BIOMERICS

Quadrathane™ and Quadraflex™

Biocompatibility Guide

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Quadrathane™ and Quadraflex™

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Introduction

Biocompatibility is an essential consideration when evaluating a material for use in a biomedical application. Biomerics adheres to the highest standards of biocompatibility to ensure its products are safe for use, and has tested its materials according to various regulatory and industry standards adopted for the evaluation of biocompatibility of polymeric materials. The introduction section of this guide provides a summary of the most common regulatory standards used in the medical device, pharmaceutical, and biotech industries.

Biomerics has completed a variety of standard test on its biomedical urethanes to provide customers with information that can be applied to their specific application. These test results are outlined by product family in this guide. This guide is periodically updated as regulations change and new test data becomes available. Please contact your sales representative for the latest data or specific test results.

FDA Regulations and Standards

Medical Devices. The U.S. Food and Drug Administration requires biological evaluation of medical devices submitted either for premarket notification via the 510(k) process or for premarket approval. The FDA has adopted the ISO-10993 standard (see below) as its criteria for guiding the selection of biocompatibility testing for a given type of device. The ISO standard lists recommended tests based on the type and duration of body contact. Guidance from the FDA in Memorandum #G95-1 stresses that while ISO-10993 should be used as a guide, some devices may require fewer or more tests than what is indicated in ISO-10993, and manufacturers are encouraged to discuss testing plans with the appropriate review division in the Office of Device Evaluation within the Center for Devices and Radiological Health prior to initiation of testing.

Biocompatibility testing must be completed on the finished device. Generally, demonstration of biocompatibility of each individual material component alone is not accepted by the FDA. However, device manufacturers often screen potential raw materials or components (colorants, additives, etc…) for compatibility by conducting a subset of the required tests for the raw materials, or by taking note of test results performed by the raw material manufacturer. To provide its customers with the confidence that devices made from Biomerics polyurethane resins will pass the biocompatibility tests required by the FDA, Biomerics has conducted a series of biocompatibility tests (via a third-party testing laboratory) on its materials and provides a summary of the test results in this document.

Food Contact. The FDA also regulates plastics used in food contact applications. These regulations and requirements are found in Title 21, Section 177 of the Code of Federal Regulations. Subsection 177.1680 deems polyurethane resins made from certain specified raw materials as safe for use in food contact applications, subject to passing an abrasion test in the form of the finished product. All of the raw materials used to manufacture Quadraflex™ ALE and ARE resins are included in this list.

ISO-10993 Standard

ISO-10993 "Biological Evaluation of Medical Devices" details a set of standards for evaluating the biocompatibility of a medical device or its components. Part 1 of the standard guides the appropriate selection of which tests may be necessary for a given type of device. The remaining Parts of ISO-10993 (-2 through -20) consist of the specific test standards for each of the following categories. Depending on the nature and duration of body contact of a medical device, tests for some or all of the following effects may be recommended:

- Cytotoxicity (ISO 10993-5)
- Sensitization (ISO 10993-10)
- Irritation or intracutaneous reactivity (ISO 10993-10)
- Acute systemic toxicity (ISO 10993-11)
- Subacute/subchronic toxicity (ISO 10993-11)
- Genotoxicity (ISO 10993-3)
- Implantation (ISO 10993-6)
- Hemocompatibility (ISO 10993-4)
- Chronic toxicity (ISO 10993-11)
- Carcinogenicity (ISO 10993-3)

For each of the above categories, one or more specific test options are described in the corresponding Part of the standard. A subset of tests commonly used for materials screening is described below in the Test Descriptions section of the guide.

Table 1, FDA / ISO-10993 Evaluation Tests for Consideration, contains a matrix identifying the tests that are recommended for each device category, contact type, and contact duration. For example, an inflatable blood pressure cuff is a surface device that contacts the skin for less than 24 hours. This type of device corresponds to the topmost row of Table 1, for which cytotoxicity, sensitization, and irritation tests are recommended. On the other end of the spectrum, a chronic dialysis catheter is an implant device with blood contact for potential use exceeding 30 days. This corresponds to the bottommost row of Table 1, for which all ten types of tests are indicated. ISO-10993 also contains standards for biodegradation (Part 9) and reproductive and developmental toxicity (Part 3), although neither of these tests is specifically recommended for any of the device classes shown in Table 1.

Table 1. FDA / ISO-10993 Evaluation Tests for Consideration.

