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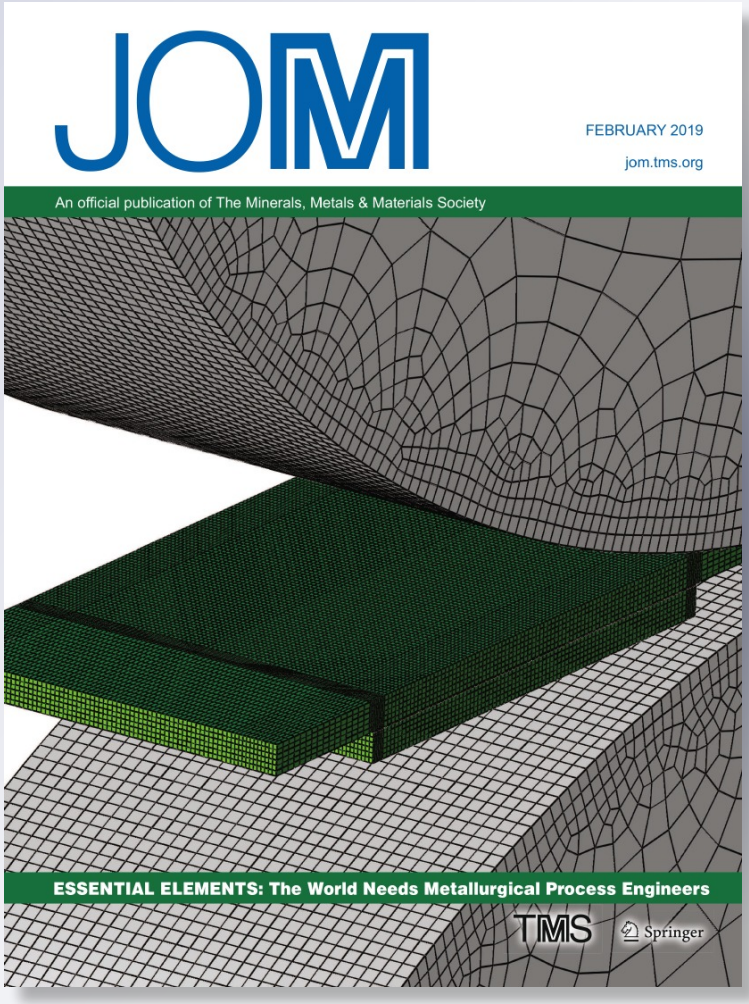

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Towards Qualification of Additively Manufactured Ti6Al4V (ELI) Medical Implants

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In recent years, the production of customized medical implants through additive manufacturing by the Centre for Rapid Prototyping and Manufacturing in South Africa has grown significantly. While satisfactory results have been obtained and the quality of life of many patients has been improved, further research is required to enable the production of qualified components. This paper shares the growing acceptance of additive manufacturing, as well as the establishment of a South African Additive Manufacturing Strategy. An overview of the progress made by the Collaborative Programme in Additive Manufacturing is presented. The scope of the metals research performed towards the qualification of additive manufacturing of Ti6Al4V medical implants is discussed. Examples are given of internationally leading work on utilizing these implants, which were additively manufactured under an ISO 13485 system, in maxillofacial reconstructive surgery. Lastly, the development of an affordable polyurethane artificial heart valve is presented as a different type of medical implant.

