

〈1031〉 THE BIOCOMPATIBILITY OF MATERIALS USED IN DRUG CONTAINERS, MEDICAL DEVICES, AND IMPLANTS

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This chapter provides guidance on the identification and performance of procedures for evaluating the biocompatibility of drug containers, elastomeric closures, medical devices, and implants. Biocompatibility refers to the tendency of these products to remain biologically inert throughout the duration of their contact with the body. The biocompatibility testing procedures referenced in this chapter are designed to detect the nonspecific, biologically reactive, physical or chemical characteristics of medical products or the materials used in their construction. In combination with chemical assays, these biological procedures can be used to detect and identify the inherent or acquired toxicity of medical products prior to or during their manufacturing and processing.

Preclinical testing procedures to evaluate the safety of the elastomers, plastics, or other polymers used in the construction of medical products are referenced or described in the following general chapters: *Injections and Implanted Drug Products* 〈1〉, *Biological Reactivity Tests, In Vitro* 〈87〉, *Biological Reactivity Tests, In Vivo* 〈88〉, *Medical Devices—Bacterial Endotoxin and Pyrogen Tests* 〈161〉, *▲Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems* 〈381〉▲ (CN 1-Dec-2020), *Plastic Packaging Systems and Their Materials of Construction* 〈661〉, *Plastic Materials of Construction* 〈661.1〉, and *Plastic Packaging Systems for Pharmaceutical Use* 〈661.2〉. Specific in vitro and in vivo testing procedures to evaluate the biocompatibility of medical products in patients are described under *Biological Reactivity Tests, In Vitro* 〈87〉 and under *Biological Reactivity Tests, In Vivo* 〈88〉.

The procedures used to evaluate the biocompatibility of a medical product or its construction materials have been categorized as a panel of biological effects (toxicity procedures): cytotoxicity, sensitization, irritation or intracutaneous reactivity, acute systemic toxicity, subchronic toxicity (repeated), genotoxicity, implantation, hemocompatibility, chronic toxicity (extending beyond 10% of the life span of the test animal or beyond 90 days), carcinogenicity, reproductive or developmental toxicity, and biodegradation.¹ The USP general chapters referring to the toxicity procedures for these categories are indicated in *Table 1*. In addition, pyrogenicity, an area of special toxicity, is evaluated under *Pyrogen Test* 〈151〉 and under *Bacterial Endotoxins Test* 〈85〉. There are currently no general chapters that detail subchronic toxicity, genotoxicity, chronic toxicity, carcinogenicity, hemotoxicity, reproductive toxicity, or biodegradation testing² requirements.

Table 1. Toxicity Procedures in the USP General Chapters

Biological Effect	USP General Chapter
Cytotoxicity	<i>Biological Reactivity Tests, In Vitro</i> 〈87〉*
Sensitization	<i>Sensitization Testing</i> 〈1184〉
Irritation or intracutaneous reactivity	<i>Biological Reactivity Tests, In Vivo</i> 〈88〉†
Systemic toxicity (acute toxicity)	<i>Biological Reactivity Tests, In Vivo</i> 〈88〉
Implantation	<i>Biological Reactivity Tests, In Vivo</i> 〈88〉

* Additional general chapters referring to this biological effect include *Medical Devices—Bacterial Endotoxin and Pyrogen Tests* 〈161〉, *▲Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems* 〈381〉▲ (CN 1-Dec-2020), *Plastic Packaging Systems and Their Materials of Construction* 〈661〉, *Plastic Materials of Construction* 〈661.1〉, and *Plastic Packaging Systems for Pharmaceutical Use* 〈661.2〉.

† Additional general chapters referring to this biological effect include 〈1〉, *Medical Devices—Bacterial Endotoxin and Pyrogen Tests* 〈161〉, *▲Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems* 〈381〉▲ (CN 1-Dec-2020), *Plastic Packaging Systems and Their Materials of Construction* 〈661〉, *Plastic Materials of Construction* 〈661.1〉, and *Plastic Packaging Systems for Pharmaceutical Use* 〈661.2〉.