Device Category			Biological Effect									
Body Contact		Contact duration A – Limited (≤ 24 h) B – Prolonged (24 h to 30 days) C – Permanent (> 30 days)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Systemic Toxicity (Acute)	Sub-chronic Toxicity (Sub-acute Toxicity)	Genotoxicity	Implantation	Hemocompatibility	Chronic toxicity	Carcinogenicity
Surface devices	Skin	A	X	X	X							
		B	X	X	X							
		C	X	X	X							
	Mucosal membrane	A	X	X	X							
		B	X	X	X	O	O		O			
		C	X	X	X	O	X	X	O		O	
	Breached or compromised surfaces	A	X	X	X	O						
		B	X	X	X	O	O		O			
		C	X	X	X	O	X	X	O		O	
External communicating 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/dentin communicating	A	X	X	X	O						
		B	X	X	O	O	O	X	X			
		C	X	X	O	O	O	X	X		O	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
Implant devices	Tissue/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

X = ISO Evaluation Tests for Consideration
O = Additional Tests which may be applicable
Note * For all devices used in extracorporeal circuits

Information tabulated from FDA Memorandum - #G95-1, "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,'" Tables 1 and 2 (Attachments A and B)

USP Class VI Standard

U.S. Pharmacopeia (USP) is a private (non-governmental) organization that "promotes the public health by establishing state-of-the-art standards to ensure the quality of medicines and other health care technologies". Chapter 88of the standard delineates a set of *in vivo* biological reactivity tests to conduct biocompatibility screening of plastics. Six classes of plastics are defined based on the application and duration (similar to ISO-10993), and each class has a different set of testing requirements. The most stringent, Class VI, requires three types of tests:

- Systemic injection test
- Intracutaneous test
- Implantation test

USP standards for the first two tests in the list above are nearly identical to ISO-10993 standards for acute systemic toxicity and irritation/intracutaneous reactivity, respectively. The implantation test also has much in common with the standards in Part 6 of ISO-10993 (see the Test Descriptions section below for details).

USP Class VI tests are often of more interest to pharmaceutical manufacturers than to those in the medical device marketplace. As stated above, the FDA requires testing of finished devices; however, the demonstration of biocompatibility of Biomerics polyurethane resins according to USP Class VI standards is provided as an aid to device manufacturers in their materials selection process.

Other Industry Standards

Animal Derived Component Free Origin

The pharmaceutical, food, and biomedical industries often desire that materials used in these applications be free of animal based raw materials – or animal derived component free (ADCF). To the best of its knowledge, Biomerics does not use any products of animal origin in the production of its Quadrathane™ ALC, Quadrathane™ ARC, Quadraflex™ ALE, Quadraflex™ ARE, or Quadraplast™ AR resins.

Phthalate Free

Many elastomers, such as PVC, use plasticizers such as phthalate esters to increase flexibility and soften elastomers. Many of these plasticizers have been shown to leach and provide health risks. Biomerics Quadrathane™ ALC, Quadrathane™ ARC, Quadraflex™ ALE, Quadraflex™ ARE, and Quadraplast™ AR resins **do not** contain or come into contact with phthalate-based plasticizers. No plasticizers are used in the manufacture of Biomerics polyurethanes.

Evaluation of Biocompatibility

Test Descriptions

ISO-10993 Biological Evaluation Tests:

Cytotoxicity (ISO-10993-5)

MEM elution: This test is a common cytotoxicity assessment designed to assess the toxicity to cells of leachable components of the material. The material is extracted in cell culture media (Minimum Essential Medium, or "MEM"). Extracts are placed in contact with a monolayer of L-929 mouse fibroblast cells. Cells are incubated at controlled temperature and CO_2 level for an additional period of time, after which they are examined microscopically for indications of cytotoxicity including malformation, degeneration, and lysis.

Irritation or intracutaneous reactivity (ISO-10993-10)

Intracutaneous test: This test involves the intradermal injection of material extracts into a rabbit. The injection sites are then observed over a period of time and scored for edema (swelling) and erythema (redness).

Systemic toxicity (ISO-10993-11)

Acute systemic toxicity test: This test detects leachable components of the material that produce systemic (as opposed to local) toxic effects. The material is extracted in one or more solvents, and mice are injected either intravenously or intraperitoneally, depending on the extracting media, with the extracts as well as negative control blanks. The mice are evaluated immediately following injection and at four additional time points for mortality, weight loss, or clinical signs of pharmacological or toxicological effects.

Material mediated pyrogen test: This test evaluates the potential of the material to induce a pyrogenic response (fever). It can be performed *in vitro* using the bacterial endotoxin test, or *in vivo* using a rabbit model. In the latter case, the rabbit is injected with an extract of the material and observed for signs of fever.

Genotoxicity (ISO-10993-3)

Ames mutagenicity test: This test evaluates the capacity of sample extracts to induce point mutations in DNA. An extract of the material is introduced to a culture of a strain of the bacteria *Salmonella typhimurium* that carries mutations in genes involved in the synthesis of histidine (an essential amino acid), such that these bacteria do not grow unless they are cultured in media containing histidine. Any mutagens present in the extract have the potential to cause a mutation reverting the bacteria to permit growth without an external source of histidine. The mutagenicity of the extract is therefore proportional to the number of bacterial colonies observed growing in histidine-free media.