INTRODUCTION

In 2015, Richard D'Aveni stated in an article in *Harvard Business Review*: "Industrial 3-D printing is at a tipping point, about to go mainstream in a big way."[1] This has indeed become a reality since 2015, and additive manufacturing (AM) has been accepted as a key technology of the 4th Industrial Revolution, also known as Industry 4.0. Over the past decade, since the first prototypes, the production of customized medical implants through AM of Ti6Al4V (ELI) in South Africa has been growing strongly.[2] Through the collaboration between engineers of the Centre for Rapid Prototyping and Manufacturing (CRPM) of the Central University of Technology, Free State (CUT) in Bloemfontein, South Africa, and leading prosthodontic, maxillofacial and orthopedic surgeons the quality of life of many patients has been restored. Patients whose faces had been disfigured through cancerous tumors gained renewed acceptance in their communities after reconstructive surgery to restore their features and functions through customized titanium alloy implants.[3] While the CRPM engineers in collaboration with surgeons pushed ahead with cutting-edge work on customizing Ti6Al4V (ELI) implants for various skeletal reconstruction needs, it was realized by the AM community that, for full qualification of such implants, significant research was required. Qualification of the materials used in AM,[4] as well as the AM process chain,[5] was essential for acceptance by not only the medical industry but also by aerospace.

During 2013 and 2014, the South African Department of Science and Technology commissioned the development of an AM Technology Roadmap for the country. The outcome of this process was the publication of the South African Additive Manufacturing Strategy in August 2015.[6] This document serves as guide to South African and international players in identifying economic opportunities, addressing technology gaps, focusing on development programmes and informing investment decisions that would eventually enable local companies and industry sectors to become global leaders in selected areas of AM.[7] One of the four main priority focus areas of this South African AM Strategy was research and development towards qualified AM technology for final part manufacturing for the medical and aerospace markets.[6]

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QUALIFICATION OF ADDITIVELY MANUFACTURED MEDICAL IMPLANTS

In a pro-active response to the recommendations of the SA AM Strategy, research leaders from South African universities involved in AM [CUT, Stellenbosch University (SU), Vaal University of Technology (VUT) and North West University (NWU)] in collaboration with the National Laser Centre (NLC) at the Council for Scientific and Industrial Research (CSIR) and a leading aerospace manufacturer, Aerosud, developed and aligned the Collaborative Program in Additive Manufacturing (CPAM) with the priority focus areas of this strategy. A relevant sub-program of the CPAM is titled Qualification of Additive Manufacturing of Ti6Al4V for Medical Implants and Aerospace Components. The institutions collaborating with CUT in this sub-programme are SU, University of Cape Town (UCT), NWU, NLC and CSIR.

In support of the drive towards commercialization of medical implants and devices, an ISO 13485 quality management system was successfully established in the CRPM at CUT. To comply with the requirements of this quality management system, an EOSINT M280 DMLS machine is dedicated exclusively to the AM of Ti6Al4V (ELI) medical implants. The system was audited by TÜV in February 2016 and certification of the CUT-CRPM was officially awarded on 20 June 2016. The scope of this certification supports commercialization as follows:

- Design, development and production of patient specific custom-made titanium implants by means of 3D printing/AM.
- Design, development and production of patient specific custom-made preoperative models, jigs, cutting guides in nylon by means of 3D printing/AM.
- Contract production of titanium implants by means of 3D printing/AM.
- Contract production of preoperative models, jigs, cutting guides in nylon by means of 3D printing/AM.

Although this quality management system provided the framework for ensuring the reliability and repeatability of the AM performed at the CRPM, the generation of data to validate the individual processes in the AM process chain had become imperative. Sufficient research data had to be produced and published to prove that parts produced through AM can fully comply with the accepted international standards for the material, physical, chemical and mechanical properties of such parts. To achieve this, a process chain for the qualification of medical implants was developed, as shown in Fig. 1. This diagram indicates the different areas (yellow blocks) where the CPAM research projects are focused to generate the data and establish the techniques and processes that will underpin the qualification procedures.