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DRUG CONTAINERS

Biocompatibility of Plastic and Other Polymeric Drug Containers

Pharmaceutical containers consist of a container and a closure. Plastic containers may consist of polymers that upon extraction do not alter the stability of the contained product or do not exhibit toxicity. The biocompatibility testing requirements for drug containers are stated under 〈1〉, *Plastic Packaging Systems and Their Materials of Construction* 〈661〉, *Plastic Materials of Construction* 〈661.1〉, and *Plastic Packaging Systems for Pharmaceutical Use* 〈661.2〉. As directed in these chapters, the plastic or other polymeric portions of these products are tested according to the procedures set forth under *Biological Reactivity Tests, In Vitro* 〈87〉. A plastic or other polymer that does not meet the requirements of *Biological Reactivity Tests, In Vitro* 〈87〉 is not a suitable material for a drug container. Materials that meet the in vitro requirements qualify as biocompatible materials without the need for further testing and may be used in the construction of a drug container. If a class designation (classes I–VI) for plastics or other polymers is desired, the appropriate testing procedures are performed as discussed in the section *In Vivo Testing and Class Designation*.

¹ ISO document 10993-1:1997 (or latest version) entitled *Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing*.

² See OECD Guidelines for Testing of Chemicals at www.oecd.org.

Elastomeric Closures

Elastomeric closures are closures that can be pierced by a syringe and maintain their integrity because of their elastic properties. Elastomeric materials may be composed of several chemical entities including fillers, pigments, plasticizers, stabilizers, accelerators, vulcanizing agents, and a natural or a synthetic polymer. These materials are used for manufacturing a product with the desired elastomeric physical properties, and they frequently demonstrate biological reactivity—cellular degeneration and malformation—when tested with in vitro cell cultures.

The biocompatibility of an elastomeric material is evaluated according to the two-stage testing protocol specified in the *Biological Test Procedures* under *▲Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems* (381)▲ (CN 1-Dec-2020). Unlike plastics or other polymers, an elastomeric material that does not meet the requirements of the first-stage (in vitro) testing may qualify as a biocompatible material by passing the second-stage (in vivo) testing, which consists of the *Systemic Injection Test* and the *Intracutaneous Test* described under *Biological Reactivity Tests, In Vivo* (88). No class or type distinction is made between elastomeric materials that meet the requirements of the first stage of testing and those that qualify as biocompatible materials by meeting the second-stage requirements. Elastomeric materials are not assigned class I–VI designation.

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MEDICAL DEVICES AND IMPLANTS

Medical devices and implants, labeled nonpyrogenic, in direct or indirect contact with the cardiovascular system or other soft body tissues, meet the requirements described under *Medical Devices—Bacterial Endotoxin and Pyrogen Tests* (161). The products listed in this chapter that meet the criteria are solution administration sets, extension sets, transfer sets, blood administration sets, intravenous catheters, dialyzers and dialysis tubing and accessories, transfusion and infusion assemblies, and intramuscular drug delivery catheters. The outlined criteria do not apply to medical products such as orthopedic products, latex gloves, and wound dressings.

The testing requirements described or referenced under *Medical Devices—Bacterial Endotoxin and Pyrogen Tests* (161) include *Sterility*, *Bacterial endotoxins*, *Pyrogen*, and *Other requirements*. A procedure to evaluate the presence of bacterial endotoxins is set forth under *Bacterial Endotoxins Test* (85), and the limits are set in *Bacterial Endotoxins* under *Medical Devices—Bacterial Endotoxin and Pyrogen Tests* (161). For devices that cannot be tested by the *Bacterial Endotoxins Test* (85) because of nonremovable inhibition or enhancement, the *Pyrogen Test* (151) is applied. The procedures for evaluating medical devices purported to contain sterile pathways are set forth in *Sterile Devices* under *Sterility Tests* (71). A procedure for evaluating the safety of medical devices is set forth in the *Safety Test* under *Biological Reactivity Tests, In Vivo* (88).

The plastic or other polymer components of medical devices meet the requirements specified for plastics and other polymers under *Plastic Packaging Systems and Their Materials of Construction* (661), *Plastic Materials of Construction* (661.1), and *Plastic Packaging Systems for Pharmaceutical Use* (661.2); those made of elastomers meet the requirements under *▲Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems* (381)▲ (CN 1-Dec-2020). As directed in these chapters, the biocompatibility of the plastic, other polymeric, and elastomeric portions of these products are tested according to the procedures described under *Biological Reactivity Tests, In Vitro* (87). If a class designation for a plastic or other polymer is also required, the appropriate testing procedures described under *Biological Reactivity Tests, In Vivo* (88) are performed.

