MICROFABRICA®

MICA Freeform™

MATERIALS DOSSIER

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MICROFABRICA®

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Palladium Materials Data Sheet

Composition			
Palladium	99.99%	99.99%	
Physical Properties			
Crystal Structure	FCC	FCC	
Resistivity @ RT	14.9µohm-cm	5.87	µohm-in
Density	12g/cc	0.43	lb/in³
Thermal Conductivity (RT)	71W/m-K	494	BTU-in/hr-ft²
CTE (RT)	11.76µm/m-°C	6.5	µin/in-°F
Melting Point	1552°C	2826	°F
Mechanical Properties*			
Yield Strength (0.2%)	1,100MPa	160	x 10³ psi
Young's Modulus	110GPa	16	x 10⁶ psi
Tensile Elongation	5%	5%	
Ultimate Tensile Strength	1,500MPa	220	x 10³ psi
Hardness	400HV	41	HRC
Poissons Ratio	0.39	0.39	

Valloy-120™ Materials Data Sheet

Composition		
Nickel	80.00%	80.00%
Cobalt	20.00%	20.00%
Physical Properties		
Crystal Structure	FCC	FCC
Resistivity @ RT	11.6µohm-cm	4.57µohm-in
Density	8.9g/cc	0.32lb/in³
Thermal Conductivity (RT)	91W/m-K	631BTU-in/hr-ft²
CTE (RT)	13.4µm/m-°C	7.4µin/in-°F
Melting Point	1726°C	3139°F
Mechanical Properties[1)]		
Yield Strength (0.2%)	900MPa	130x 10³ psi
Young's Modulus	170GPa	25x 10⁶ psi
Tensile Elongation	3%	3%
Ultimate Tensile Strength	1,100MPa	160x 10³ psi
Hardness	425HV	43HRC
Poissons Ratio	0.31	0.31

Palladium Materials Comparison Table

		as cast/drawn	Palladium (as fabricated)
UTS	MPa	896	1,500
Elongation		1-2%	5%
Hardness	HV (Vickers)	150-180	400
Modulus of Elasticity	GPa	200-215	110
Electrical Resistivity (@20C)	ohm - meters	2.50E-07	1.49E-07
CTE (0-100C)	/K	8.40E-06	1.18E-05

		Pt-10% Ir as cast/drawn	Microfabrica Palladium (as fabricated)
UTS	ksi	130	220
Elongation		1-2%	5%
Hardness	HV (Vickers)	150-180	400
Modulus of Elasticity	10^6 psi	29-31.2	16
Electrical Resistivity (@68F)	ohm - in	9.84E-06	5.87E-06
CTE (32-212F)	/F	4.67E-06	6.56E-06

Valloy-120™ Materials Comparison Table

		Stainless Alloys			Microfabrica
		304 (half hard)	304 (Full hard)	17-4 H900	Valloy
UTS	MPa	1035	1275	1340	1,100
Yield .2%	MPa	760	965	1240	900
Elongation		10%	2-5%	7%	3%
Hardness	Rockwell C	30-32	40	44	43
Modulus of Elasticity	GPa	200	200	196	170
Electrical Resistivity (@20C)	ohm - meters	7.20E-07	7.20E-07	7.70E-07	1.16E-07
CTE (0-100C)	/K	1.66E-05	1.66E-05	1.08E-05	1.34E-05

		Stainless Alloys			Microfabrica
		304 (half hard)	304 (Full hard)	17-4 H900	Valloy
UTS	ksi	150	185	195	160
Yield .2%	ksi	110	140	180	130
Elongation		10%	2-5%	7%	3%
Hardness	Rockwell C	30-32	40	44	43
Modulus of Elasticity	10^6 psi	29	2900%	28	25
Electrical Resistivity (@68F)	ohm - in	2.84E-05	2.84E-05	3.03E-05	4.57E-06
CTE (32-212F)	/F	9.20E-06	9.20E-06	6.00E-06	7.44E-06

MICROFABRICA®

BIOCOMPATIBILITY

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Biocompatibility of Palladium

Introduction

The primary standard for biological evaluation of medical devices is International Standard ISO 10993. An overview of test requirements is provided in ISO 10993-1:2003(E) [Reference 1]. For both ISO and FDA, the chart shown in Appendix 1 [Reference 2] applies. For the Japanese Ministry of Health and Welfare, the chart shown in Appendix 2 [Reference 2] applies. The categorization of medical devices according to the nature and duration of contact with the body is very similar between the ISO/FDA and Japanese MHW guidelines, though there are some differences with respect to specific test procedures and protocols. Microfabrica has opted to test its materials according to the criteria for a *permanent implant device having blood contact* (shown as the bottom row in the tables of Appendices 1 and 2). Per both tables, the prescribed tests are therefore:

- Cytotoxicity
- Sensitization
- Irritation or intracutaneous reactivity
- Acute systemic toxicity
- Subacute and subchronic toxicity
- Genotoxicity
- Pyrogen
- Implantation
- Haemocompatibility
- Chronic toxicity
- Carcinogenicity

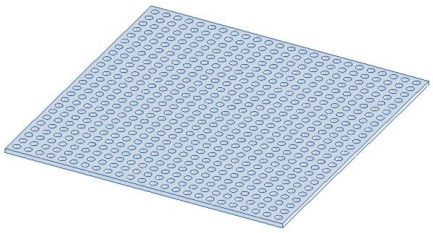

Figure 1. Single layer Pd test specimen.

Biocompatibility of Palladium

Brief descriptions of these tests are provided in Appendix 3. Suggestions for specific tests to perform from the above list, as well as test protocols, were made by the primary independent testing lab performing the biocompatibility tests (Wuxi AppTec) and Microfabrica consultants. The resulting test plan proceeded as follows:

- Tests were performed using single-layer test specimens such as the perforated square shown in Figure 1. Implantation tests were performed with non-perforated disk-shaped test specimens that were steam sterilized. In the case of the pyrogen test, it was performed using a three-layer specimen sterilized using the irradiation method.
- All tests were performed non-GLP (Good Laboratory Practice) since the tests were aimed at characterizing MICA Freeform™ materials, rather than final devices.
- The MEM Elution test for cytotoxicity was selected.
- An intracutaneous reactivity test was selected.
- The Ames test was selected as the only genotoxicity test to be performed.
- Implantation tests in rabbit muscle were chosen to be for 2 and 12-week duration.
- Haemocompatibility tests were chosen to encompass direct contact hemolysis (ASTM), platelet and leukocyte counts, and partial thromboplastin time.
- Chronic toxicity and carcinogenity tests were not performed.
- Extraction protocols were chosen to be 121° C for 1 hr.
- Extraction vehicles and sterilizations were chosen as follows:
    - Normal saline and cottonseed oil for the sensitization test (no sterilization)
    - Normal saline and cottonseed oil for the acute systemic injection test (steam)
    - Normal saline and cottonseed oil for the intracutaneous reactivity test (steam)
    - Normal saline for the pyrogen test (radiation)
    - Normal saline for the subchronic intravenous toxicity test (steam)
    - Cottonseed oil for the subacute intraperitoneal toxicity test (steam)
    - Saline/dimethylsulfoxide for the Ames test (no sterilization)
    - E-MEM for the MEM Elution cytotoxicity test (steam)
- Extraction ratios were chosen to be 4g/20 mL, 60 cm^2/20 mL, 120 cm^2/20 mL, and 4 cm^2/1 mL, 21 cm^2/7 mL, depending on the test.

