Regulatory Changes related to personalised and 3D printed Medical Devices

- Submission by Griffith University -

Attention:

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BE REMARKABLE

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Introduction

Manufacturing and product development, design and prototyping are undergoing rapid disruptive change. Companies now are able to rapidly design, prototype and test new products, utilising digital design and advanced manufacturing methods. Among other technologies, additive manufacturing with 3D printers accelerates prototyping, but also has the potential to disrupt classical centralised high-throughput manufacturing of goods and respective established logistic chains, by enabling local manufacturing of a host of products.

As a second key enabler, computer-aided design (CAD) software profoundly changed product development, including in the field of medical devices. Based on medical images (e.g. X-ray, Ultrasound, CT and MRT), biomedical engineers utilise CAD software to create three-dimensional (3-D) models of the human body. Such models are now extended to include muscles, tendons and activation patterns to provide functional models of the human neuro-musculoskeletal system.

There is a unique opportunity for digitally designed and 3D-printed medical implants and surgical tools to revolutionise orthopaedics and reconstructive surgery. The classical model of mass-manufactured one-fits-all orthopaedic implants (***mass produced medical devices***[1]) is challenged by local manufacturing of ***personalised medical devices***, with the promise of better outcomes for patients. In addition, point-of-care production of ***personalised medical devices*** may replace established logistic and value chains and provide major economic benefits for the health system.

However, ***personalised medical devices*** also challenge traditional regulatory frameworks. Many countries are now considering new frameworks for such devices.

Griffith University is establishing the "Advanced Design and Prototyping Technology" (ADaPT) facility that will be located in the emerging Gold Coast Health and Knowledge Precinct, next to the Gold Coast University Hospital, the Gold Coast Private Hospital and Griffith University's Gold Coast campus. ADaPT will be the space where Griffith University will apply its know-how and capabilities in functional 3D modelling, simulation, digitally enabled product design, advanced manufacturing and material research, in collaboration with the local hospitals and industry, and international partners. We expect the facility to be operational in 2020.

1 In this document, any term defined in the Consultation Paper "Proposed regulatory changes related to personalised and 3D printed medical devices" is highlighted in italics and bold.

This industry-focused facility will be a place for rapid prototype development. For customers ADaPT will design prototype products that combine optimal functional characteristics of the right material with the best look and feel for end-users.

A key activity will be the creation of functional models of the human neuro-musculoskeletal system. Such models will be high-fidelity tools that will allow diagnosis of neuro-musculoskeletal conditions, rapid design, functional simulation and fabrication of ***personalised medical devices***, surgery planning, and appropriate physiotherapeutic rehabilitation.

The University welcomes the consultation by the TGA relating to the regulatory framework for ***personalised medical devices***, including 3D-printed devices, and wishes to contribute to shape the regulatory framework to become an effective enabler for ***personalised medical devices*** and point-of-care manufacturing of such devices.

With this submission, Griffith University would like to provide some comments and suggestions, with a focus on enabling software tools and advanced manufacturing, e.g. 3D printing.

[redacted]
Griffith University

Proposal 1: New definitions for personalised devices

Question 1.1

Is the proposed definition for custom made device clear enough?

> ***custom made medical device*** **- means any device**
>
> - that is specifically made in accordance with a written request of any person authorised by Australian law by virtue of that person's professional qualifications as a healthcare provider which gives, under that person's responsibility, specific design characteristics; and
> - that is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs; and
> - for which there is no commercially available alternative medical device.
>
> ***Mass produced devices*** **which need to be adapted to meet the specific requirements of any professional user and** ***patient specific devices*** **shall not be considered to be custom-made devices.**

The scope of this definition is not clear.

The definition assumes that **custom made medical devices** "*are specifically made in accordance with a written request of any person authorised by Australian law by virtue of that person's professional qualifications as a healthcare provider which gives, under that person's responsibility, specific design characteristics*". However, a healthcare provider, e.g. an orthopaedic surgeon, typically collaborates with a biomedical engineer or another qualified person, who (digitally) designs and then develops the respective files for e.g. 3D printing of a **custom made medical device**. Devices then are typically fabricated by a technician or other appropriately qualified person.

