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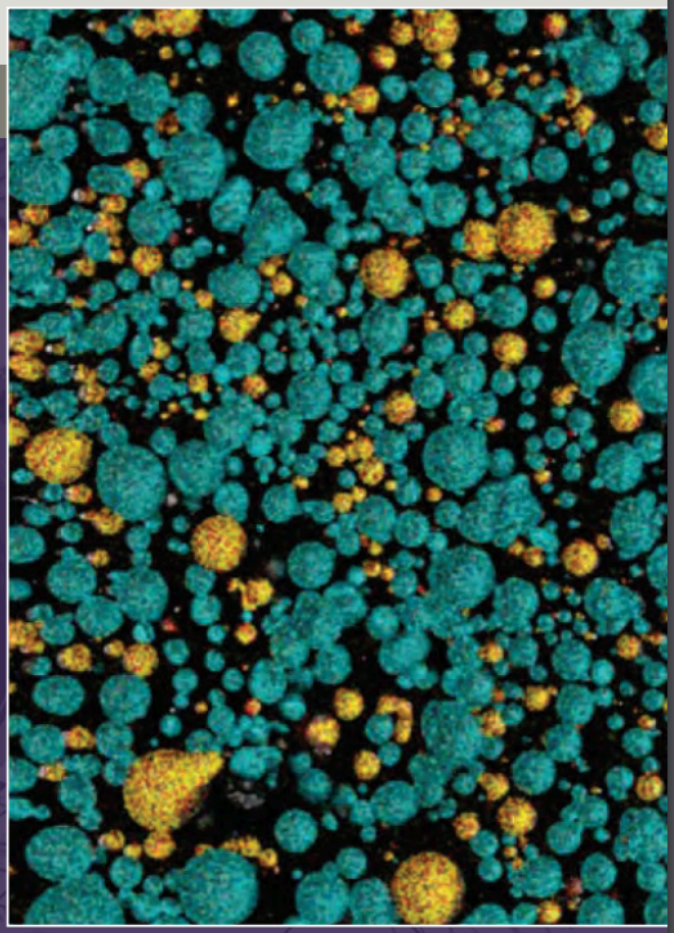

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Medical applications for (MIM) have been commercialized since the 1990's, ranging from orthodontic dental brackets to laparoscopic surgical instrumentation, mainly focusing on 316L and 17-4 PH stainless-steel materials. Since the mid-2000's there has been significant interest in developing implantable MIM components made from titanium alloys. The certification requirements for commercial acceptance of such products are quite stringent. An overview is provided of the requirements for the development of such parts and the steps necessary for their approval and commercialization.

METAL INJECTION MOLDING FOR IMPLANTABLE DEVICE APPLICATIONS

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METAL INJECTION MOLDING (MIM) MEDICAL OVERVIEW

Since the mid-2000's, there have been considerable efforts towards commercialization of medically implantable MIM components focusing on cobalt-chromium and titanium materials.

The use of MIM has long been of interest to manufacturers desiring to reduce the manufacturing cost of their implantable products. Titanium materials are utilized for long-term implants and are preferred due to their superior biocompatibility over cobalt-chromium materials. Because of the multiple challenges of processing highly reactive titanium powder in an ISO 13485[1] environment, few MIM companies have made successful entries into the implant market, Figure 1. ISO 13485 is the certification required to manufacture medical/implantable components and devices; it outlines the quality management system requirements for regulatory purposes and is quite similar to the FDA's 21 CFR Part 820[2] (FDA's Quality System Regulation of Medical Devices).

In order to penetrate the orthopaedic market, a MIM process for titanium parts needs to be robust enough to demonstrate that the product can consis-

Figure 1. *All-electric injection molding machine in an ISO 13485 environment*

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tently meet the chemical and mechanical performance requirements of the specifications that were used in the design of the device. Initially, this must be demonstrated in order to give the manufacturers the degree of comfort they need to make the substantial investment in titanium MIM. This investment includes not only the required tooling (sometimes multiple sets for a family of parts, which can be as high as 20 individual sizes) but process validation, functional testing of the device, and potentially biocompatibility testing. Medical devices undergo substantial functional testing to demonstrate that the device is effective and safe prior to manufacturing. Notwithstanding this testing, it is important to have an understanding of the properties of the materials to benchmark the performance of the manufacturing process, independent of specific device performance.

Once in production, a robust, statistically capable process is necessary so sampling plans can be instituted for the acceptance criteria that must be monitored by destructive testing, such as chemical analysis of interstitial content.

