Response to Consultation: Proposed regulatory scheme for personalised medical devices, including 3D-printed devices

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The 3dMedLab based at Austin Health, The University of Melbourne, is a unique multidisciplinary, multi-specialty medical 3d printing laboratory undertaking research into the feasibility, application and value of 3d printing in the healthcare environment, particularly in the hospital setting. We welcome this opportunity to provide feedback to the Therapeutic Goods Administration regarding the proposed regulatory scheme for personalised medical devices, including 3D-printed devices.

About the 3dMedLab

Founded in 2015, the 3dMedLab aims to assess and understand 3d technologies including 3D visualisation, 3d modelling, Virtual Reality (VR), augmented reality (AR) and 3d printing in a public hospital setting. Our laboratory is based in the Austin Health Department of Vascular Surgery with collaborations with The University of Melbourne School of Biomedical Engineering, Melbourne School of Design and Research Platforms. We also exchange knowledge and expertise with a number of domestic and international research groups.

Unique to our laboratory is active involvement of multiple specialist medical disciplines from Vascular and Orthopaedic Surgery, Cardiac Surgery, Radiology, Respiratory Medicine, Ear Nose and Throat Surgery, Plastic Surgery, Maxillofacial Surgery, Radiation Oncology, Urology and Liver Surgery, along with allied health input from Orthotics, Prosthetics and Podiatry.

The primary focus of work within 3dMedLab is 3d modelling to support surgical decision making, medical implant development, procedural training, simulation and teaching, as well as patient education. To date, 3dMedLab has not engaged in and has no direct plans to engage in bioprinting or tissue engineering.

Background Statements

3dMedLab recognises and supports the cogent arguments made for reform of the personalised medical device regulatory scheme. Current definitions of personalised and customised medical devices vs custom-made medical devices (particularly internally placed implants) do not adequately allow for developing and future evolution in the medical device manufacturing space, and the growth of personalised medicine and implant customisation.

Comments on Definitions for Personalised Medical Devices

Currently medical devices are, by and large, mass-produced in large batches of identical or near-identical products. The design and quality control of these products are reviewed through assessment and inspection of the design and manufacturing process and facility, and performance characteristics are documented and monitored through destructive sampling or in-production testing of batches or lots as they are produced. In-market and post-market surveillance is also a mandatory part of safety monitoring for these products.

In many cases (particularly with implanted medical devices) a one-size fits all approach is not feasible and therefore there is scope within the current regulatory scheme for variations in size and design to be accommodated within the same regulatory approval providing they are not substantially different to the original product to the point where performance characteristics are impacted. An example of this is knee or hip prostheses which come in a variety of sizes but are not substantially different. Where these are mass-produced the same quality testing procedures will generally be applied. These would match the proposed definition of a **patient-matched medical device**.

In some cases the device may be modified by the physician who is using the device. An example of this may be a mass-produced fixation plate that is screwed into bones across a fracture to maintain position. Sometimes this fixation plate will be bend or shaped to maintain the degree of fixation required. The same device may be applied to different parts of the body. In most cases, these devices will be used within predicted and specified application envelopes provided by the manufacturer or distributor (qualifying for the proposed definition of an **adaptable medical device**). Another example may be an endovascular aortic stent graft which is designed with certain degrees of tolerance in the variation of its deployment, in order to match the patient's anatomy.

Nevertheless, there will be a variety of devices and procedures where a currently listed, on-market device will be utilised in a manner which is outside the manufacturer's documented or intended applications (off label use, or non-IFU where IFU stands for Instructions for Use). An example would be a stent that is deployed in a location or for a pathology which is not specifically listed in the ARTG listing or the IFU, whether or not this would be accepted practice amongst the specialty group or internationally. In our current regulatory landscape these uses are permitted though there are some obligations that rest upon the physician as a result of such use. At this time it is unclear whether the proposed regulations will change this.

Increasingly, however, modern computer-controlled manufacturing techniques such as CNC milling or additive manufacturing (3d Printing) mean that we are able to produce single or small-batch products, devices and implants which are completely personalised to an application or an individual patient, and which may not be produced in such numbers as to undergo traditional sampling and destructive testing, nor undergo large-scale clinical trials in the traditional randomised methodology.

In this setting, the only effective means to assess and regulate these products is to stratify and group them by some form of commonality and then to apply regulatory oversight, approval and listing based on that stream.

For example, a personalised hip prosthesis might be based on a standard stem design, but modified digitally based on acetabular or pelvic anatomy. The final device might be based on a standard component and a personalised 3d printed component which may go through several design and prototype iterations before a final product is printed, in single-digit quantities.

Alternatively a novel partial hepatectomy cut-guide, an organically-inspired structural support ankle-foot orthosis (AFO) or a once-off spinal-reconstruction rig may not be directly comparable to any existing device and only ever be produced on small scales. Its manufacture may only be possible via 3d-printing and it may only ever be used a handful of times in that unique setting.

