of Materials and Devices by End-Use Applications

5.1 *General*:

5.1.1 When new materials are sought for a medical application for use on humans, the material(s) may comprise the whole final device product, or may be one of many component materials in the device. The first step is a thorough literature search for previous use of the material or biocompatibility testing studies to assure that it has not been known to produce an adverse biological response that exceeds the expected benefit in the use of the device. Note that the final fabricated product may differ chemically, physically, or biologically from the raw materials used to fabricate the product due to processing and this has to be considered when designing test protocols. For some devices it may be necessary or desirable to take material test samples directly from the final device product. Samples should be fully representative of the finished product in terms of processing, cleaning, packaging, sterilization, and any other procedures that are performed on the materials before the device is used.

5.1.2 At this point preliminary material screening may be employed, depending on the expertise of the organizations evaluating the materials. Since preliminary screening is normally an option to minimize the economic impact of a candidate material failing final biological tests after extensive time and effort, it is not a required procedure. The investigator should be aware that, should an adverse tissue response be observed with a final product, it may be impossible to determine which component or process is responsible without these initial screening tests.

5.1.3 This practice addresses two dimensions of tissue-material interactions: duration and tissue type. A third dimension, which should be considered is the relative size difference between the host and the material, that is, to how much material surface area is the host exposed. The material surface area to body weight ratio may become a significant factor for porous materials, and devices of repeated short-term applications (for example, dialysis products). While this practice does not address the issue of "intensity factor" of increased surface area, the biocompatibility testing facility personnel should consider it in their material screening and testing protocol design.

5.1.4 For the purposes of this document, devices, and the materials that comprise them, are classified as to end-use human application as outlined in 5.2-5.4.

5.2 *External Devices*:

5.2.1 *Devices That Contact Intact Body Surfaces Only*—examples include electrodes, splints, external prostheses, certain dressings, monitors of various types, or ostomy appliances.

5.2.2 *Devices That Contact Breached Body Surfaces*—examples include ulcer, burn, and granulation tissue dressings, or healing devices.

5.3 *Externally Communicating Devices*:

5.3.1 *Devices Communicating with Intact Natural Channels*:

5.3.1.1 *Intraoperative (<24 hours)*—examples include intraintestinal devices (such as sigmoidoscopes, colonoscopes, stomach tubes, or gastroscopes), tracheal tubes, bronchoscopes and any parts of ancillary equipment that are in contact with materials entering the body, and irrigation sets.

5.3.1.2 *Short-term (up to and including 30 days)*—examples include contact lenses, urinary catheters, and intravaginal devices.

5.3.1.3 *Chronic (>30 days)*—examples include urinary catheters for chronic use and intrauterine devices.

5.3.2 *Devices Communicating with Body Tissues and Fluids*:

5.3.2.1 *Intraoperative (<24 hours)*—examples include hypodermic needles, penetrating electrodes, biopsy instruments,

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

[5] Available from CDRH, Rockville, MD.

TABLE 1 Applicable Tests

Classification of Material or Device and Application	Cell Culture Cytotoxicity	Sensi-tization	Skin Irritation or Intra-cutaneous	Mucous Membrane Irritation	Systemic Toxicity, Acute or Subchronic	Blood Compatibility	Hemolysis	Pyrogen Test	Short-term Implantation	Long-term Implantation	Immune Response	Genotoxicity	Carcinogenicity
External devices													
Intact surfaces (all time periods)	x	x	x										
Breached surfaces													
Intraoperative	x	x	x										
Short-Term	x	x	x		x								
Chronic	x	x	x		x							x	
External Devices Communicating with:													
Intact Natural Channels													
Intraoperative	x	x	x	x									
Short-term	x	x	x	x	x				x				
Chronic	x	x	x	x	x				x		x	x	x
Body Tissues and Fluids													
Intraoperative	x	x	x		x			i[A]					
Short-term	x	x	x		x			i[A]	x		x		
Chronic	x	x	x		x			i[A]	x		x	x	x
Blood Path, indirect													
Intraoperative	x	x	x		x	x	x	x					
Short-term	x	x	x		x	x	x	x					
Chronic	x	x	x		x	x	x	x			x	x	
Blood Path, direct													
Intraoperative	x	x	x		x	x	x	x					
Short-term	x	x	x		x	x	x	x	x		x		
Chronic	x	x	x		x	x	x	x	x		x	x	x
Implanted Devices principally contacting Bone/Tissue/tissue fluid													
Intraoperative	x	x	x		x								
Short-term	x	x	x		x			x	x				
Chronic	x	x	x		x			x	x	x	x	x	x
Blood													
Intraoperative	x	x	x		x	x	x	x					
Short-term	x	x	x		x	x	x	x	x			x	x
Chronic	x	x	x		x	x	x	x	x	x	x	x	x

[A](i) Pyrogenicity testing may be considered for all devices contacting the central nervous system.