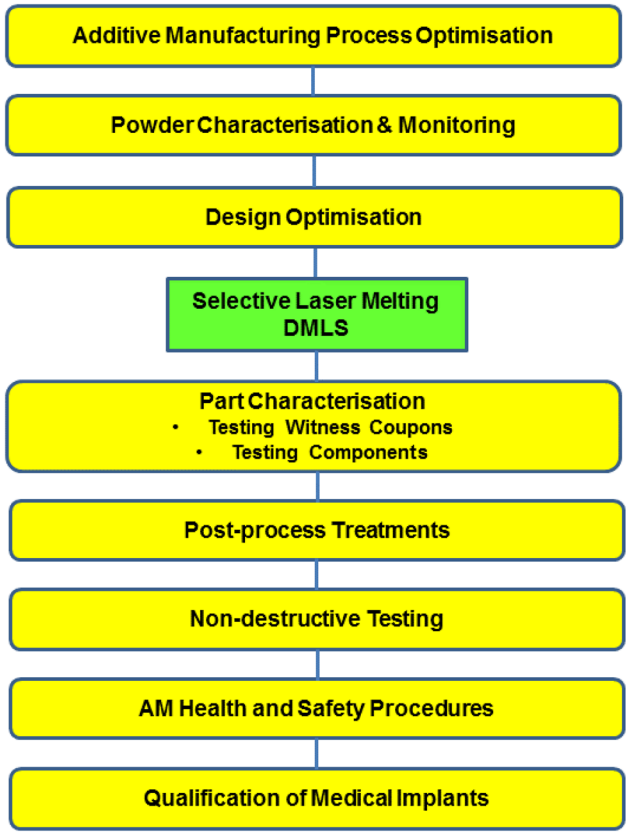

Fig. 1. Research areas in the additive manufacturing process chain for qualification of medical implants.

RESEARCH IN SUPPORT OF QUALIFICATION

Research topics that are being investigated towards full qualification of medical implants include:

- Characterization of Ti6Al4V (ELI) powder and monitoring of powder re-use.
- Evaluation of the microstructure of Ti6Al4V (ELI) as a function of AM build parameters.
- Residual stress analysis through x-ray and neutron diffraction.
- Establishment of stress-relieving heat treatments.
- Development of heat treatments to obtain desired mechanical and fatigue properties.
- Determination of fatigue properties as-built and after high-temperature annealing heat treatments.
- High strain rate performance of direct metal laser sintering (DMLS) Ti6Al4V (ELI) parts.
- High-velocity impact properties of DMLS Ti6Al4V (ELI) parts.
- Non-destructive evaluation of AM part integrity.
- Multi-material titanium-based structures through in situ alloying.

Two of the research projects in these focus areas are discussed in more detail here.

Characterisation and Monitoring of Ti6Al4V (ELI) Powder

The full description of the methodology followed to characterize the virgin as-received powder and monitor the powder properties after repeated re-use is given in Thejane et al.[8] and in Thejane.[9] In this study, Ti6Al4V (ELI) powder with differing particle size distributions, used in two different selective laser melting (SLM) systems, were studied. It was found that the powder used in the DMLS system, which was operated in the ISO 13485 quality management environment, could be re-used indefinitely, provided it was topped up with virgin powder to maintain the required levels on the machine's build platform. Even after 35 build cycles, the chemical composition of the powder still complied with the ASTM F3001-14 standard.[10] The powder morphology also displayed no significant changes on repeated re-use, as can be seen in Fig. 2.

The particle size distribution (PSD) of the virgin powder was determined by micro-CT scanning and laser diffraction, while the PSD of this powder after the different re-use cycles was determined by laser diffraction. From the laser diffraction results (see Fig. 3), it was clear that negligible changes occurred in the particle size distribution, and after 35 build cycles it still complied with the requirement for the machine.

In addition, the internal porosity of individual particles was determined by micro-CT scanning, using a technique described by du Plessis et al.[11] The volume fraction of porosity in the DMLS powder was found to be negligibly small (between 0.00% and 0.01%).

From this study,[9] it was concluded that Ti6Al4V (ELI) powder quality can be effectively established and monitored through a range of tests performed to international standards. Provided a quality management system is maintained, the unused Ti6Al4V (ELI) powder in a DMLS system can be re-used until fully consumed.