Hemocompatibility (ISO-10993-4)

Hemolysis test: This procedure is designed to assess blood compatibility for materials intended for blood contacting applications. Standard practices are set forth in ASTM F756, which includes an extract method as well as a direct contact method. Both methods rely on the measurement of free hemoglobin

released into the plasma when blood cells are damaged. Depending on which method is used, either the material or its extracts are incubated with diluted blood. During this incubation, any lysis of blood cells releases hemoglobin into the plasma. The solution is centrifuged, and the supernatant (containing the plasma and any released hemoglobin) is reacted with Drabkin's reagent. The reaction product between hemoglobin and Drabkin's reagent is a cyanoderivative that is easily quantified by measuring absorbance at 540 nm with a spectrophotometer.

USP Class VI Plastics *In Vivo* Biological Reactivity Tests:

Acute Systemic Injection

Similar to the ISO-10993 acute systemic toxicity test, this test consists of an injection of mice with extracts of the material in one or more solvents, followed by observation of the mice for signs of toxicity.

Intracutaneous Reactivity

This test assesses the potential for local irritation of the material. The material is extracted in one or more solvents, and the extracts and negative control blanks are injected intracutaneously into albino rabbits, which are observed daily for redness and/or swelling at the injection site.

Intramuscular Implant

This test is designed to evaluate the biocompatibility of materials in direct contact with living tissue. Strips of the material and a HDPE control are implanted in the paravertebral muscles of a rabbit. Following the implant period, the rabbit is euthanized, and the implant site is examined for hemorrhaging, necrosis, discoloration, and infection. Additionally, encapsulation of the sample is evaluated by measuring the width of the capsule.

Other Tests:

USP Physicochemical Tests for Plastics

This series of tests is used to determine certain chemical and physical properties of leachable components of the material. The material is extracted in purified water, and the extracts are subjected to a variety of tests.

Buffering Capacity Test: This test evaluates the acidity or alkalinity of the extract by titration with either HCl or NaOH (depending on the starting pH of the extract) to a pH of 7.0.

Heavy Metals Test: This test is used to detect the presence of certain metals such as lead, zinc, tin, etc. In this test, the extract is mixed with thioacetamide, which reacts with such metals to form metal sulfide precipitates that are visibly detectable by a darkening or discoloration of the solution.

The Nonvolatile Residue Test: This test measures the total content of the extract by evaporation of the water and any volatile components, followed by weighing the residue.

Residue on Ignition Test: When the Nonvolatile Residue Test results exceed a certain value, a Residue on Ignition Test (sometimes referred to as the Sulfated Ash Test) is conducted. The extract is mixed with sulfuric acid and subjected to intense heat in a crucible to burn off the carbon content. Finally, the residue is weighed.

Biomerics Polyurethane Resin Families

Biomerics tested representative samples from each of five product families, grouped according to polyol type and isocyanate type, as summarized in Table 2. Within each product family, a variety of clear and radiopaque grades are offered. Each grade of material within a single family is made using the same polyol, chain extender, isocyanate, and additives. The only difference between grades within the same family is the ratio of the respective raw materials selected to result in a targeted hardness. Therefore, the biocompatibility of different durometer grades is expected to be the same for all grades within a product family, including blends of different grades.

Table 2. Biomerics Product Families.

Product Family	Polyol Type	Isocyanate Type
Quadrathane™ ALC	Polycarbonate	Aliphatic
Quadrathane™ ARC	Polycarbonate	Aromatic
Quadraflex™ ALE	Polyether	Aliphatic
Quadraflex™ ARE	Polyether	Aromatic

Quadrathane™ ALC Resin Results

The Quadrathane™ ALC family of resins comprises a group of aliphatic polycarbonate-based polyurethanes. It is offered in a variety of clear and radiopaque standard grades. Representative samples from this family of materials were tested for biocompatibility according to ISO 10993 and USP Class VI standards by a third party testing laboratory. A summary of the results is shown in Table 3; complete reports are available upon request.

Table 3. Quadrathane™ ALC Biocompatibility Test Results.

Test	ISO 10993	USP Class VI	Acceptance Criteria	Result	Note
MEM Elution	✓		≤ 2	0	Pass
Hemolysis, Extract	✓		≤ 5	0	Pass
Hemolysis, Direct Contact	✓		≤ 5	0	Pass
Acute Systemic Toxicity, Normal Saline	✓	✓	Fatalities < 2 Clin. tox. < 3 Wt. loss < 3	0 0 0	Pass
Acute Systemic Toxicity, Cottonseed Oil	✓	✓	Fatalities < 2 Clin. tox. < 3 Wt. loss < 3	0 0 0	Pass
Acute Systemic Toxicity, 5% EtOH in Saline		✓	Fatalities < 2 Clin. tox. < 3 Wt. loss < 3	0 0 0	Pass
Acute Systemic Toxicity, Polyethylene Glycol 400		✓	Fatalities < 2 Clin. tox. < 3 Wt. loss < 3	0 0 0	Pass
Intramuscular Implant		✓	≤ 1	0.0	Pass, Normal
Physicochemical: Buffering Capacity			≤ 10 mL	0.5 mL	Pass
Physicochemical: Nonvolatile Residue			≤ 15 mg	< 1 mg	Pass
Physicochemical: Heavy Metals			1 ppm	< 1 ppm	Pass