As required for elastomeric closures, elastomeric materials that do not meet the in vitro requirements may qualify as biocompatible materials and may be used in the construction of medical devices if they meet the requirements of the *Systemic Injection Test* and the *Intracutaneous Test* under *Biological Reactivity Tests, In Vivo* (88). As required for drug containers, plastics and other polymers that do not meet the in vitro testing requirements are not suitable materials for use in medical devices.

IN VITRO TESTING, IN VIVO TESTING, AND CLASS DESIGNATION FOR PLASTICS AND OTHER POLYMERS

The testing requirements specified under *Biological Reactivity Tests, In Vitro* (87) and *Biological Reactivity Tests, In Vivo* (88) are designed to determine the biological reactivity of mammalian cell cultures and the biological response of animals to elastomeric, plastic, and other polymer materials with direct or indirect patient contact. The biological reactivity of these materials may depend on both their surface characteristics and their extractable chemical components. The testing procedures set forth in these chapters can often be performed with the material or an extract of the material under test, unless otherwise specified.

Preparation of Extracts

Evaluation of the biocompatibility of a whole medical product is often not realistic; thus, the use of representative portions or extracts of selected materials may be the only practical alternative for performing the assays. When representative portions of the materials or extracts of the materials under test are used, it is important to consider that raw materials may undergo chemical changes during the manufacturing, processing, and sterilization of a medical product. Although in vitro testing of raw materials can serve as an important screening procedure, a final evaluation of the biocompatibility of a medical product is performed with portions of the finished and sterilized product.

The preparation of extracts is performed according to the procedures set forth under *Biological Reactivity Tests, In Vitro* (87) and under *Biological Reactivity Tests, In Vivo* (88). Extractions may be performed at various temperatures (121°, 70°, 50°, or 37°), for various time intervals (1 hour, 24 hours, or 72 hours), and in different extraction media. The choice of extraction medium for the procedures under *Biological Reactivity Tests, In Vitro* (87) includes *Sodium Chloride Injection* (0.9% NaCl) or tissue culture medium with or without serum. When medium with serum is used, the extraction temperature cannot exceed 37°. In vivo

extraction medium includes the choices described under *Biological Reactivity Tests, In Vivo* (88) or the solvent to which the drug or medical device is exposed.

When choosing extraction conditions, select the temperature, solvent, and time variables that best mimic the “in use” conditions of the product. The performance of multiple tests at various conditions can be used to simulate variations in the “in use” conditions. Although careful selection of extraction conditions allows the simulation of manufacturing and processing conditions in the testing of raw materials, an evaluation of the biocompatibility of the product is performed with the finished and sterilized product.

In Vitro Testing

The procedures described under *Biological Reactivity Tests, In Vitro* (87) include an *Agar Diffusion Test* (indirect contact test), a *Direct Contact Test*, and an *Elution Test* (extraction test). The sample is biocompatible if the cell cultures do not exhibit greater than a mild reactivity (Grade 2) to the material under test, as described under *Biological Reactivity Tests, In Vitro* (87). The *Agar Diffusion Test* is designed to evaluate the biocompatibility of elastomeric materials. The material is placed on the agar overlay of the cell monolayer, which cushions the cells from physical damage by the material and allows leachable chemicals or materials to diffuse from the elastomer and contact the cell monolayer. Extracts of elastomeric materials are tested by placing the filter paper saturated with an extract of the elastomer on the solidified surface of the agar. The *Direct Contact Test* is designed for elastomeric or plastic materials that will not physically damage cells with which they are in direct contact. Any leachable chemicals diffuse from the material into the serum-supplemented growth medium and directly contact the cell monolayer. The *Elution Test* is designed to evaluate the extracts of polymeric materials. The material may be applied directly to the tissue culture media.

The performance of either the *Agar Diffusion Test* or the *Direct Contact Test* in combination with the *Elution Test* is the preferred testing protocol. Extraction of the product or materials for the *Agar Diffusion Test* or the *Elution Test* is performed as described in the *Preparation of Extracts*.