Biocompatibility of Palladium

Test Results

The results of testing the biocompatibility of palladium are shown in Table 1.

Table 1. Test results for Microfabrica palladium

Test	Result
Cytotoxicity (ISO)	Excellent: 0 cytotoxicity score, no cell lysis, non-toxic
Sensitization (ISO maximization)	Excellent: 0% sensitization response
Intracutaneous irritation (ISO)	Excellent: Negligible primary irritation index
Acute systemic toxicity (USP, ISO)	Excellent: No evidence or systemic toxicity
Subacute intraperitoneal toxicity (ISO)	Excellent: Negative for signs of systemic toxicity
Subchronic intravenous toxicity (ISO)	Excellent: Negative for signs of systemic toxicity
Ames mutagenicity (ISO)	Excellent: Non-mutagenic
Pyrogen (ISO)	Excellent: Non-pyrogenic
2- and 12-week rabbit muscle implantation (ISO)	Excellent: Non-Irritant
Haemocompatibility—Hemolysis (ASTM)	Excellent: Hemolytic index 0.4% (non-hemolytic)
Haemocompatibility—Partial thromboplastin time (ISO)	Excellent: Non-activator of intrinsic coagulation pathway
Haemocompatibility—Platelet and leukocyte counts (ISO)	Excellent: Equivalent to HDPE

Biocompatibility of Palladium

Conclusions

The test results summarized in Table 1 indicate that palladium is a suitable material for short-term (<24 hours) exposure applications in manufacturing surface and external devices which work in contact with skin or mucosal membranes, breached or compromised surfaces, bone, dentin, and circulating blood. Palladium is also suitable for short- and long-term implanation in the body and the circulatory system.

Since the material has good corrosion resistance, we do not consider that the material biocompatibility can be influenced by the sterilization method. For pyrogenecity, the biocompatibility result may be directly dependent on the sterilization method and the ability of this method to eliminate the pyrogenic effect induced by the water based processes.

References

[1] *Biological evaluation of medical devices — Part 1: Evaluation and testing*, Third edition 2003-08-01, reference number ISO 10993-1:2003(E).

[2] Vasudev P. Anand, “Biocompatibility Safety Assessment of Medical Devices: FDA/ISO and Japanese Guidelines”, Medical Device & Diagnostic Industry, January 2000. Available online at http://www.devicelink.com/mddi/archive/00/01/017.html.

Biocompatibility of Palladium

APPENDICES

Appendix 1: ISO/FDA test chart [Reference 2]

Device Categories			Initial Evaluation								Supplemental Evaluation	
	Body Contact	Contact Duration	Cytotoxicity	Sensitization	Imitation or intracutaneous reactivity	Systemic toxicity (acute) pyrogenicity	Subchronic toxicity	Genotoxicity	Implantation	Hemocompatability	Chronic toxicity	Carcinogenicity
Surface Devices	Skin	A	•	•	•							
		B	•	•	•							
		C	•	•	•							
	Mucosal Membrane	A	•	•	•							
		B	•	•	•	0	0		0			
		C	•	•	•	0	•	•	0		0	
	Breached / compromised surface	A	•	•	•	0						
		B	•	•	•	0	0		0			
		C	•	•	•	0	•	•	0		0	
External Communicating Devices	Blood path indirect	A	•	•	•	•				•		
		B	•	•	•	•	0			•		
		C	•	•	0	•	•	•	0	•	•	•
	Tissue / bone dentin communicating	A	•	•	•	0						
		B	•	•	0	0	0	•	•			
		C	•	•	0	0	0	•	•		0	•
	Circulating blood	A	•	•	•	•		0		•		
		B	•	•	•	•	0	•	0	•		
		C	•	•	•	•	•	•	0	•	•	•
Implant Devices	Bone / tissue	A	•	•	•	0						
		B	•	•	0	0	0	•	•			
		C	•	•	0	0	0	•	•		•	•
	Blood	A	•	•	•	•			•	•		
		B	•	•	•	•	0	•	•	•		
		C	•	•	•	•	•	•	•	•	•	•

A = Limited exposure (≤ 24 hours) B = Prolonged exposure (24 hours - 30 days) C = Permanent contact (> 30 days)

• = FDA and ISO evaluation tests 0 = Additional tests for FDA

Biocompatibility of Palladium

APPENDICES

Appendix 2: Japanese Ministry of Health and Welfare (MHW) test chart [Reference 2]

Device Categories			Initial Evaluation								Supplemental Evaluation	
	Body Contact	Contact Duration	Cytotoxicity	Sensitization	Imitation or intracutaneous reactivity	Systemic toxicity (acute) pyrogenicity	Subchronic toxicity	Genotoxicity	Implantation	Hemocompatability	Chronic toxicity	Carcinogenicity
Surface Devices	Skin	A	•	•	•							
		B	•	•	•							
		C	•	•	•							
	Mucosal Membrane	A	•	•	•							
		B	•	•	•	0	0		0			
		C	•	•	•	0	•	•	0		0	
	Breached / compromised surface	A	•	•	•	0						
		B	•	•	•	0	0		0			
		C	•	•	•	0	•	•	0		0	
External Communicating Devices	Blood path indirect	A	•	•	•	•				•		
		B	•	•	•	•	0			•		
		C	•	•	0	•	•	•	0	•	•	•
	Tissue / bone dentin communicating	A	•	•	•	0						
		B	•	•	0	0	0	•	•			
		C	•	•	0	0	0	•	•		0	•
	Circulating blood	A	•	•	•	•		0		•		
		B	•	•	•	•	0	•	0	•		
		C	•	•	•	•	•	•	0	•	•	•
Implant Devices	Bone / tissue	A	•	•	•	0						
		B	•	•	0	0	0	•	•			
		C	•	•	0	0	0	•	•		•	•
	Blood	A	•	•	•	•			•	•		
		B	•	•	•	•	0	•	•	•		
		C	•	•	•	•	•	•	•	•	•	•

A = Limited exposure (≤ 24 hours) B = Prolonged exposure (24 hours - 30 days) C = Permanent contact (> 30 days)

• = FDA and ISO evaluation tests 0 = Additional tests for FDA

Biocompatibility of Palladium

Appendix 3: Test Descriptions

The following are brief descriptions of the tests described above. More detailed descriptions may be found in the ISO standard [Reference 1].