The wording of the 2nd bullet point ("*that is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs*") could be interpreted very broadly and then would encompass **patient-specific medical devices**, as these are utilised to meet a patient's "*individual conditions and needs*". When taking functional aspects of implants into consideration, conditions and needs are highly individual. If the definition were to be interpreted very narrowly, only medical devices for rare or highly complex conditions would fall under this definition.

The 3rd bullet point ("*for which there is no commercially available alternative medical device*") also is open to interpretation. What are the criteria that define

whether there is "*no commercially available alternative medical device"*? In a broad interpretation, there would be a "*commercially available alternative medical device"* for a large number of implantable medical devices. However, such "*commercially available alternative medical device"*, may not the best fit for a patient's "*individual conditions and needs"* and therefore not be recommended by a healthcare provider.

In addition, availability currently is biased towards commercial interest, as commercial providers need to create value for their shareholders – therefore areas of medical need may not be addressed and there may be no *commercially available alternative medical devices*.

We would suggest that the TGA clarifies the scope of this definition.

- The term "*specific design characteristics*" should be clarified to acknowledge how such devices are designed.
- The term "*individual conditions and needs*" should be clarified to clearly delineate ***custom made medical devices*** from ***patient-specific medical devices***.
- The term "*commercially available alternative medical device*" should be clarified to ensure that a healthcare provider can choose the type of device that will provide the best outcome for a patient.

Question 1.2

- *Should the number of custom made devices that a manufacturer or sponsor can supply in one year be limited? The FDA limits this number to 5 per year in the USA, a country whose population is more than 10 times that of Australia.*

The field of ***custom made medical devices*** is evolving and it is not yet clear, to which extend they will replace ***mass produced medical devices***, ***customised medical devices*** and ***patient-specific devices***. With the next generation of neuro-musculoskeletal functional models, patient outcomes can be predicted more accurately and therefore ***custom made medical devices*** may become more prevalent.

In addition, Hospitals may become point-of-care manufacturers of ***custom made medical devices***. In this case, large hospitals may provide more than a few ***custom made medical devices*** to patients per annum.

Accordingly, limiting the number of ***custom made medical devices***, which a manufacturer or sponsor can provide, can have unintended consequences.

We would suggest that the TGA does not limit the number of ***custom made medical devices*** that a manufacturer or sponsor can supply in one year.

Question 1.3

- *Should the TGA implement an application and approval process for the use of a custom made device? This is the approach taken by Health Canada.*

As discussed later in this submission (section "General") the TGA may consider an alternative pathway and provide a regulatory approval for any ***personalised medical devices*** that has been designed and manufactured with an approved / certified ***medical device production system***. That would require a regulatory approval process for ***medical device production systems*** and respective quality control standards for the application of the system.

As a key enabler for development of ***medical device production systems***, the TGA should consider approving / certifying:

- raw materials for printing;
- digital modelling, design and 3D printing software tools, including functional models and their utilisation for simulation of outcomes and surgery, creation of physical anatomical models, diagnostic and rehabilitation services; and,
- 3D printers and the respective finishing devices.

Question 2

- *Do you have any other comments or suggestions about the proposed definitions?*

The wording of the definitions is not intuitive. We would suggest to use slightly different, but more intuitive terms:

Term utilised in Consultation Paper	Proposed Term
mass produced medical devices	mass produced medical devices
customised medical device	adapted medical device
patient-specific medical device	customised medical device
custom made medical device	patient-specific medical device
personalised medical device	personalised medical device
medical device production system	medical device production system

Also, consistent terminology would help to clarify the scope and intent of the Consultation Paper. For example, it is not clear, whether the terms "health care provider" and "health care practitioner" have the same meaning.

- ***patient-specific medical device*** – a medical device based on a standard device template model that is matched to a patient's anatomy using techniques such as scaling of the device based on anatomic references, or by using the full anatomic features from patient imaging, and which is produced through a process that is capable of being validated

The term "*standard device template model*" is not defined within the Consultation Paper. It is not clear, whether these models are physical or digital, or both. In both cases, such models need to be of high fidelity, to provide safe and reliable benefits for patients.

The same applies for the techniques utilised to match the *standard device template model* to a patient. There is a high risk that multiple techniques would be utilised that have not sufficient fidelity to provide reliable and safe outcomes.