In Vivo Testing and Class Designation

According to the injection and implantation requirements specified in *Table 1* under *Biological Reactivity Tests, In Vivo* (88), plastics and other polymers are assigned a class designation between class I and class VI. To obtain a plastic or other polymer class designation, extracts of the test material are produced according to the specified procedures in various media.

To evaluate biocompatibility, the extracts are injected systemically and intracutaneously into mice and rabbits or guinea pigs. According to the specified injection requirements, a plastic or other polymer may initially be graded as class I, II, III, or V. If in addition to injection testing, implantation testing using the material itself is performed, the plastic or other polymer may be classified as class IV or class VI.

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BIOCOMPATIBILITY OF MEDICAL DEVICES AND IMPLANTS

In addition to evaluating medical products for compendial purposes according to the procedures specified under (1), *Sterility Tests* (71), *Biological Reactivity Tests, In Vitro* (87), *Biological Reactivity Tests, In Vivo* (88), *Medical Devices—Bacterial Endotoxin and Pyrogen Tests* (161), ▲*Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems* (381)▲ (CN 1-Dec-2020), *Plastic Packaging Systems and Their Materials of Construction* (661), *Plastic Materials of Construction* (661.1), and *Plastic Packaging Systems for Pharmaceutical Use* (661.2), medical devices and implants are evaluated for sensitization, subchronic toxicity, genotoxicity, hemocompatibility, chronic toxicity, carcinogenicity, reproductive or developmental toxicity, and biodegradation as required by the regulatory agencies.

The guidance provided by the regulatory agencies indicates that the extent of testing that is performed for a medical device or an implant depends on the following factors: (1) the similarity and uniqueness of the product relative to previously marketed (“predicate”) products as considered in the *Decision Flowchart*; (2) the extent and duration of the contact between the product and the patient as described in the *Categorization of Medical Devices*; and (3) the material composition of the product as considered in the sections *Decision Flowchart* and *In Vivo Testing and Class Designation*.

Decision Flowchart

Guidance on comparing a medical device or an implant to previously marketed products is provided by the Biocompatibility Decision Flowchart (see *Figure 1*³) as adapted from the FDA’s Blue Book Memorandum #G95-1. The purpose of the flowchart is to determine whether the available data from previously marketed devices are sufficient to ensure the safety of the device under consideration. As indicated by the flowchart, the material composition and the manufacturing techniques of a product are compared to those of the previously marketed products for the devices that come in direct contact with the body. In addition, the flowchart requires an evaluation of the toxicity of any unique material that has not been used in predicate devices. Responses to the questions posed in the flowchart lead to the conclusion that either the available data are sufficient or additional testing is required to ensure the safety of the product. When additional testing is required, guidance on the identification of appropriate testing procedures is provided in the section *Test Selection Matrix*.

³ Adapted from the FDA Blue Book Memorandum #G95-1 (“Use of International Standard ISO-10993. ‘Biological Evaluation of Medical Devices-Part 1: Evaluation and Testing.’”)