High Cycle Fatigue Properties of As-Built and Heat-Treated Ti6Al4V (ELI) Specimens

As part of an investigation to generate data on the fatigue properties of Ti6Al4V (ELI) parts built through DMLS, Malefane et al.[12] determined the fatigue properties of as-built specimens. Rectangular bars were built in the three orthogonal (*X*-, *Y*- and *Z*-) build directions (the *X*-axis was aligned with the direction of movement of the powder re-coater of the EOSINT M280 machine). No stress-relieving heat treatment was applied to these specimens. The bars were machined and polished to standard fatigue specimen geometry (ASTM E466 and ISO 1099). For the tension–tension fatigue tests, the following fatigue test parameters were applied: A 50-kN Instron 1342, axial, servo-hydraulic machine was used. An *R*-ratio of 0.1 was used with a cycling frequency of 10 Hz. The tests were executed at an environmental temperature of $20 \pm 2°C$. As run-out, 5×10^6 cycles was accepted.

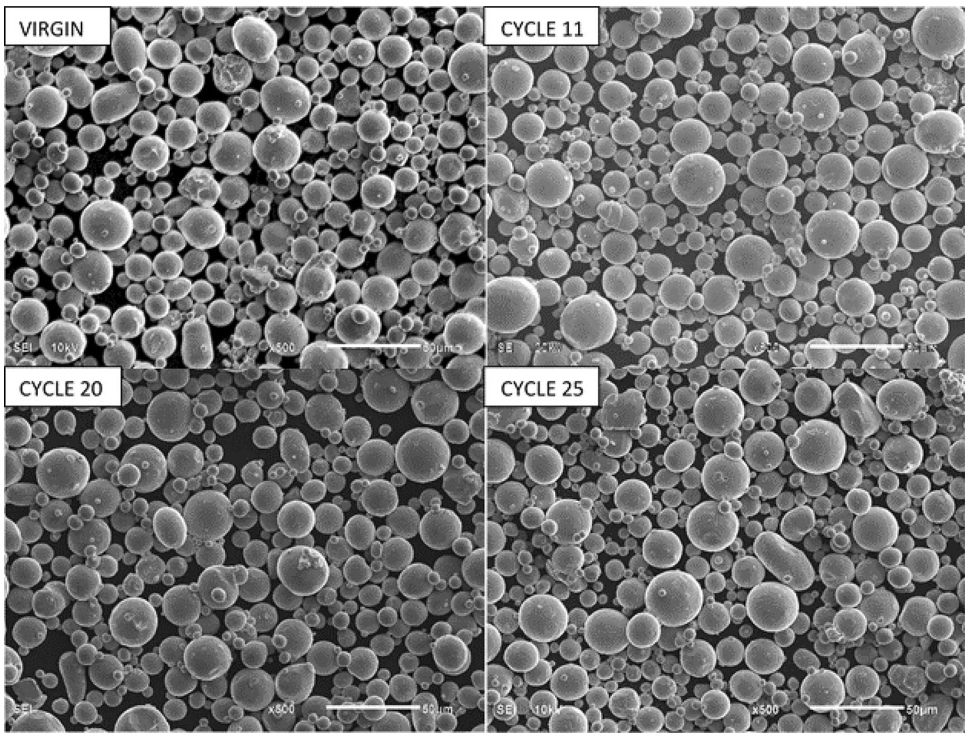

Fig. 2. Scanning electron micrographs of the Ti6Al4V (ELI) powder used in the EOSINT M280 DMLS machine as received (virgin) and after various re-use cycles. Scale bar 50 μm. Magnification $\times$ 500. Reprinted with permission from Ref. 8.