- Cytotoxicity. Evaluates the material's effect on cell growth, cell depth, and other effects.
- Sensitization. Estimates the potential for contact sensitization; even small amounts of potential leachables can produce allergic or sensitization reactions.
- Irritation. Estimates the potential for irritation in a suitable model using sites such as skin, eye and mucous membranes.
- Intracutaneous reactivity. Assesses the localized reaction of tissue. Applicable when devices have access to circulating blood, etc. such that determination of irritation by dermal or mucosal tests are inappropriate.
- Acute systemic toxicity. Estimates, using an animal model, the potential harmful effects of single or multiple exposures during a brief period.
- Subacute and subchronic toxicity. Determines the effects of single or multiple exposures for a period not less than 24 hours, and not greater than 10% of the life span of the animal used for testing.
- Genotoxicity. Uses cell cultures or other techniques to determine gene mutations, changes in chromosome structure or number, or other DNA or gene toxicities.
- Pyrogen. Assesses pyrogenic (fever-producing) reactions in test animals.
- Implantation. Evaluates local pathological effects on tissue at both gross and microscopic levels, of a specimen that is surgically implanted in appropriate tissue appropriate in a test animal.
- Haemocompatibility. Evaluates the effects of blood-contact with devices or materials. Tests may assess the potential for hemolysis, thrombogenicity, etc.
- Chronic toxicity. Determines the effects of single or multiple exposures during at least 10 % of the life span of the test animal.
- Carcinogenicity. Assesses the tumorigenic potential during the major portion of a test animal's life span. Carcinogenicity tests should be performed only if there are suggestive data from other sources.

Biocompatibility of Valloy-120™

Introduction

The primary standard for biological evaluation of medical devices is International Standard ISO 10993. An overview of test requirements is provided in ISO 10993-1:2003(E) [Reference 1]. For both ISO and FDA, the chart shown in Appendix 1 [Reference 2] applies. For the Japanese Ministry of Health and Welfare, the chart shown in Appendix 2 [Reference 2] applies. The categorization of medical devices according to the nature and duration of contact with the body is very similar between the ISO/FDA and Japanese MHW guidelines, though there are some differences with respect to specific test procedures and protocols. Microfabrica has opted to test its materials according to the criteria for a *permanent implant device having blood contact* (shown as the bottom row in the tables of Appendices 1 and 2). Per both tables, the prescribed tests are therefore:

- Cytotoxicity
- Sensitization
- Irritation or intracutaneous reactivity
- Acute systemic toxicity
- Subacute and subchronic toxicity
- Genotoxicity
- Pyrogen
- Implantation
- Haemocompatibility
- Chronic toxicity
- Carcinogenicity

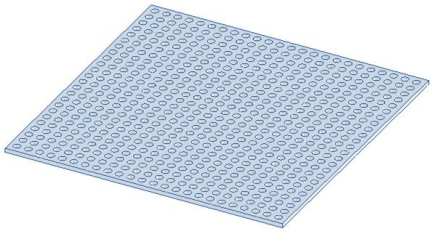

Figure 1. Single layer Valloy-120™ test specimen.

Biocompatibility of Valloy-120™

Brief descriptions of these tests are provided in Appendix 3. Suggestions for specific tests to perform from the above list, as well as test protocols, were made by the primary independent testing lab performing the biocompatibility tests (Wuxi AppTec) and Microfabrica consultants. The resulting test plan proceeded as follows:

- Tests were performed using multi-layer devices in some cases and in other cases, using single-layer test specimens such as the perforated square shown in Figure 1. Implantation tests were performed with non-perforated disk-shaped test specimens that were steam sterilized. Acute systemic injection and intracutaneous reactivity tests performed by NAMSA were performed on Valloy-120™ foils.
- All tests were performed non-GLP (Good Laboratory Practice) since the tests were aimed at characterizing MICA Freeform™ materials, rather than final devices. All tests were performed on samples that were sterilized using the steam sterilization method, with the exception of the pyrogenecity test for which the test article was sterilized using the irradiation sterilization method. Since the material has good corrosion resistance, we do not consider that the material biocompatibility can be influenced by the sterilization method. For pyrogenecity, the biocompatibility result may be directly dependent on the sterilization method and the ability to eliminate the pyrogenic effect induced by the water based processes.
- The MEM Elution test for cytotoxicity was selected.
- An intracutaneous reactivity test was selected.
- The Ames test was selected as the only genotoxicity test to be performed.
- Implantation tests in rabbit muscle were chosen to be for 2 and 12-week duration.
- Haemocompatibility tests were chosen to encompass direct contact hemolysis (ASTM), platelet and leukocyte counts, and partial thromboplastin time.
- Chronic toxicity and carcinogenity tests were not performed.
- In most cases (other than for the implantation test) specimens were not sterilized prior to testing.
- Extraction protocols were generally chosen to be 121° C for 1 hr.
- Extraction vehicles and sterilizations were chosen as follows:
    - Ethanol in saline and PEG were used for the acute systemic injection and intracutaneous reactivity tests performed by AppTec (no sterilization)
    - Normal saline and sesame oil were used for the acute systemic injection and intracutaneous reactivity tests performed by NAMSA (no sterilization)
    - Normal saline and cottonseed oil for the sensitization test (no sterilization)
    - Normal saline for the pyrogen test (steam)
    - Normal saline for the subchronic intravenous toxicity test (steam)
    - Cottonseed oil for the subacute intraperitoneal toxicity test (steam)
    - Saline/dimethylsulfoxide for the Ames test (no sterilization)
    - E-MEM for the MEM Elution cytotoxicity test (no sterilization)
- Extraction ratios were chosen to be 4g/20 mL, 60 cm^2/20 mL, 120 cm^2/20 mL, and 4 cm^2/1 mL, 21 cm^2/7 mL, depending on the test.

Biocompatibility of Valloy-120™

Test Results

The results of testing the biocompatibility of Valloy-120™ are shown in Table 1.