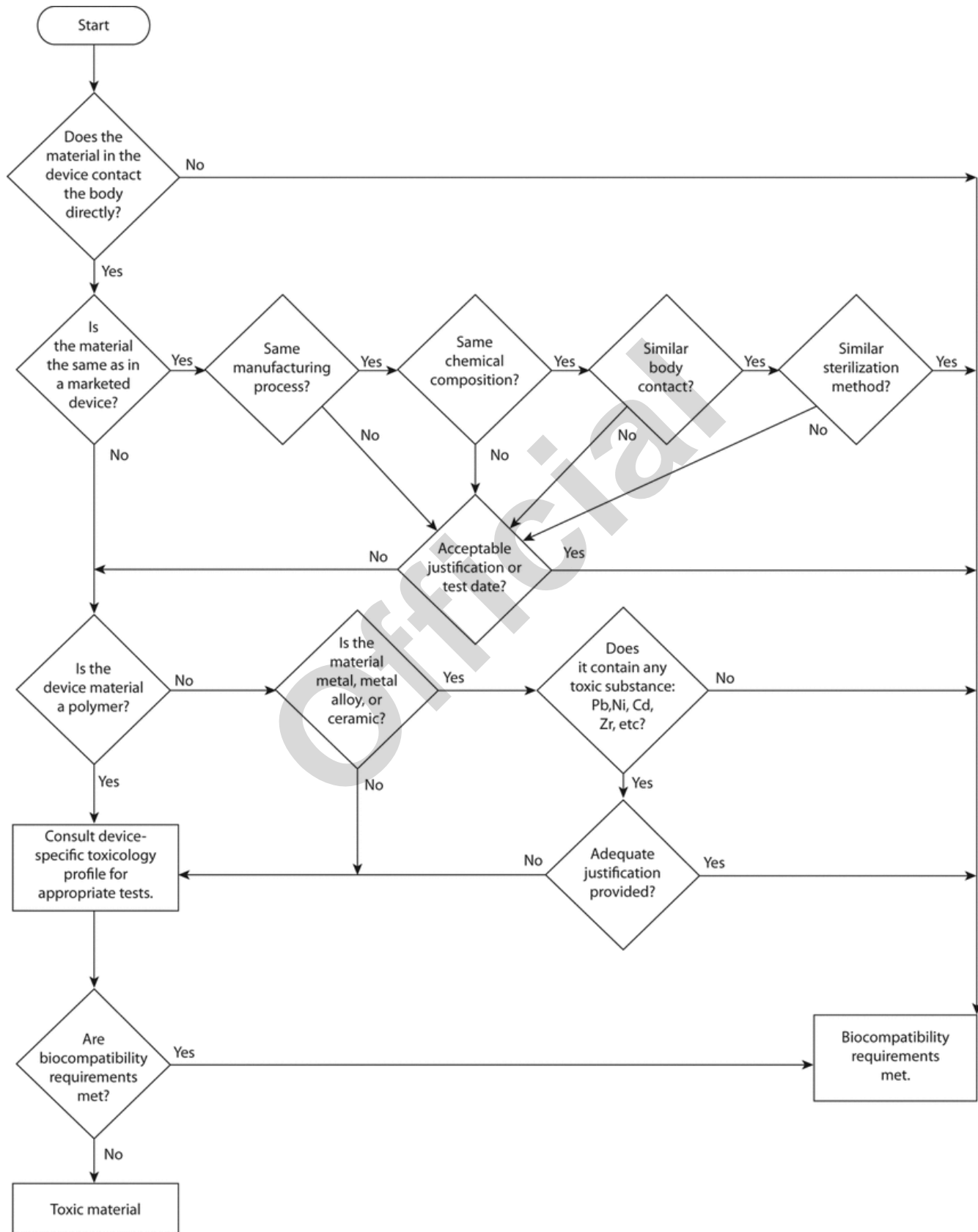


Figure 1. Biocompatibility flowchart.

Categorization of Medical Devices

To facilitate the identification of appropriate testing procedures, medical devices are divided and subdivided, as shown in *Table 2*, according to the nature and extent of their contact with the body. Major categories of medical devices are surface devices, external communicating devices, and implant devices. These are then further subcategorized. Some examples of medical devices and implants belonging to each of the subcategories are also presented in *Table 2*.

Table 2. Classification and Examples of Medical Devices

Device Category	Device Subcategory	Nature or Extent of Contact	Some Examples
Surface Devices	Skin	Devices that contact intact skin surfaces only	Electrodes, external prostheses, fixation tapes, compression bandages, and monitors of various types
	Mucosal Membrane	Devices communicating with intact mucosal membranes	Contact lenses, urinary catheters, intravaginal and intrainestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gas troscopes), endotracheal tubes, bronchoscopes, dental prostheses, orthodontic devices, and intrauterine devices
	Breached or Compromised Surfaces	Devices that contact breached or otherwise compromised body surfaces	Ulcer, burn, and granulation tissue dressings or healing devices and occlusive patches
External Communicating Devices	Blood Path, Indirect	Devices that contact the blood path at one point and serve as a conduit for entry into the vascular system	Solution administration sets, extension sets, transfer sets, and blood administration sets
	Tissue, Bone, or Dentin Communicating	Devices and materials communicating with tissue, bone, or pulp and dentin system	Laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials, and skin staples
	Circulating blood	Devices that contact circulating blood	Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialyzers, dialysis tubing and accessories, hemoadsorbents, and immunoadsorbents
Implant Devices	Tissue or Bone	Devices principally contacting bone or principally contacting tissue and tissue fluid	Examples of the former are orthopedic pins, plates, replacement joints, bone prostheses, cements, and intraosseous devices; examples of the latter are pacemakers, drug supply devices, neuromuscular sensors and simulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants, and ligation clips
	Blood	Devices principally contacting blood	Pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug delivery catheters, and ventricular-assist devices

