



Biocompatibility Evaluation Endpoints

X = Prerequisite information needed for a risk assessment.

E = Endpoints to be evaluated in the risk assessment either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the end point does not require an additional data set assessment.

O = Additional FDA recommended endpoints for consideration. All X's, O's, and E's should be addressed in the biological safety evaluation.

Device Characterization			Biological Effect																
Nature of Body Contact		Contact Duration	Physical and/or Chemical Information	Cytotoxicity	Sensitization	Irritation / Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute Toxicity	Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity	Degradation		
Category	Contact	A: Limited (≤ 24h)																	
		B: Prolonged (> 24h to 30d)																	
		C: Permanent (> 30d)																	
Surface Device	Intact Skin	A	X	E	E	E													
		B	X	E	E	E													
		C	X	E	E	E													
	Mucosal Membrane	A	X	E	E	E													
		B	X	E	E	E	E	O	E	O		E							
		C	X	E	E	E	E	E	O	E	E	E	E		E				
	Breached or Compromised Surface	A	X	E	E	E	E	E											
		B	X	E	E	E	E	E	E	O		E							
		C	X	E	E	E	E	E	E	E	E	E	E		E	E			
Externally-Communicating Device	Blood Path, Indirect	A	X	E	E	E	E	E					E						
		B	X	E	E	E	E	E	E	O		E							
		C	X	E	E	E	E	E	E	E	E	E	E	E	E	E			
	Tissue / Bone / Dentin	A	X	E	E	E	E	E											
		B	X	E	E	E	E	E	E	O	E	E							
		C	X	E	E	E	E	E	E	E	E	E	E		E	E			
	Circulating Blood	A	X	E	E	E	E	E				E		E					
		B	X	E	E	E	E	E	E	O	E	E	E						
		C	X	E	E	E	E	E	E	E	E	E	E	E	E	E			
Implant Device	Tissue / Bone	A	X	E	E	E	E	E											
		B	X	E	E	E	E	E	E	O	E	E							
		C	X	E	E	E	E	E	E	E	E	E		E	E				
	Blood	A	X	E	E	E	E	E				E	E	E					
		B	X	E	E	E	E	E	E	O	E	E	E						
		C	X	E	E	E	E	E	E	E	E	E	E	E	E	E			

Sample Requirements for Standard Studies

Cytotoxicity Tests	
MTT	30 cm ² if < 0.5 mm thick; 15 cm ² ≥ 0.5 mm; 1 gram
Neutral Red Uptake (NRU)	30 cm ² if < 0.5 mm thick; 15 cm ² ≥ 0.5 mm; 1 gram
MEM Elution	USP: 120 cm ² if < 0.5 mm thick; 4 grams
	ISO: 120 cm ² if < 0.5 mm thick; 60 cm ² if > 0.5 mm thick; 4 grams
	MHLW: 8 grams; 120 cm ² , 240 cm ²
Agar Diffusion	USP: 2 pieces, each 1 cm ²
	ISO: 3 pieces, each 100 mm ²

Genotoxicity / Mutagenicity Tests	
Ames Assay	ISO: 240 cm ² if < 0.5 mm thick; 120 cm ² if ≥ 0.5 mm thick; 8 grams
	MHLW: 20 mL; 8 grams; 120 cm ² ; 240 cm ²
Mouse Micronucleus Assay	ISO: 600 cm ² if < 0.5 mm; 300 cm ² if ≥ 0.5 mm thick; 25 grams
Chromosomal Aberration Assay	ISO: 240 cm ² if < 0.5 mm thick; 120 cm ² if ≥ 0.5 mm thick; 8 grams
	MHLW: 8 grams, 120 cm ² or 240 cm ²
Mouse Lymphoma Forward Mutation Assay	ISO: 240 cm ² if < 0.5 mm thick; 120 cm ² if ≥ 0.5 mm thick, 8 grams