Table 1. Test results for Valloy-120™

Test	Result
Cytotoxicity (ISO)	Excellent: 0 cytotoxicity score, no cell lysis, non-toxic
Sensitization (ISO maximization)	Excellent: 0% sensitization response
Intracutaneous irritation (ISO)	Excellent: Negligible primary irritation index
Acute systemic toxicity (USP, ISO)	Excellent: No evidence or systemic toxicity
Subacute intraperitoneal toxicity (ISO)	Excellent: Negative for signs of systemic toxicity
Subchronic intravenous toxicity (ISO)	Excellent: Negative for signs of systemic toxicity
Ames mutagenicity (ISO)	Excellent: Non-mutagenic
Pyrogen (ISO)	Excellent: Non-pyrogenic
2- and 12-week rabbit muscle implantation (ISO)	Very poor: Severe irritant
Haemocompatibility—Hemolysis (ASTM)	Excellent: Hemolytic index 0.4% (non-hemolytic)
Haemocompatibility—Partial thromboplastin time (ISO)	Excellent: Non-activator of intrinsic coagulation pathway
Haemocompatibility—Platelet and leukocyte counts (ISO)	Excellent: Equivalent to HDPE

Biocompatibility of Valloy-120™

Conclusions

The test results summarized in Table 1 indicate that Valloy-120™ is a suitable material for short-term (<24 hours) exposure applications in manufacturing surface and external devices which work in contact with skin or mucosal membranes, breached or compromised surfaces, bone, dentin, and circulating blood. Valloy-120™ is also qualified for short-term (<24 hours) implantation in bone and tissue. It is not, however, suitable for long-term implantation or for implantation in the circulatory system.

References

[1] *Biological evaluation of medical devices — Part 1: Evaluation and testing*, Third edition 2003-08-01, reference number ISO 10993-1:2003(E).

[2] Vasudev P. Anand, "Biocompatibility Safety Assessment of Medical Devices: FDA/ISO and Japanese Guidelines", Medical Device & Diagnostic Industry, January 2000. Available online at http://www.devicelink.com/mddi/archive/00/01/017.html.

Biocompatibility of Valloy-120™

APPENDICES

Appendix 1: ISO/FDA test chart [Reference 2]

Device Categories			Initial Evaluation								Supplemental Evaluation	
	Body Contact	Contact Duration	Cytotoxicity	Sensitization	Imitation or intracutaneous reactivity	Systemic toxicity (acute) pyrogenicity	Subchronic toxicity	Genotoxicity	Implantation	Hemocompatability	Chronic toxicity	Carcinogenicity
Surface Devices	Skin	A	•	•	•							
		B	•	•	•							
		C	•	•	•							
	Mucosal Membrane	A	•	•	•							
		B	•	•	•	0	0		0			
		C	•	•	•	0	•	•	0		0	
	Breached / compromised surface	A	•	•	•	0						
		B	•	•	•	0	0		0			
		C	•	•	•	0	•	•	0		0	
External Communicating Devices	Blood path indirect	A	•	•	•	•				•		
		B	•	•	•	•	0			•		
		C	•	•	0	•	•	•	0	•	•	•
	Tissue / bone dentin communicating	A	•	•	•	0						
		B	•	•	0	0	0	•	•			
		C	•	•	0	0	0	•	•		0	•
	Circulating blood	A	•	•	•	•		0		•		
		B	•	•	•	•	0	•	0	•		
		C	•	•	•	•	•	•	0	•	•	•
Implant Devices	Bone / tissue	A	•	•	•	0						
		B	•	•	0	0	0	•	•			
		C	•	•	0	0	0	•	•		•	•
	Blood	A	•	•	•	•			•	•		
		B	•	•	•	•	0	•	•	•		
		C	•	•	•	•	•	•	•	•	•	•

A = Limited exposure (≤ 24 hours) B = Prolonged exposure (24 hours - 30 days) C = Permanent contact (> 30 days)

• = FDA and ISO evaluation tests 0 = Additional tests for FDA

Biocompatibility of Valloy-120™

APPENDICES

Appendix 2: Japanese Ministry of Health and Welfare (MHW) test chart [Reference 2]

Device Categories			Initial Evaluation									Supplemental Evaluation	
	Body Contact	Contact Duration	Cytotoxicity	Sensitization	Imitation or intracutaneous reactivity	Systemic toxicity (acute) pyrogenicity	Subchronic toxicity	Genotoxicity	Pyrogen	Implantation	Hemocompatability	Chronic toxicity	Carcinogenicity
Surface Devices	Skin	A B C	• • •	• • •	• • •								
	Mucosal Membrane	A B C	• • •	• • •	• • •		•	•					
	Breached / compromised surface	A B C	• • •	• • •	• • •		•	•					
External Communicating Devices	Blood path indirect	A B C	• • •	• • •	• •	• • •	•	•	• • •		• • •	•	•
	Tissue / bone dentin communicating	A B C	• • •	• • •	•			• •		• •			•
	Circulating blood	A B C	• • •	• • •	• • •	• • •	•	• •	• • •		• • •	•	•
Implant Devices	Bone / tissue	A B C	• • •	• • •	•			• •		• •		•	•
	Blood	A B C	• • •	• • •	• • •	• • •	•	• •	• • •	• • •	• • •	•	•

A = Temporary contact (≤ 24 hours) B = Short and medium term contact (24 hours - 30 days C = Long term contact (> 30 days)

Biocompatibility of Valloy-120™

Appendix 3: Test Descriptions

The following are brief descriptions of the tests described above. More detailed descriptions may be found in the ISO standard [Reference 1].

- Cytotoxicity. Evaluates the material's effect on cell growth, cell depth, and other effects.
- Sensitization. Estimates the potential for contact sensitization; even small amounts of potential leachables can produce allergic or sensitization reactions.
- Irritation. Estimates the potential for irritation in a suitable model using sites such as skin, eye and mucous membranes.
- Intracutaneous reactivity. Assesses the localized reaction of tissue. Applicable when devices have access to circulating blood, etc. such that determination of irritation by dermal or mucosal tests are inappropriate.
- Acute systemic toxicity. Estimates, using an animal model, the potential harmful effects of single or multiple exposures during a brief period.
- Subacute and subchronic toxicity. Determines the effects of single or multiple exposures for a period not less than 24 hours, and not greater than 10% of the life span of the animal used for testing.
- Genotoxicity. Uses cell cultures or other techniques to determine gene mutations, changes in chromosome structure or number, or other DNA or gene toxicities.
- Pyrogen. Assesses pyrogenic (fever-producing) reactions in test animals.
- Implantation. Evaluates local pathological effects on tissue at both gross and microscopic levels, of a specimen that is surgically implanted in appropriate tissue appropriate in a test animal.
- Haemocompatibility. Evaluates the effects of blood-contact with devices or materials. Tests may assess the potential for hemolysis, thrombogenicity, etc.
- Chronic toxicity. Determines the effects of single or multiple exposures during at least 10 % of the life span of the test animal.
- Carcinogenicity. Assesses the tumorigenic potential during the major portion of a test animal's life span. Carcinogenicity tests should be performed only if there are suggestive data from other sources.

Palladium Sterility

Sterility Testing

Product sterility tests are normally performed to validate sterilization processes, as well as to monitor sterilization cycles. The sterility tests may involve a rinse method, membrane filtration, or total immersion. The samples tested, the growth medium used and the incubation conditions are based on the particular standard involved – USP, AAMI/ISO, or FDR/CFR. The USP standard was chosen for Microfabrica's tests.