Test Selection Matrix

The matrix provides guidance on the identification of appropriate biological testing procedures for the three categories of medical devices: tests for *Surface Devices* (see *Table 3*), tests for *External Communicating Devices* (see *Table 4*), and tests for *Implant Devices* (see *Table 5*). Each category of devices is subcategorized and then even further subdivided according to the duration of the contact between the device and the body. The duration of contact is defined as (A) limited (less than 24 hours); (B) prolonged (24 hours to 30 days); or (C) permanent (more than 30 days). The biological effects that are included in the matrix are cytotoxicity, sensitization, irritation or intracutaneous reactivity, systemic toxicity, subchronic toxicity, genotoxicity, implantation, hemocompatibility, chronic toxicity, carcinogenicity, reproductive or developmental toxicity, and biodegradation. The general chapters that contain toxicity testing procedures for these biological effects are indicated in *Table 1*.

Each subcategory in the matrix has an associated panel of testing requirements. Generally, the number of tests in the panel increases as the duration of the contact between the device and the body is extended and as the device or implant comes in closer contact with the circulatory system. Within several subcategories, the option of performing additional tests beyond those required should be considered on a case-by-case basis. Specific situations such as use of permanent implant devices or external communicating devices for pregnant women and children have to be taken into consideration in the manufacturer's decision to include reproductive or developmental testing. Guidance on the identification of possible additional testing procedures is provided in the matrix for each subcategory of medical devices.

GUIDANCE IN SELECTING THE PLASTIC OR OTHER POLYMER CLASS DESIGNATION FOR A MEDICAL DEVICE

To provide guidance on selecting the appropriate plastic or other polymer class designation for a medical device, each subcategory of *Surface Devices* (see *Figure 2*)

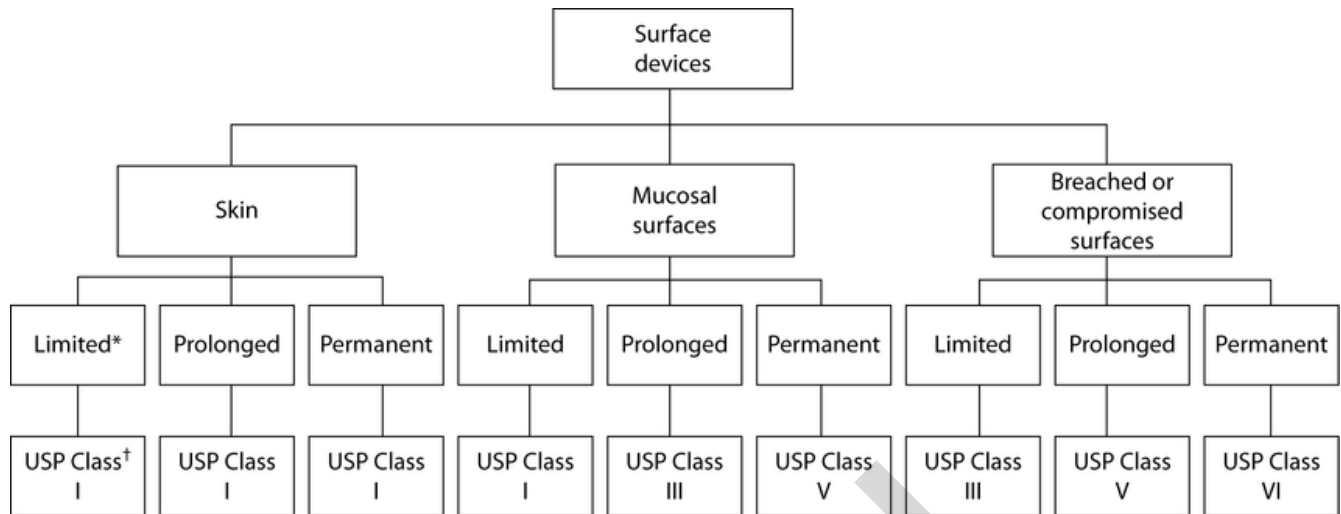


Figure 2. USP plastic and other polymer class requirements for surface devices. *Categorization based on duration of contact: limited—less than 24 hours; prolonged—24 hours to 30 days; permanent—more than 30 days. †USP Plastic Class designation.