There are two standards for titanium MIM materials for surgical implant applications: ASTM F2885-17[3] (Ti-6Al-4V grade 5) and ASTM F2989-13[4] (commercially pure grades). Most titanium implantable applications focus on Ti-6Al-4V due to its higher mechanical performance. ASTM F2885-17 covers two versions of the product. Type 1 is a densified version having higher ultimate and yield strength requirements, and Type 2 is an as-sintered version having lower mechanical requirements. The interstitial requirements for both are the same. Type 1 is a preferred material choice because the specification for Type 1 is more similar to other ASTM specifications used for titanium implantable devices and presents less adoption challenges to the device OEM's.

Table I is a reference table for the chemical and mechanical requirements of MIM Ti-6Al-4V material (ASTM F2885-17) for implantable components compared with machined, wrought Ti-6Al-4V material (ASTM F136-13[5]).

TABLE I. TI-6AL-4V - ASTM COMPARISON BETWEEN MIM AND WROUGHT (wt.%)

Standard	ASTM F2885-17	ASTM F136-13
Material	MIM - Grade 5 Ti-6Al-4V	Wrought - Grade 23 Ti-6Al-4V ELI
Element / Property		
Nitrogen	0.05% max	0.05% max
Carbon	0.08% max	0.08% max
Hydrogen	0.015% max	0.012% max
Iron	0.30% max	0.25% max
Oxygen	0.20% max	0.13% max
Aluminum	5.5–6.75%	5.5–6.5%
Vanadium	3.5–4.5%	3.5–4.5%
Yttrium	0.005%	N/A
Titanium*	Balance	Balance
Ultimate Tensile Strength	900 MPa min	860 MPa min
Yield Strength	830 MPa min	795 MPa min
Elongation	10% min	10% min
Reduction of Area	15% min	25% min

TABLE II. MEDICAL MARKET SECTORS AND APPLICATIONS FOR MIM

Market Sector	Implant Applications
Orthopaedics	Acetabular cups, tibial trays, femoral knees, hip steps, shoulders, elbows, ankles, and extremeties components (hand and feet implants)
Spine	Fusion cages (lumbar, thoracic and cervical), expandable cage components
Trauma	Fixation plates
Vascular Access	Port components, heart pump components
Cardiac Rhythm Management/ Neurostimulation	Internal components or modified casings
Dental	Artificial tooth implants

APPLICATIONS AND REQUIREMENTS

The implantable component market is vast and diverse with products ranging from less than 1 gram to over 200 g. Annual product volumes are just as diverse, ranging from 10's to over 1 million. Table II is a summary of common market sectors and implantable components within the medical implantable field.

Most orthopaedic, spine, and trauma products have tabulated sizes which volumes are typically normally distributed across. MIM can be leveraged to take advantage of the low-volume/high-variety mix on these complex, tight-tolerance geometry parts. Most large orthopaedic total-joint implants require functional surfaces as ingrowth mediums as shown in Figure 2.

Although MIM can hold relatively tight tolerances, some applications require secondary CNC machining for improved dimensional tolerances and additional secondary processing for surface finish requirements. Passivation and anodization are often secondary processes performed on titanium MIM implantable components.

CONSIDERATIONS FOR MIM

MIM consideration falls into two groups: (1) replacing an existing CNC machined component to provide cost savings to the customer or, (2) designing a new component/device for MIM from the start. MIM conversions are currently much more prevalent. Design collaboration is critical so that the component is redesigned for MIM manufacturability and also meets the needs of the device. Draft, fillets, gate location, parting line, and ejector pin marks are just a few of the items that require discussion and potentially, drawing revisions. In the end, timelines and costs drive the MIM decision pathway.

Figure 2. Ti-6Al-4V MIM orthopaedic implant with porous ingrowth features

Timeline

For successful product launches, both suppliers and buyers should mutually and openly discuss the specific considerations for developing a MIM implantable product. Implantable products have long timelines; typical durations can range from 12 months up to 36 months depending the complexity of the project and device. Collaboration on the overall timeline and agreement on milestone deliverables is critical for aligning all departments involved on the project including engineering, regulatory, biocompatibility, quality, manufacturing, and procurement.

Costs

Costs are the major driver; preliminary MIM component costs are used to understand the potential return on investment (ROI) prior to initiating a project. The elements that typically feed into the MIM ROI equation are: tooling costs, non-recurring engineering (NRE) costs for validation requirements at the MIM supplier, costs for customer functional testing of the products (this will go into the FDA submission), potential biocompatibility testing performed by the customer, and overall resources to conduct the project. These costs are compared with the project cost savings on a component level over a period of time (i.e., 6 months, 12 months, etc.) in conjunction with the projected sales volume. Based on the level of costs and time required for a given component, the customer needs to ensure the cost savings are sufficient to meet the ROI and the supplier needs to ensure the revenue opportunity is sufficient for the level of resources required for product validation.