For the sterility testing of Microfabrica's Palladium products, 2 sets of samples were selected and tested. The samples were initially irradiated using gamma radiation at a dosage level of 27 kGy. The samples were then exposed to a small quantity of media (100-200mL), using both Soybean-Casein Digest Medium (SCDM) and Fluid Thioglycollate Medium (FTM) per USP guidelines.

Test Results

Test Parameters	Palladium Sample Set 1	Palladium Samples Set 2
Portion / SIP tested	1.0	1.0
Number tested	5	4
Type of Media	SCD	FTM
Media Volume	100mL	100mL
Incubation Period	14 Days	14 Days
Incubation temperature	20° C to 25° C	30° C to 35° C
RESULTS	5 NEGATIVE	4 NEGATIVE

Valloy-120™ Sterility

Sterility Testing

Product sterility tests are normally performed to validate sterilization processes, as well as to monitor sterilization cycles. The sterility tests may involve a rinse method, membrane filtration, or total immersion. The samples tested, the growth medium used and the incubation conditions are based on the particular standard involved – USP, AAMI/ISO, or FDR/CFR. The USP standard was chosen for Microfabrica's tests.

For the sterility testing of Microfabrica's Valloy-120™ products, 2 sets of samples were selected and tested. The samples were initially irradiated using gamma radiation at a dosage level of 27 kGy. The samples were then exposed to a small quantity of media (100-200mL), using both Soybean-Casein Digest Medium (SCDM) and Fluid Thioglycollate Medium (FTM) per USP guidelines.

Test Results

Test Parameters	Valloy-120™ Sample Set 1	Valloy-120™ Samples Set 2
Portion / SIP tested	1.0	1.0
Number tested	5	5
Type of Media	SCD	FTM
Media Volume	100mL	100mL
Incubation Period	14 Days	14 Days
Incubation temperature	20° C to 25° C	30° C to 35° C
RESULTS	5 NEGATIVE	5 NEGATIVE

Palladium Corrosion Resistance

Background

Palladium parts fabricated using MICA Freeform™ at Microfabrica have been tested to determine their resistance to corrosion in saline environments. **ASTM F2129-06** was used as the guideline under which a polarization curve was found to determine palladium's corrosion resistance.

Cyclic potentiodynamic polarization method was used to obtain the polarization curve. This is a technique in which the potential of the test specimen is controlled and the corrosion current measured by a potentiostat. The device is placed in an appropriate deaerated, simulated physiological solution (e.g. saline), and the rest potential (or Open Circuit Potential – OCP) is recorded for 1hour, or, alternatively, until the rest potential stabilizes to a rate of change less than 3mV/min. The potentiodynamic scan is then started at the OCP and scanned in the positive or noble (forward) direction. The scan is reversed after either the vertex potential is reached or the current density has reached a value approximately two decades greater than the current density measured at the breakdown potential. The reverse scan is stopped after the current has become less than that in the forward direction or the potential reaches the OCP. The data is plotted with the current density in mA/cm^2 in the x-axis (log axis) versus the potential in mV on the y-axis (linear axis).

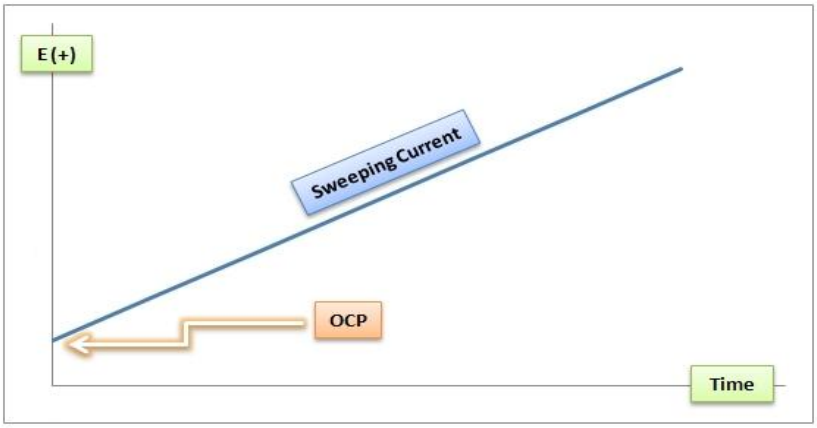

Figure 1. Illustration of a theoretical OCP (Open Circuit Potential).

If the potential is plotted against time and a sweeping potential is applied, typically a line is generated from the OCP in the positive direction. Generally*, a material that exhibits a polarization curve with high OCP value is more noble, and therefore, resistant to corrosion*. However, it must be noted that OCP inherently depends on the history of the working electrode. This means that the surface of the working electrode must be clean from contamination to reproduce valid results.

Palladium Corrosion Resistance

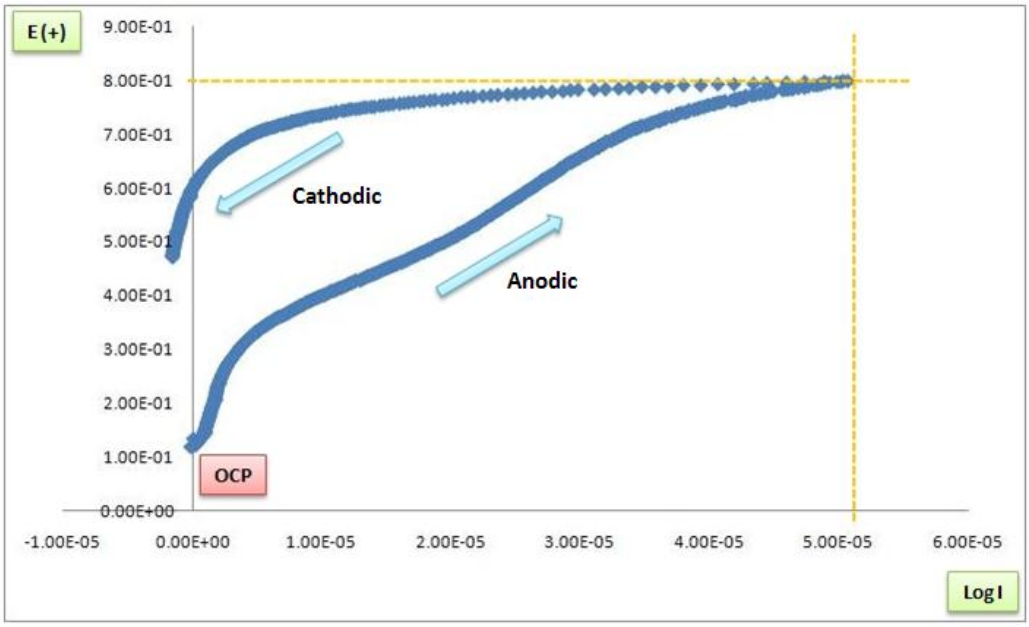

Figure 2. Example of defining the vertex of a polarization curve for a corrosion resistant material (palladium of platinum group is shown).