There is no guidance, what "*is capable of being validated*" encompasses and how the respective process would be validated.

We suggest that the TGA clarifies this definition and provides guidance about the respective validation of processes utilised to match a *standard device template model* to a patient.

- ***medical device production system*** – a collection of products, including specified raw materials, that is intended to be used by a health care practitioner to produce a finished medical device and that may include the input of a digital patient image file.

  The system output must be validated with the specified components. The classification of the system is determined by the classification of the finished device.

Typically, a *health care practitioner* would request e.g. a ***custom made medical device*** from a company and contribute a general specification of what is required to help a specific patient. Full design, production and finishing of a *custom made medical device* then would be done by a biomedical engineer, designer and technician in the company. Therefore, in almost all cases, a health care practitioner will not produce a finished medical device.

Also, there is no guidance, how the ***medical device production system*** would be validated.

We suggest that the TGA amends the definition to include qualified non-health care practitioners to reflect the current practice.

The TGA also could provide training requirements and a certification process for non-health care professionals to enable them to produce finished medical devices with a validated ***medical device production system***. From a health economics perspective, this will allow health care practitioners to focus on ensuring that their patient's needs are met without the burden of having to produce finished medical devices.

In addition, the TGA should provide guidelines and a process, how the ***medical device production system*** would be validated, tiered to the classification of medical devices the system is capable of producing.

Ideally, such validation would certify a ***medical device production system*** to enable the production of class III medical devices, provided that the facility has all required quality management systems, including demonstration of compliance with the essential principles through the application of international standards.

Question 3

- *Do you have any other comments or suggestions for alternative or additional strategies?*

The TGA's definition "***patient-specific medical devices***" appears to focus on matching a patient's anatomy. We believe that this needs to be expanded to ensure the device also matches the patient's function, is able to sustain the patient's load demands (how the device mitigates and translates any weight, pressure and movement) and well integrate into patient's tissues. This is consistent with the US FDA's suggested directions (please see section "General").

Computer modelling and simulation (CM&S) is a key method to ensure a patient-specific medical device is designed, evaluated and manufactured to match the patient's anatomy, function, loading, and integration.

Importantly, we believe that the design of ***patient-specific medical devices*** must not be solely rely on geometric modelling. Geometric modelling is a component of CM&S, which entails and is not limited to neuro-musculoskeletal modelling, finite element modelling, integrated computational materials engineering, computational biology, and data analytics. CM&S also needs to be able to include new methods, as these are a key topic of world-wide academic and industrial R&D in the field of ***patient-specific medical devices***.

The current TGA's definition of ***patient-specific medical devices*** relies solely on scaling anatomic references, or the full anatomic features available through patient imaging. However, to accurately match the patient's anatomy, function, loading,

and integration, other imaging and measurement methods, as well as big data (e.g. incorporating feedback from or about devices after implantation) must be employed. All these tools must be capable of being validated. Some examples of other data include motion capture and wearable sensors.

Also please refer to section “General”.

Proposal 2: Changes to the custom made conformity assessment procedure

Question 4

- *Are there any issues or unintended consequences that may arise out of these proposed changes to the custom made conformity assessment procedure?*

Question 5

- *If there are issues, can you provide suggestions for addressing them?*

Question 6

- *Do you have any other comments or suggestions for alternative or additional strategies?*

Griffith University supports the proposed changes.

Proposal 3: Changes to the definition of manufacturer

(3) However, a person is not the manufacturer of a medical device if:

(a) the person assembles or adapts the device for an individual patient; and

(b) the device has already been supplied by another person; and

(c) the assembly or adaptation does not change the purpose intended for the device by means of information supplied by that other person, on or in any one or more of the following:

(i) the labelling on the device;

(ii) the instructions for using the device;

(iii) any advertising material relating to the device;

(iv) technical documentation describing the mechanism of action of the device.

the assembly or adaptation must be in accordance with validated instructions provided by the manufacturer of the device to be adapted; and that, if an individual modifies a device already placed on the market or put into service in such a way that compliance with the essential principles may be affected, they shall assume the obligations incumbent on manufacturers.