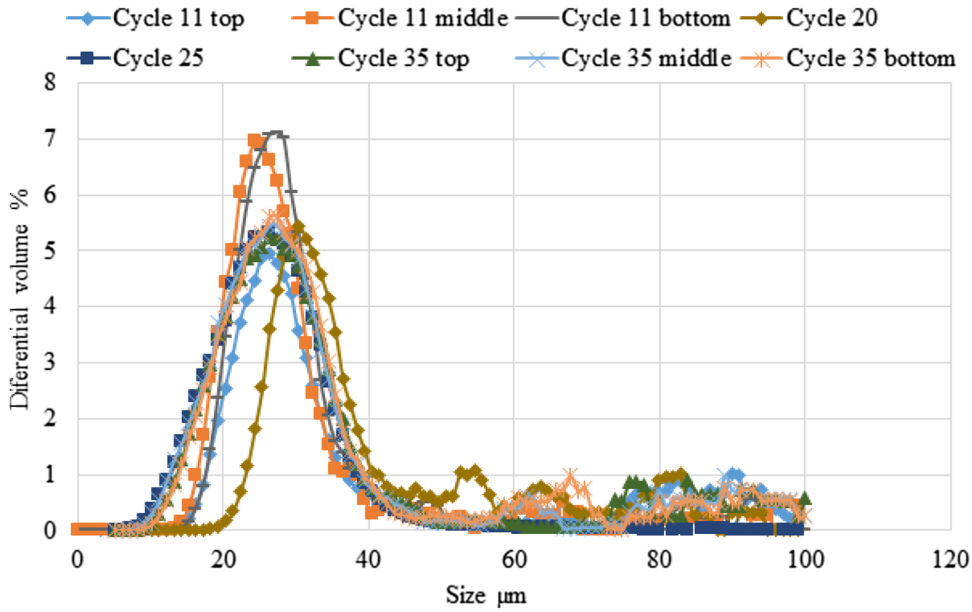

Fig. 3. Particle size distribution of the Ti6Al4V (ELI) powder after increasing numbers of re-use cycles in the EOSINT M280 DMLS system. Reprinted with permission from Ref. 9.

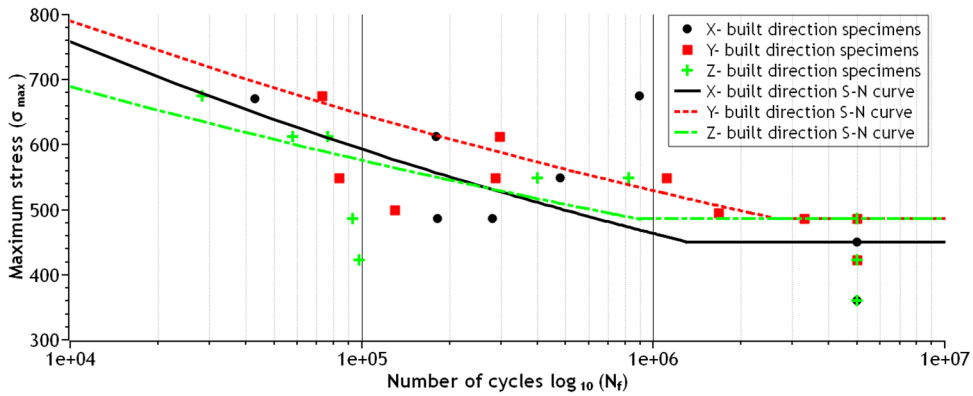

Fig. 4. *S–N* curves of the as-built Ti6Al4V (ELI) specimens built in the *X*-, *Y*- and *Z*-build directions. Reprinted with permission from Ref. 12.

The semi-log graphs of maximum stress (S) (MPa) against life (N) of the specimens produced along the three orthogonal build directions were plotted and the displayed endurance limits were compared, as shown in Fig. 4.

From the run-out levels in Fig. 4, the following estimated fatigue endurance limits were found: *X*-built specimens: 450 MPa; *Y*- and *Z*-built specimens: 486 MPa. This difference between the build directions were considered to be statistically insignificant, given the spread of the data points. (Linear curve fitting for the fractured as-built specimens gave an average correlation coefficient $R = -0.639$.)