Typically, the forward sweep of the curve will be anodic, and the reverse sweep will be cathodic. *For characterizing corrosion resistance, the shape of the polarization curve is not critical*. *Rather, the two points of interest are the OCP and the* vertex. The look of a polarization curve depends on multiple factors (electrolyte, sweep regime, direction it was recorded, surface conditions of the electrode, etc.).

By ASTM standards, the vertex is defined to be the value of the current when electrical potential reaches 800mV or 10mA. *The more noble a material, the lower the current will be at 800mV*. Sometimes, a non-noble material may reach a value of 10 mA in current before ever achieving 0.8 E in potential. In such cases, the 10 mA-line serves as the standard cut-off for the vertex. In general, *the lower the current is at 800mV, the more corrosion resistant the material*. In other words, for polarization curves, the vertex is determined by the 800mV or 10mA lines, whichever occurs first.

Palladium Corrosion Resistance

Corrosion Resistance of Palladium

In Figure 3, the polarization curve of Microfabrica's Palladium-A is plotted alongside other known biocompatible materials. As the figure shows, MFI Palladium-A offers better corrosion resistance than other biocompatible metals such as platinum and stainless steel. Palladium-A exhibits both higher OCP and lower current at 800mV, which are the two criteria for determining a material's nobleness. Generally, a more noble material can be found in the upper-left corner of a polarization chart. In addition, palladium is biocompatible and qualified as a long term implant (>30 days) in the circulatory system (exposure to ionic environment). Palladium has demonstrated long term chemical and electrochemical stability when exposed to ionic environment.

In conclusion, Palladium parts fabricated using MICA Freeform™ at Microfabrica are corrosion resistant for long term implantation applications. There are several factors that may impact the corrosion resistance of Microfabrica's Palladium when employed in finished medical devices. These may range from the surface finish to process conditions, its interaction with other metals, and the clinical environment. Ultimately, the corrosion resistance test may be repeated on the finished medical product according to the specific indications for use.

Palladium Corrosion Resistance

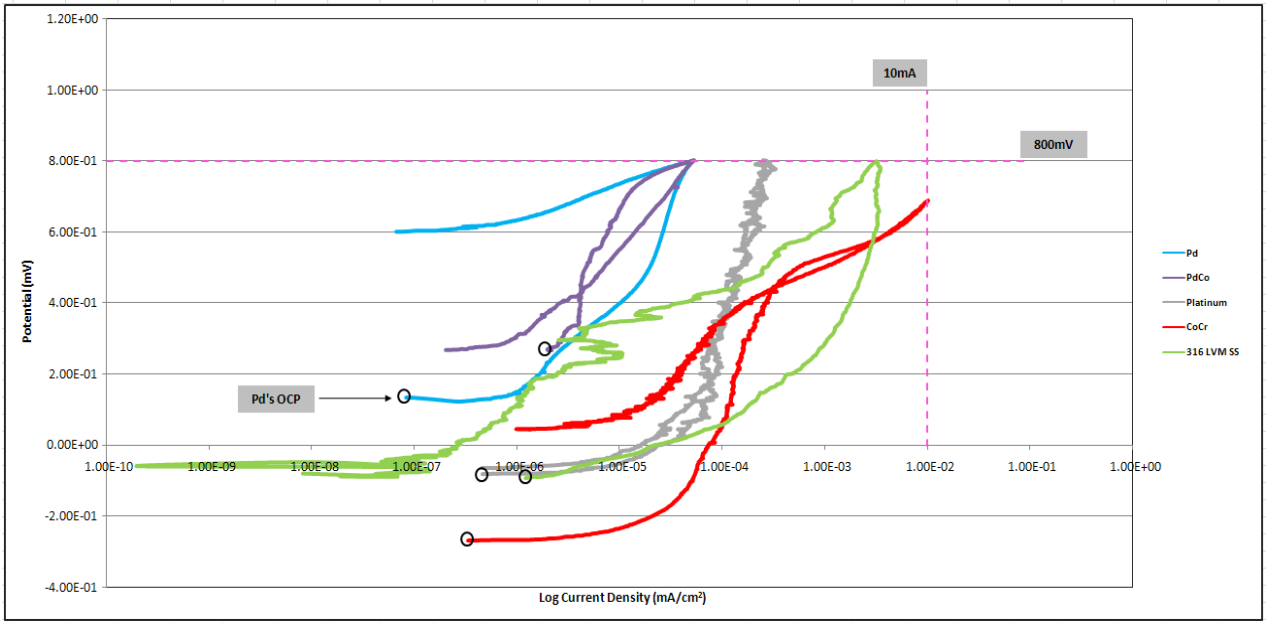

Figure 3: Polarization curves for Pd and other known biocompatible materials.

Valloy-120™ Corrosion Resistance

Background

Valloy-120™ parts fabricated using MICA Freeform™ at Microfabrica have been tested to determine their resistance to corrosion in saline environments. **ASTM F2129-06** was used as the guideline under which a polarization curve was found to determine Valloy-120™ corrosion resistance.

Cyclic potentiodynamic polarization method was used to obtain the polarization curve. This is a technique in which the potential of the test specimen is controlled and the corrosion current measured by a potentiostat. The device is placed in an appropriate deaerated, simulated physiological solution (e.g. saline), and the rest potential (or Open Circuit Potential – OCP) is recorded for 1hour, or, alternatively, until the rest potential stabilizes to a rate of change less than 3mV/min. The potentiodynamic scan is then started at the OCP and scanned in the positive or noble (forward) direction. The scan is reversed after either the vertex potential is reached or the current density has reached a value approximately two decades greater than the current density measured at the breakdown potential. The reverse scan is stopped after the current has become less than that in the forward direction or the potential reaches the OCP. The data is plotted with the current density in mA/cm^2 in the x-axis (log axis) versus the potential in mV on the y-axis (linear axis).