and External Communicating Devices (see Figure 3)

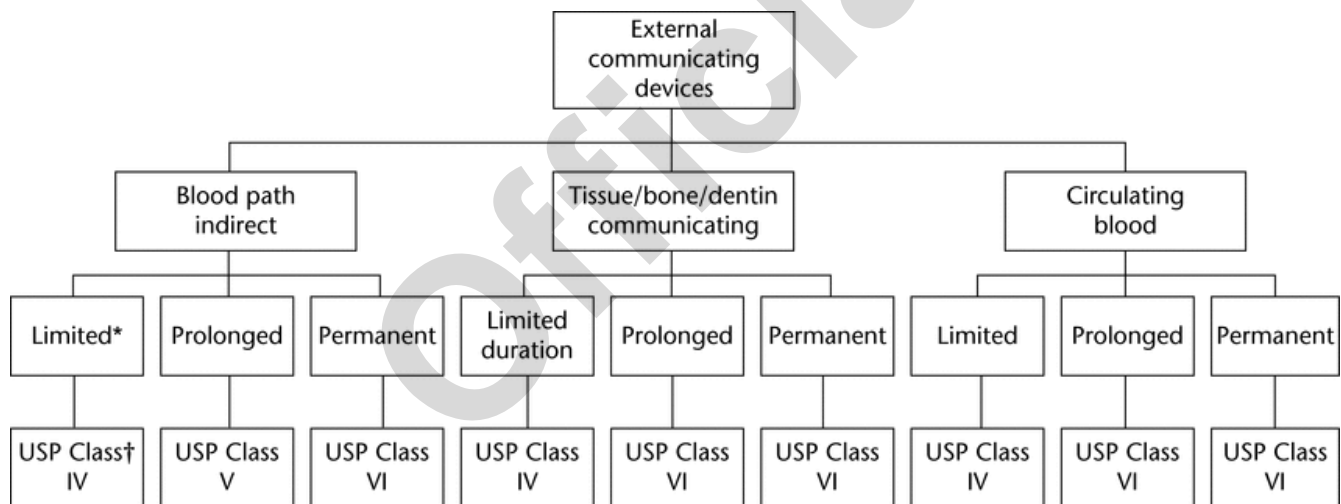


Figure 3. USP plastic and other polymer class requirements for external communicating devices. *Categorization based on duration of contact: limited—less than 24 hours; prolonged—24 hours to 30 days; permanent—more than 30 days. †USP Plastic Class designation.

is assigned a USP Plastic Class designation (see *Biological Reactivity Tests, In Vivo* (88)). If the tests for each USP class designation are not sufficient for a specific device, the manufacturer or the practitioner must develop an appropriate set of tests. The indicated numerical class number increases relative to the duration (risk) of contact between the device and the body. In the category of *Implant Devices*, the exclusive use of class VI is mandatory. The assignment of USP Plastic Class designation is based on the test selection matrices illustrated in *Tables 3, 4, and 5*.

The assignment of a plastic or other polymer class designation to a subcategory is not intended to restrict the use of higher classes of plastics or other polymers. Although the assigned class defines the lowest numerical class of plastic or other polymer that may be used in the corresponding device, the use of a numerically higher class of plastic is optional. When a device can be defined as belonging to more than one device category, the plastic or other polymer should meet the requirements of the highest numerical class.