More recently tension–tension fatigue tests, with the same fatigue test parameters as those used for the as-built specimens, were performed by Malefane et al.[13] on Ti6Al4V (ELI) DMLS specimens that were stress-relieved at 650°C for 3 h and subsequently annealed at 950°C for 2 h. For these specimens, the estimated fatigue endurance limits were: *X*-built specimens: 450 MPa; *Y*-built specimens: 450 MPa; *Z*-built specimens: 486 MPa. However, a smaller scatter of data points was observed, indicating more consistent fatigue behavior due to improved ductility of these specimens. (Linear curve fitting for the fractured as-built specimens gave an average correlation coefficient $R = -0.779$.) The beneficial effect of the high-temperature anneal was confirmed in a recent study by Yadroitsev et al.[14]

It should be noted that neither the as-built specimens nor the stress-relieved and annealed specimens were submitted to hot isostatic pressing before the fatigue testing.

MEDICAL IMPLANT APPLICATIONS

Additive Manufacturing for Facial Reconstruction

In the Kimberley Hospital Complex in South Africa, doctors successfully performed the country's first 3D-printed jaw bone implantation.[15] The patient, a 31-year-old man, was suffering from facial disfigurement due to cancer. The surgery to implant a titanium jaw was headed by Dr. Cules van den Heever, a prosthodontist, who has extensive experience in prosthetic jaw implantations and works closely with the CRPM engineers. He was assisted by Dr. Kobus Hoek, a maxillofacial surgeon, as well as doctors at the Kimberley Hospital's Dental Department. The implant was intended to fix the facial contour and restore its normal appearance and function. The customized jaw was designed (Fig. 5a) and manufactured on site at the CRPM from Ti6Al4V (ELI) powder in an EOSINT M280 DMLS machine. The capabilities of the DMLS technology, such as rapid production of patient-specific implants, reduction of trauma of the patient and improved cost-effectiveness of procedures through shorter surgical theatre time leading to quicker patient recovery, were demonstrated through this application.

Based on the confidence levels established with respect to implant integrity (validation of density, mechanical properties and fatigue performance through the data obtained from the various research projects, as well as the process repeatability and part traceability provided by the ISO 13485 system), a next generation of customized mandibular implant incorporating a cage for bone graft, shown in Fig. 5b, was designed and implanted successfully. After full recovery of the patient from this surgery, bone grafted from the patient was inserted in the cage and allowed to densify. The presence of solid bone in the cage to which the patient's soft tissue could attach, would offer the potential to implant dental implants into this bone. At the time of publication, the implantation of dental implants had not yet occurred.

Polyurethane Artificial Heart Valve Development

Cardiac valve replacement can be with either biological valves or artificial valves. Biological valves deteriorate with time, calcify and fail. This usually requires multiple surgeries. Artificial heart valves have been developed over the past six to seven decades and represent one of the most widely used cardiovascular devices. Some of the existing devices cause thromboembolic episodes and require anticoagulation. In developing countries, such as South Africa, it is not always possible to monitor the level of anticoagulation properly because international normalized ratio clinics are not always in close proximity to patients, and uncontrolled anticoagulation can lead to traumatic internal bleeding episodes.[16] Commercially available mechanical valves suffer from clotting, while biological alternatives suffer from a short fatigue life. Polyurethane valves have been perceived as potential means to address both of the problems of current heart valves, as well as being biocompatible.[16] It was estimated that the worldwide number of patients needing heart valve replacement will triple from 290,000 in 2003 to over 850,000 by 2050.[17] If an artificial heart valve, affordable for developing and emerging economies, could be developed and produced, the potential for meeting this need could be significantly improved.

In a collaborative research program between the CRPM at CUT and the Robert W.M. Frater Cardiovascular Research Centre at the University of the Free State, a reliable, affordable dip-molding

(a) (b)

Fig. 5. (a) Initial customised mandibular implant produced through DMLS of Ti6Al4V (ELI) and (b) the next generation mandibular implant with a cage for bone graft.