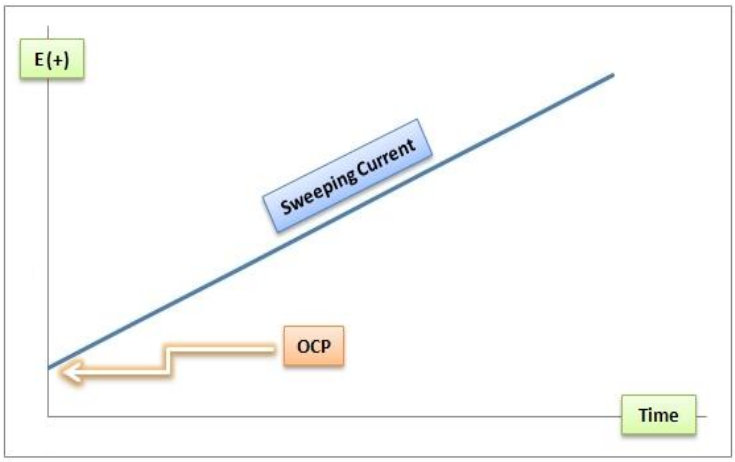

Figure 1. Illustration of a theoretical OCP (Open Circuit Potential).

If the potential is plotted against time and a sweeping potential is applied, typically a line is generated from the OCP in the positive direction. Generally*, a material that exhibits a polarization curve with high OCP value is more noble, and therefore, resistant to corrosion*. However, it must be noted that OCP inherently depends on the history of the working electrode. This means that the surface of the working electrode must be clean from contamination to reproduce valid results.

Valloy-120™ Corrosion Resistance

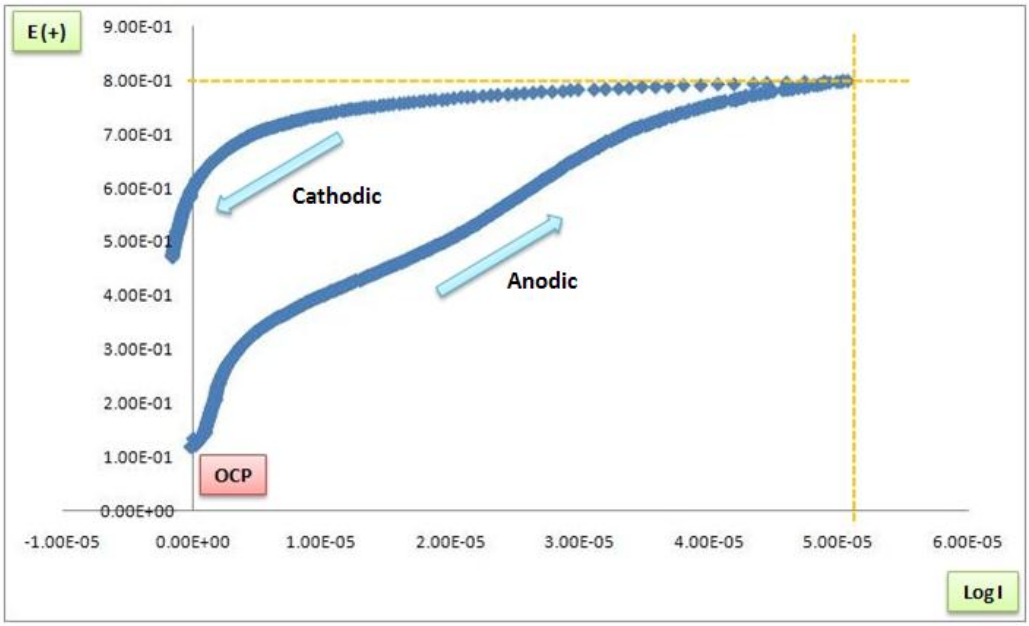

Figure 2. Example of defining the vertex of a polarization curve for a corrosion resistant material (for illustrative purpose, the curve for palladium is shown).

Typically, the forward sweep of the curve will be anodic, and the reverse sweep will be cathodic. For characterizing corrosion resistance, the shape of the polarization curve is not critical. Rather, the two points of interest are the OCP and the vertex. The look of a polarization curve depends on multiple factors (electrolyte, sweep regime, direction it was recorded, surface conditions of the electrode, etc.).

By ASTM standards, the vertex is defined to be the value of the current when electrical potential reaches 800mV or 10mA. *The more noble a material, the lower the current will be at 800mV*. Sometimes, a non-noble material may reach a value of 10 mA in current before ever achieving 0.8 E in potential. In such cases, the 10 mA-line serves as the standard cut-off for the vertex. *In general, the lower the current is at 800mV, the more corrosion resistant the material.* In other words, for polarization curves, the vertex is determined by the 800mV or 10mA lines, whichever occurs first.

Valloy-120™ Corrosion Resistance

Corrosion Resistance of Valloy-120™

In Figure 3, the polarization curve of Microfabrica's Valloy-120™ is plotted alongside other known biocompatible materials. As the figure shows, MFI Valloy-120™ offers relatively good corrosion resistance in a saline environment. Its low current at 800mV speaks to its good corrosion resistance, but its OCP is relatively low, lower than the other known biocompatible materials, and this can be seen as reflective of its short term biocompatibility. That is, Valloy-120™ is biocompatible, but not an implantable material.

In conclusion, Microfabrica's Valloy-120™ parts are corrosion resistant for short term (<24 hours) applications. There are several factors that can impact the corrosion resistance of Microfabrica's Valloy-120™ when employed in finished medical devices. These range from the surface finish to process conditions, its interaction with other metals, and the clinical environment. Ultimately, the corrosion resistance test may be repeated on the finished medical product according to the specific indications for use.