That commonality may not rest solely within the use-case of the device, or the materials of its construction, or the manufacturing equipment or process used to create it, or the designer who conceives and crafts it.

If such a commonality can be defined, then regulation principles can be applied to that aspect or that process, hence the definition of a **Medical Device Production System** which encompasses part or all of the variables which contribute to the construction of these devices including physician request processing, image analysis and 3d segmentation, engineering or other design requirements, software used for these purposes, 3d-slicing and print file generation, material selection and properties, 3d printing parameters, device or product outcome parameters, post-processing, delivery, packaging and sterilisation if appropriate.

The consequence of defining such a Medical Device Production System is that manufacturers, suppliers or sponsors will need to be extremely specific as to the use of such a system, and either they need to encompass a very wide range of use-cases or they will have to be very restrictive as to the permitted and regulated uses. Users will have to decide whether the products and devices being manufactured fit within existing specified applications as approved by TGA or whether they are out of scope.

This leads to either a market where a large number of MDP Systems will exist with very specific use cases, or a small number of MDP Systems that will be either housed in hospitals or service bureaus which have a large and comprehensive of approved use cases. Nevertheless, any of these outcomes will restrict innovation and exploration of novel applications.

3dMedLab supports the definitions of patient-matched, adaptable and custom-made medical devices. These are not too dissimilar to existing definitions and it would not be expected to create excessive regulatory burden. The need to provide patient statements, submit annual reports, maintain usage and implantation records are real, however we would make the following comments:

- Any information provided to patients must be in plain language and should not be voluminous.
- The length of time by which an implantable device should have records maintained should probably relate to the risk level of the device, the intended life of the device, and the age of the patient.
- If the proposed time period is problematic for a manufacturer then the TGA may consider a scheme where device and implantation details are lodged with a TGA-controlled registry to be kept in perpetuity.

Regarding Medical Device Production Systems (MDP Systems)

Consideration should be given as to how restrictive or specific the definition of such systems should be. For example, of the following variables, which ones should be a necessary part of the ARTG listing and which ones should be permitted to be open ended:

- indication for and intended use-case for medical device
- physician request processing system
- tomographic image capture technique (CT/MRI/US protocols etc)
- analysis and 3d segmentation techniques, software
- qualification or training of operators of such software
- engineering or other design requirements, software used for these purposes, qualification and training of operators
- 3d-slicing and print file generation algorithms and software
- raw material selection and properties of such
- 3d printing parameters for intended use-case(s)
- device or product outcome parameters
- post-processing techniques, qualification and training of operators
- packaging and sterilisation techniques, or instructions

Obviously highly restrictive and specific requirements will limit the usefulness of any such MDP Systems and dramatically increase its costs of implementation and operation. It would also reduce the number of use cases to those where volume is high, and stifle the most innovative and useful applications being uniquely uncommon, rare or complex cases requiring extensive personalisation of models, moulds, guides or implants.

The requirement to limit MDP Systems to low-risk devices does not provide for the future concept of in-hospital, just-in-time implant manufacture. It is inevitable that over the next few decades, if not years, MDP Systems will evolve to the point where reliable implantable functional devices can be placed within hospitals as a point-of-care manufacturing system. If the MDP System regulatory framework is to be limited to Class IIa and below devices then a roadmap should exist for future development of MDP System regulation of higher risk devices.

In addition, the concept behind definition of an MDP System is predicated upon healthcare providers or facilities contracting out regulatory responsibility to a third-party manufacturer. In the absence of an effective or affordable market for such services, or if such third-parties decline to seek ARTG listing, those hospitals that utilise 3d printing will not be able to avoid this regulatory responsibility. If that is the intended outcome it should be made clear in the proposals.

Upgraded classification of medical devices that record diagnostic images

Diagnostic images include a wide range of materials ranging from traditional x-rays, CT, MRI, and ultrasound scans in DICOM format, to fused PET or SPECT images, nuclear imaging and radioisotope studies, clinical photographs, hand-drawn ultrasound diagrams and worksheets, electro-encephalograms, spirometry charts, and more. The definition of "X-ray diagnostic images" is unclear and arguably incorrect.

The definition as provided would include all forms of Picture Archiving and Communications Systems (PACS) used for storage of patient images, and also electronic medical records, and physical or electronic filing systems where such images were kept. The effect of this definition would be wide-ranging with potential unintended consequences.

It would appear that the intent of this definition is specifically related to the software used for 3D segmentation of anatomical models used for diagnosis or procedural planning, but also for those systems used to review diagnostic images for clinical purposes.

Currently it is unclear under what parameters TGA would assess such software for conformity. Vendors of commonly available and widely used software packages for review of diagnostic images will usually indicate whether they are FDA compliant but TGA and ARTG listing status is generally unknown.

The proposed recommendation would appear to equate anatomical models to software when this is not really the case. Virtual anatomical models are generated using software and physical anatomical models are then manufactured using 3d printers. Any one piece of software or printer may be able to generate a wide variety of anatomical models.