APPROVAL PROCESS & GUIDANCE

In addition to a MIM supplier product validation process (i.e., IQ-OQ-PQ [IQ: Installation Qualification—pertaining to equipment, OQ: Operational Qualification—pertaining to worst-case processing conditions, and PQ: Performance Qualification—pertaining to three (3) independent groups of product produced at nominal processing conditions]) meeting the stringent requirements of 21 CFR Part 820, approving a MIM product for a human implant involves a thorough review of the entire MIM process. In addition to meeting the chemical and mechanical requirements of the material, the functional requirements of the product or device must be met as well as biocompatibility testing to ensure safety.

Typically, MIM implantable products follow one of three pathways: (1) 510(k) submission which requires a 90-day approval process, (2) special 510(k) submission which requires a 30-day approval process or, (3) an internal letter to file conducted by the customer covering the equivalency. The submission pathway is determined by the type of device, material or compositional changes, and potentially new manufacturing materials used throughout the MIM process.

MIM differs from conventional CNC machining as a metal-forming route in many ways. One critical aspect is the material used in the MIM process—which can vary from one MIM company to another. MIM vendors use various binder systems and different methods for for debinding. These require testing to ensure there are no extractable/leachable compounds that would have a negative effect on the implant. Guidance on the extensive testing that is required to reduce the risk of using MIM for implantable components is specifically called out in ISO 10993-1,[6] and is based on the type of product. Most titanium MIM parts will fall under the category of permanent (>30 days implanted), tissue, or bone contacting implants.

Table III summarizes the types of medical devices and relevant biocompatibility testing required for approval.

FUTURE OUTLOOK

Since the mid-2000's, implantable MIM products have been approved and commercialized. The adoption of MIM implantable components has been slow due to factors ranging from technology to regulatory approv-

TABLE III. ISO 10993-1 BIOCOMPATIBILITY EVALUATION ENDPOINTS (GUIDANCE FOR FDA APPROVAL OF IMPLANTABLE DEVICES)

Medical Device Categorization by			Biological Effect												
Nature of Body Contact		Contact Duration	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Category	Contact	A - limited (≤24 h) B - prolonged (>24 h to 30 d) C - permanent (>30 d)													
Surface Device	Intact 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		O					
		C	X	X	X	O	O	X	X	O		O			
	Breached or Compromised Surface	A	X	X	X	O	O								
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O	O		
External Communicating Device	Blood Path, Indirect	A	X	X	X	X	O				X				
		B	X	X	X	X	O	O			X				
		C	X	X	O	X	O	X	X	O	X	O	O		
	Tissue*/Bone/ Dentin	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Circulating Blood	A	X	X	X	X	O		O		X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		
Implant Device	Tissue*/Bone	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Blood	A	X	X	X	X	O		O	X	X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		

als. The focus of cost reduction in the medical sector heightens over time as well as the interest in MIM as a way to reduce costs. The number of MIM implantable devices increases each year as OEM's build confidence in both the technology and their suppliers.

REFERENCES

1. ISO 13485-16, "Medical Devices—Quality Management Systems—Requirements for regulatory purposes," ISO, Geneva, Switzerland, 2016, www.iso.org.
2. 21 CFR Part 820, April 1, 2017, "Quality System (QS) Regulation/Medical Device", www.fda.gov.
3. ASTM Standard F2885, 2017, "Standard Specification for Metal Injection Molded Titanium-6Aluminum-4Vanadium Components for Surgical Implant Applications," ASTM International, West Conshohocken, PA, 2017, DOI: 10.1520/F2885-17, www.astm.org.
4. ASTM Standard F2989, 2013, "Standard Specification for Metal Injection Molded Unalloyed Titanium Components for Surgical Implant Applications," ASTM International, West Conshohocken, PA, 2013, DOI: 10.1520/F2989-13, www.astm.org.
5. ASTM Standard F136, 2013, "Standard Specification for Wrought Titanium-6Aluminum-4Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications (UNS R56401)," ASTM International, West Conshohocken, PA, 2013, DOI: 10.1520/F136-13, www.astm.org.
6. ISO 10993-1:2009-10, "Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process," ISO, Geneva, Switzerland, 2010, www.iso.org. ijpm