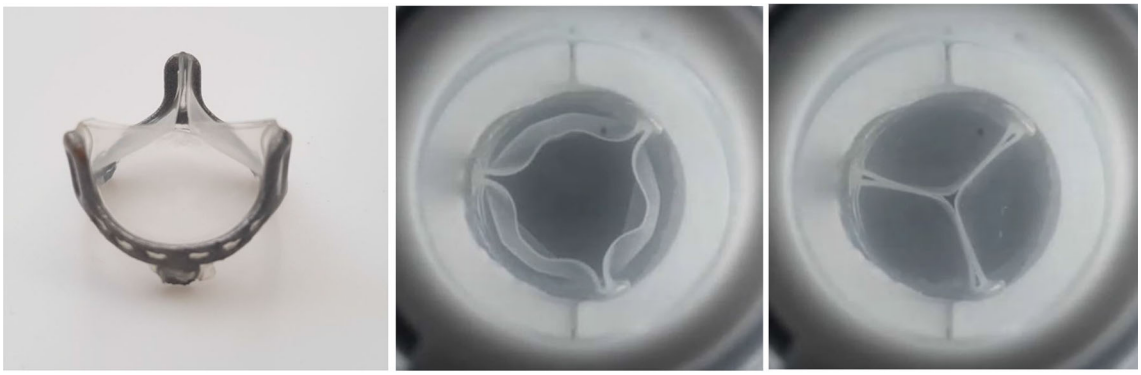

Fig. 6. Pulse duplication performance of a prototype polyurethane tri-leaflet heart valve (a); fully opened (b) and fully closed (c). (b) and (c) reprinted with permission from Ref. 16.

process for repeatable production of tri-leaflet polyurethane heart valves was developed. DMLS of Ti6Al4V (ELI) was used for producing the mold assembly and the valve frame onto which the dip-molded leaflets attach. This was found to be an efficient and cost-effective means of expediting the product development process. A number of prototype valves were produced and evaluated with respect to compliance of properties such as leaflet thickness, surface finish and mechanical strength. Pulse duplication trials with these prototypes provided data on the heart valve pressure drop, effective orifice area and percentage regurgitation, as required by the ISO 5840-2:2015 standard.[18] Particle imaging velocimetry was employed to measure the velocity flow field through the heart valve and to determine the viscous shear stress acting on the valve. The magnitude of the viscous shear stress determines the likelihood of hemolysis (damage to red blood cells) and platelet activation (clotting of the blood). A prototype polyurethane heart valve and its functioning during pulse duplication trials are shown in Fig. 6.

These prototype polyurethane tri-leaflet heart valves displayed performances that complied at levels of 80% or better with the ISO 5840-2:2015 standard. Based on the density, mechanical properties and fatigue performance confirmed through the research, as well as the process repeatability and part traceability provided by the ISO 13485 system, the DMLS produced Ti6Al4V (ELI) heart valve frames were accepted for this application. This confirmed that the goal of producing a fully functional, durable and affordable heart valve, capable of regulating the one-way flow of blood, was indeed achievable.[17]

CONCLUSION

The focused research conducted by the participants in the Collaborative Program in Additive Manufacturing has been delivering data that are raising the level of confidence in the ability of well-managed SLM machines to produce high-quality medical implants. Characterization and monitoring of the feedstock Ti6Al4V (ELI) powder can lead to improved cost-effectiveness of the production process through minimizing material wastage and complete consumption of the material. Through DMLS process control and appropriate post-process heat treatment, fatigue properties of components that compare favorably with those of wrought Ti6Al4V (ELI) can be achieved. Available research results have provided strong evidence that there is no reason to doubt the fit-for-purpose properties of the medical implants produced under the ISO 13485 quality management system of the CRPM.

However, for full qualification and acceptance of DMLS-produced components by the aerospace industry, continued research is required to accumulate AM validation data that would satisfy the more stringent specifications of this sector. For aerospace applications, hot isostatic pressing of AM parts would be required at this stage of the technology. Higher numbers of cycles for acceptable run-out levels during high cycle fatigue testing will also be required.

ACKNOWLEDGEMENTS

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