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.*

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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	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		
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		
	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		
	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		
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		

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.)	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.
• 2 Week	
• 4 Week	
• 6 Week	
• 8 Week	
• 12 Week	
• 13 Week	
• 26 Week	
• 52 Week	
• 1 & 4 Week Implant	MHLW: 24 pieces, each 1 mm x 1mm x 10mm