Hemocompatibility Tests	
Hemolysis Complete (ASTM Method)	ISO: 500 cm ² if < 0.5 mm thick; 250 cm ² if ≥ 0.5 mm thick; 40 grams
Hemolysis Direct (ASTM Method)	ISO: 250 cm ² if < 0.5 mm thick; 125 cm ² if ≥ 0.5 mm thick; 20 grams
Hemolysis Indirect (ASTM Method)	ISO: 250 cm ² if < 0.5 mm thick; 125 cm ² if ≥ 0.5 mm thick; 20 grams
	MHLW: 600 cm ² if < 0.5 mm thick, 300 cm ² if ≥ 0.5 mm thick; 25 grams
Complement Activation Direct	ISO: 75 cm ² if < 0.5 mm thick; 50 cm ² if ≥ 0.5 mm thick; 2.5 grams
Complement Activation Indirect	ISO: 10 cm ² if < 0.5 mm thick; 5 cm ² if ≥ 0.5 mm thick; 1 grams
In Vitro Hemocompatibility Direct	ISO: 75 cm ² if < 0.5 mm thick; 50 cm ² if ≥ 0.5 mm thick; 2.5 grams
In Vitro Hemocompatibility Indirect	ISO: 10 cm ² if < 0.5 mm thick; 5 cm ² if ≥ 0.5 mm thick; 1 grams
Prothrombin Time Direct	ISO: 75 cm ² if < 0.5 mm thick; 50 cm ² if ≥ 0.5 mm thick; 2.5 grams
Prothrombin Time Indirect	ISO: 10 cm ² if < 0.5 mm thick; 5 cm ² if ≥ 0.5 mm thick; 1 grams
Thrombogenicity in Dogs	ISO: 2 units

General Chemistry Tests	
Physicochemical and other Compendial Tests	USP: 20 grams or 600 cm ² / Inquire

In Vivo Tests	
Kligman Maximization	ISO: 720 cm ² if < 0.5 mm thick; 360 cm ² if ≥ 0.5 mm thick; 24 grams
	MHLW: Inquire
Buehler Closed Patch	ISO: 120 pieces of 2.5 cm patches each; 60 grams
Intracutaneous Injection	ISO: 240 cm ² < 0.5 mm thick; 120 cm ² ≥ 0.5 mm thick; 8 grams
	MHLW: 16 grams; 240 cm ² ; 480 cm ²
Primary Skin Irritation	ISO: 240 cm ² < 0.5 mm thick; 120 cm ² ≥ 0.5 mm thick; 8 grams
Acute Systemic Injection	ISO: 240 cm ² < 0.5 mm thick; 120 cm ² ≥ 0.5 mm thick; 8 grams
	MHLW: 16 grams; 240 cm ² ; 480 cm ²
Material Mediated Rabbit Pyrogen	USP: 600 cm ² if < 0.5 mm thick; 300 cm ² if ≥ 0.5 mm thick; 20 grams
	ISO: 600 cm ² if < 0.5 mm thick; 300 cm ² if ≥ 0.5 mm thick; 20 grams
	MHLW: 600 cm ² if < 0.5 mm thick; 300 cm ² if ≥ 0.5 mm thick; 20 grams
Class Tests per USP	Class I: 120 cm ² < 0.5 mm thick; 60 cm ² ≥ 0.5 mm thick; 4 grams
	Class II: 240 cm ² < 0.5 mm thick; 120 cm ² ≥ 0.5 mm thick; 8 grams
	Class III: 480 cm ² < 0.5 mm thick; 1200 cm ² ≥ 0.5 mm thick; 16 grams
	Class IV: 360 cm ² < 0.5 mm thick; 180 cm ² ≥ 0.5 mm thick; 12 grams
	Class V: 480 cm ² < 0.5 mm thick; 240 cm ² ≥ 0.5 mm thick; 16 grams
	Class VI: 550 cm ² < 0.5 mm thick; 275 cm ² ≥ 0.5 mm thick; 22 grams
Implants (Muscle, Subcutaneous, Bone, etc.)	<ul style="list-style-type: none"> • 2 Week • 4 Week • 6 Week • 8 Week • 12 Week • 13 Week • 26 Week • 52 Week • 1 & 4 Week Implant
	ISO: 18 strips per time point, each strip 1 mm x 10 mm. Sample should be supplied by sponsor in specified size, separately packaged and sterilized, and edges should be rounded and smooth. Additional configurations can be considered.
	MHLW: 24 pieces, each 1 mm x 1mm x 10mm

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