Table 3. Test Selection Matrix for Surface Devices*

Device Categories		Biological Effect ^b													
Body Contact		Contact Du- ra- tion ^a	Cyto - tox - icity	Sen- siti- za- tion	Irritation or Intracutane- ous Reactivity	Systemic Toxicity (Acute)	Sub- chro nic Tox- icity	Gen- otoxi city	Im- plan- ta- tion	Hemo - compat - ability	Chronic Toxicity	Carci- no - genicity	Reproduc- tive or De- velopment Toxicity	Bio - de- gra- da- tion	
Surface Devices	Skin	A	X	X	X	—	—	—	—	—	—	—	—	—	
		B	X	X	X	—	—	—	—	—	—	—	—	—	
		C	X	X	X	—	—	—	—	—	—	—	—	—	
	Mucosal Mem- brane	A	X	X	X	—	—	—	—	—	—	—	—	—	
		B	X	X	X	O	O	—	O	—	—	—	—	—	
		C	X	X	X	O	X	X	O	—	O	—	—	—	
	Breached or Com- prom- ised Surfaces	A	X	X	X	O	—	—	—	—	—	—	—	—	
		B	X	X	X	X	O	O	—	O	—	—	—	—	—
		C	X	X	X	X	O	X	X	O	—	O	—	—	—

* Adapted from the FDA's Blue Book Memorandum #G95-1 (Table 1. Initial Evaluation Tests for Consideration and Table 2. Supplementary Evaluation Tests for Consideration).

^a Legend A—limited (less than 24 hours); B—prolonged (24 hours to 30 days); C—permanent (more than 30 days).

^b Legend X—ISO evaluation tests for consideration; O—additional tests that may be applicable.

Table 4. Test Selection Matrix for External Communicating Devices*

Device Categories		Biological Effect ^b												
Body Contact		Con - tact Du r - atio n ^a	Cy - to - tox - icity	Sen - siti - za - tion	Irrita - tion or Intra - cutan - eous Re - activity	Systemic Toxicity (Acute)	Sub - chro - nic Toxicity	Geno - toxicity	Implan - tation	Hemo - com - pat - abili - ty	Chro - nic Toxic - ity	Carci - no - genic - ity	Repro - ductive or Develop - ment Tox - icity	Biodegra - dation
External Commun - icating Devices	Blood Path, Indirect	A	X	X	X	X	—	—	—	X	—	—	—	—
		B	X	X	X	X	O	—	—	X	—	—	—	—
		C	X	X	O	X	X	X	O	X	X	X	—	—
	Tissue, Bone, or Dentin Communi - cating	A	X	X	X	O	—	—	—	—	—	—	—	—
		B	X	X	O	O	O	X	X	—	—	—	—	—
		C	X	X	O	O	O	X	X	—	X	X	—	—
	Circulating Blood	A	X	X	X	X	—	O	—	X	—	—	—	—
		B	X	X	X	X	O	X	O	X	—	—	—	—
		C	X	X	X	X	X	X	O	X	X	X	—	—

* Adapted from the FDA's Blue Book Memorandum #G95-1 (Table 1. Initial Evaluation Tests for Consideration and Table 2. Supplementary Evaluation Tests for Consideration).

^a Legend A—limited (less than 24 hours); B—prolonged (24 hours to 30 days); C—permanent (more than 30 days).

^b Legend X—ISO evaluation tests for consideration; O—additional tests that may be applicable.

Table 5. Test Selection Matrix for Implant Devices*

Device Categories		Biological Effect ^b												
Body Contact		Con - tact Dur - ation ^a	Cyto - toxi - city	Sen - siti - za - tion	Irritation or Intra - cutan - eous Re - activity	Sys - temic Toxicity (Acute)	Sub - chro - nic Toxicity	Geno - toxicity	Implan - tation	Hemo - com - pat - abili - ty	Chro - nic Toxic - ity	Carci - no - genic - ity	Re - pro - ductive or De - vel - op - ment Toxicity	Bio - degra - da - tion
Im - plan - t De - vices	Tis - sue or Bone	A	X	X	X	O	—	—	—	—	—	—	—	—
		B	X	X	O	O	O	X	X	—	—	—	—	—
		C	X	X	O	O	O	X	X	—	X	X	—	—
	Blood	A	X	X	X	X	—	—	X	X	—	—	—	—
		B	X	X	X	X	O	X	X	X	—	—	—	—
		C	X	X	X	X	X	X	X	X	X	X	—	—

* Adapted from the FDA's Blue Book Memorandum #G95-1 (Table 1. Initial Evaluation Tests for Consideration and Table 2. Supplementary Evaluation Tests for Consideration).

^a Legend A—limited (less than 24 hours); B—prolonged (24 hours to 30 days); C—permanent (more than 30 days).

^b Legend X—ISO evaluation tests for consideration; O—additional tests that may be applicable.