Valloy-120™ Corrosion Resistance

Exhibit #004

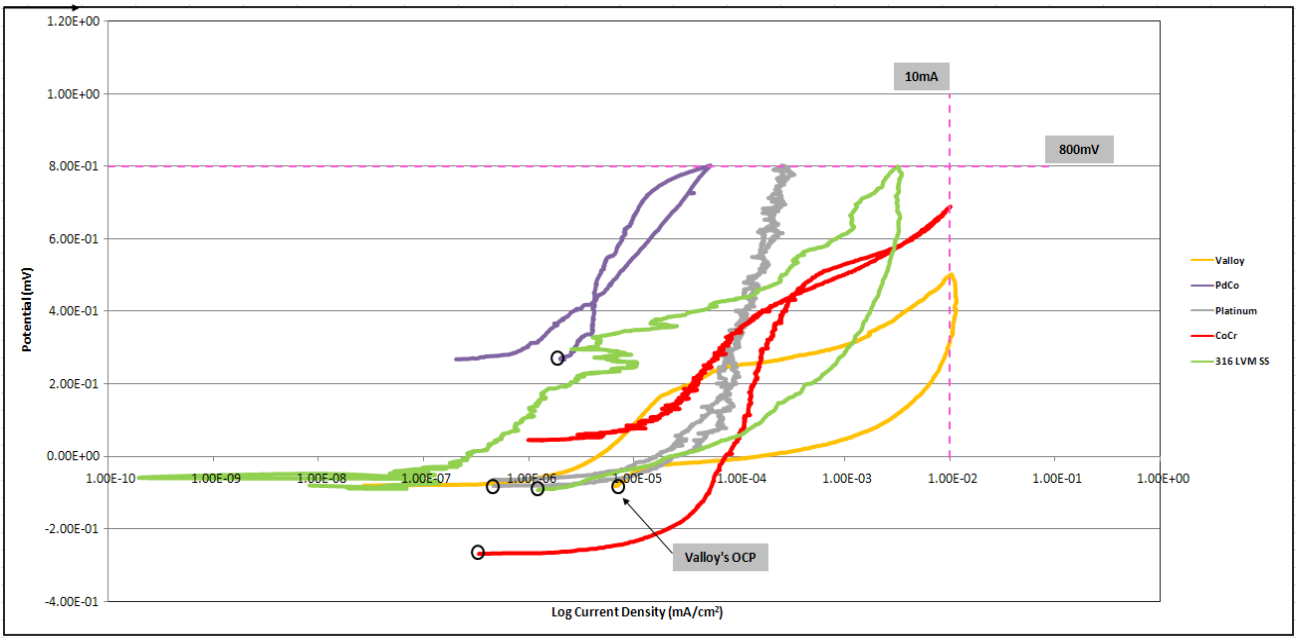

Figure 3: Polarization curves for Valloy-120™ and other known biocompatible materials.

MICROFABRICA®

MANUFACTURING PROCESSES

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- Valloy-120™ …page 36

Palladium Manufacturing Processes

Handling

Palladium is non-magnetic and therefore magnetic tools cannot be used to manipulate these parts. Manual handling of small MICA Freeform™ parts made of palladium requires great care and delicacy. Although MFI's Palladium is a relatively hard material (>375 HV), it is still very easy to damage, bend, or scratch such parts when instruments such as stainless steel tweezers are used. Teflon coated or rubber-tipped tools are recommended.

Joining

Laser Welding
It is possible to laser weld both stainless steel and nitinol wires to parts made of palladium.

Palladium tubes with wall thickness of 200ums have been successfully laser welded to nitinol wire using and IR laser as shown in the picture below. The welds have been tested up to 3.3kg of tensile load without failure. As a general rule, the laser welds have been found to perform the best when it can be made along several sections around the circumference of the tube.

Exact laser welding conditions can be optimized for the design, geometry, and desired load rating of each weld.

Machining

Palladium parts created using MICA Freeform™ may be machined. They may be machined in the following stages:

- Stage 1: Fabrication complete, but prior to release etching. At this stage, the palladium part is still encapsulated and held in place by the sacrificial copper material and therefore structurally rigid. The part is typically still on the ceramic wafer at this stage but may also be singulated and separated into die form if needed. Machining at this stage affords the greatest safety and stability to the palladium part.
- Stage 2: Fabrication is complete and the part has undergone release etching, removing the sacrificial copper and allowing it to be freely manipulated and exercised. Machining may also be performed at this stage, but there is an added risk as there is no longer a stabilizing copper matrix to hold the part in place to provide structural support. However, this stage may afford visibility of specific locations and areas that may need special scrutiny or observation during machining that would not be possible if the sacrificial copper was still in place.

Conventional dicing and slicing operations are possible with palladium parts at Stage 1, and potentially possible at stage 2 provided a suitable stabilizing matrix and fixturing is provided. The viability of other operations such as wire EDM is high but yet unconfirmed.

Palladium Manufacturing Processes

Heat Treatment

Palladium parts made by MICA Freeform™ are hard and relatively brittle, and they may be heat treated to reduce their brittleness and enhance their ductility. Temperatures above 400C have been used to dramatically soften the materials and more than double their ductility.

One important note is that an intermediate amount of heat treatment may actually increase the hardness and brittleness of the palladium parts and therefore the proper temperature regimes and time scales must be used during heat treatment.

Storage

Palladium products are stable and have an indefinite shelf life under normal (room temperature) storage conditions. In general, palladium parts are not sensitive to humidity.

Deburring

In general palladium parts manufactured by MICA Freeform™ do not have burrs and do not require deburring operations.

Valloy-120™ Manufacturing Processes

Handling

Valloy-120™ is a ferromagnetic material and therefore a recommended handling method is to use a magnetic tool to manipulate and maneuver the parts. Manual handling of small MICA Freeform™ parts made of Valloy-120™ requires great care and delicacy. Although Microfabrica's Valloy-120™ is a relatively hard material (>350 HV), it is still very easy to damage, bend, or scratch such parts when instruments such as stainless steel tweezers are used. If manual handling is required, then Teflon coated or rubber-tipped tools are recommended.

Joining

Laser Welding

It is possible to laser weld both stainless steel and nitinol wires to parts made of Valloy-120™. Valloy-120™ parts in tubular shape with wall thickness of 100ums have been successfully laser welded to nitinol wire using an IR laser. The welds have been tested up to 6kg of tensile load without failure. The exact laser welding conditions can be optimized for the design, geometry, and desired load rating of each weld. However, as a general rule, the laser welds have been found to perform the best when it can be made along several sections around the circumference of the tube.

Machining

Valloy-120™ parts created using MICA Freeform™ may be machined. They may be machined in the following stages:

- **Stage 1:** Fabrication complete, but prior to release etching. At this stage, the Valloy-120™ part is still encapsulated and held in place by the sacrificial copper material and therefore structurally rigid. The part is typically still on the ceramic wafer at this stage but may also be singulated and separated into die form if needed. Machining at this stage affords the greatest safety and stability to the Valloy-120™ part.
- **Stage 2:** Fabrication is complete and the part has undergone release etching, removing the sacrificial copper and allowing it to be freely manipulated and exercised. Machining may also be performed at this stage, but there is an added risk as there is no longer a stabilizing copper matrix to hold the part in place to provide structural support. However, this stage may afford visibility of specific locations and areas that may need special scrutiny or observation during machining that would not be possible if the sacrificial copper was still in place.

Conventional dicing and slicing operations are possible with Valloy-120™ parts at Stage 1, and potentially possible at stage 2 provided a suitable stabilizing matrix and fixturing is provided. The viability of other operations such as wire EDM is high but yet unconfirmed.

Valloy-120™ Manufacturing Processes

Heat Treatment

Valloy-120™ parts made by MICA Freeform™ are relatively hard and possess sufficient elastic strength to be used as springs and cantilevers. The material properties of the Valloy-120™ may be modified by heat treatment processes. Moderate temperatures of up to 290C do not degrade the spring constant of the Valloy-120™ significantly, although prolonged exposure to heat at this temperature will soften the part. Higher temperature annealing operations can also lower the spring constant and soften the material.

Storage

Valloy-120™ products are stable and have an indefinite shelf life under normal (room temperature) storage conditions. In general, Valloy-120™ parts are not sensitive to humidity.

Deburring

In general Valloy-120™ parts manufactured by MICA Freeform™ do not have burrs and do not require deburring operations.

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