The proposal as read suggests that each anatomical model or type of model (whether by body part, material or construction and design qualities) should be individually listed. One assumes that this is not the intent of the proposal and that intsead rule 5.4 should be changed to:

> *5.4 Medical devices intended to record diagnostic images*
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> *A medical device that is intended by the manufacturer to be used to record diagnostic images is classified as Class IIa. This includes software <u>USED TO GENERATE</u> anatomical models intended for diagnosis or investigation of the anatomy.*

Regulation of Devices with a human origin component

Whilst the 3dMedLab does not engage in bioprinting, we note that these principles may be relevant to biological materials of a non-human origin such as xenografts. Relevant principles should apply from existing regulatory frameworks for xenograft materials.

Regarding modifications or adaptations to personalise a device must have been intended by the original manufacturer

We would like to point out that there will be significant challenges to the definition and enforcement of such a regulation. Compliance with this proposal would require that every existing surgical tool and device have all possible use cases, applications, modifications and instructions specified. A wide variety of medical devices currently do not have such specifications, and their nature is such that surgeons and proceduralists use these devices in a wide range of applications which are not possible to specify in an IFU.

An example would be a surgical retractor which would either need to carry a “bailout” clause allowing its use in any manner the surgeon sees fit, or an exhaustive list of every part of the body and every incision where it could be used, and the manner in which it would have to be inserted and manipulated during the course of a wide range of operations, some of which have not been invented yet.

If an application was not within IFU or specified in the ARTG listing then its use would essentially be off-label or non-IFU even if such application were standard or best-practice internationally and accepted as such by specialists in that area. Currently no attempts are made to regulate or restrict the use of products in an off-label or non-IFU manner and it is questionable that such a rule would achieve much given that there are no real consequences for such use.

It would appear that the primary purpose of this proposal is to clarify that when a healthcare professional utilises a manufacturing technique that is not within a registered MDP System that they assume the responsibilities of a manufacturer. The current proposal risks unintentionally classifying all surgeons that utilise any medical device in a manner that was not pre-specified by the device supplier as a manufacturer.

What changes would you need to make (if any) to meet the new arrangements? If not, what are the impediments?

If the proposed changes were to be implemented then the current structure and viability of the 3dMedlab would be directly impacted. Much of our research and activity revolves around the development of workflows, processes and outcomes of low-cost 3D printing of anatomical models for teaching, education and surgical planning and rehearsal. These last two applications are directly impacted by the proposals regarding MDP Systems and Diagnostic Imaging software.

Currently the feasibility and uptake of this technology is limited by the availability of technical expertise and training. We envisage that the costs of compliance would rise dramatically, along with the costs of software and 3D printing systems. This would further limit the uptake of this technology and may render it non-viable for many or most institutions, potentially obliterating this market segment without strategic investment by government.

Given that clinical trials and research is still required to assess outcomes and benefits, we would strongly request that a pathway be created whereby this technology can be adequately researched and assessed in the clinical environment.

Without adequate investment in research either by the commercial 3d-printing software and hardware industry, or by strategic institutional, government or philanthropic funding in order to allow hospitals to develop in-house MDP Systems and take on a limited manufacturer role, there is a significant risk that this market and research sector will effectively die out.

From consultations with other hospital-based 3d-printing facilities, most will need to qualify at least part of their capacity as an MDP System manufacturer under these proposals. Currently almost all such facilities (with the exception of bioprinting research laboratories) operate with extremely small budgets in the order of $5000-$10,000/year or consumables, and in many cases pro-bono research, technical and clinical staff. Where funded, the majority of this goes to technical and research staff time and such funding is diverted from grants intended for other projects.

Compliance with these proposals will require dedicated regulatory compliance work estimated to be a minimum of $50,000/year of technical expertise, consultation, legal and filing fees, and excluding the cost of acquisition of hardware, software and raw materials which are similarly compliant. This would be estimated to be in the range of $50,000/year in software license fees and $500,000 to $1,000,000 in hardware costs as well as ongoing maintenance and service contracts for a basic non-bioprinting laboratory.

In many cases suitably compliant component equipment (software, 3d printers) have not been registered with ARTG for these purposes and significant delays would be expected for such component equipment to be registered.

There would also be significant risk that even if all of the component items used by an in-hospital 3d-printing facility were registered that the specific combination of staff, technical skill, equipment and use-case would not qualify for registration as an MDP system or that each such use-case would need to be individually registered.

3dMedLab has significant concerns that the accepted North-American model for in-hospital 3d printing facilities for multidisciplinary anatomical modelling to guide clinical decision-making, surgical planning and implant selection would not be viable from a financial or a regulatory perspective. Such labs make use of a variety of equipment together with skilled and trained staff to produce a wide variety of anatomical models for complex and unique pathology and surgical procedures. These are a critical and essential application of 3d printing and the viability of such a model must be preserved along with the research and innovation functions of such laboratories.