Question 7

- *Do you have any other comments or suggestions for alternative or additional strategies?*

Question 8

- *Are there any issues or unintended consequences that may arise out of these proposed changes to the definition of manufacturer regarding customised devices?*

Question 9

- *Are there any issues or unintended consequences that may arise out of these proposed changes regarding the use of medical device production systems?*

The proposed approach could challenge the business models in the medical device industry, (especially the implant space), for the emerging additive manufacturing industry in Australia.

Question 10

- *If there are issues, can you provide suggestions for addressing them?*

Question 11

- *Do you have any other comments or suggestions for alternative or additional strategies?*

The proposed change would enable hospitals and healthcare practitioners to use approved ***medical device production systems*** to produce medical devices of Class IIa and lower for their own patients without being classified as a manufacturer

We support this approach, which will enable hospitals, healthcare practitioners and hospital laboratories to fabricate a number of low risk medical devices; this enables point-of-care production, which has the potential to enhance outcomes for patents and lower respective cost to the health care system.

However, the TGA should consider whether hospitals and healthcare practitioners are sufficiently qualified to use ***medical device production systems*** and that facilities, where the devices are produced, conform with minimum applicable standards.

In line with our previous comments, we suggest there is a need to recognise the role of non-healthcare practitioners in the field. It would be beneficial to clearly define the term "hospital or institute laboratory", and allow non-healthcare practitioners (e.g. biomedical engineers or technicians) to fabricate such medical devices in a hospital or institute laboratory setting. In addition, the TGA should consider that fabrication may not solely occur in a hospital / hospital laboratory setting, but that medical devices also may be fabricated in associated tertiary R&D institutes and their laboratories. Griffith University's AdaPT facility may be such a place.

We also would suggest to consider specifically the dental sector, and shape the proposed changes in a way that would enable dental technicians and other qualified non-medical professionals to utilise an approved ***medical device production system*** to e.g. 3D-print crowns and comparable medical devices.

Proposal 4: New classification for anatomical models and digital 3D print files

5.4 Medical devices intended to record diagnostic images

A medical device that is intended by the manufacturer to be used to record diagnostic images is classified as Class IIa. This includes software and anatomical models intended for diagnosis or investigation of the anatomy.

Question 12

- *Are there any issues or unintended consequences that may arise out of the proposed change to the classification of anatomical models and software?*

Currently, academic institutions are on the forefront of the development of 3D computational models that enable the creation of patient-specific, bespoke 3D print files and then 3D printing of a 3D anatomical model.

There is the risk that the proposed legislation will restrict the ability of academic researchers to develop, test, validate and apply such 3D computational models for research purposes, including clinical research.

Question 13

- *If there are issues, can you provide suggestions for addressing them?*

The TGA should consider an appropriate exemption that takes into account the well-established requirements around human research ethics, that currently provide oversight and regulation for a number of academic research and development activities in the field.

Question 14

- *Do you have any other comments or suggestions for alternative or additional strategies?*

The proposal would benefit from a clear definition of the scope of the terms "*diagnosis or investigation of the anatomy*".

Currently, there is a host of models and relating digital simulation and design tools, with a broad range of applications, specialisation, accuracy and fidelity, which are utilised to transform medical images from a patient into a digital 3D print file and then to create a physical 3D anatomical model.

It is critical to ensure that these digital design tools, including 3D computational models and simulation tools, are of high fidelity and accurately represent the anatomy of the patient. This is particularly important for diagnostic use of such models or planning of surgery.

In addition, rigid models do not allow evaluation of the functional consequences of a surgical intervention. This requires 3D computational models that are 'functional' (or "4D") and represent the respective neuro-musculoskeletal system of a patient. Such models will allow personalised simulation and assessment of a patents neuro-musculoskeletal system (e.g. a knee and all respective muscles, tendons, etc.) for diagnosis, device design and post-surgery rehabilitation. These functional models can be validated through a number of tools, including non-destructive functional testing.

Accordingly, the TGA should consider a requirement for validated functional models for the creation of 3D print files and physical anatomical models.

Proposal 5: New arrangements for devices with human material

Question15

- *Are there any issues or unintended consequences that may arise out of the proposed change to the pathway for medical devices that incorporate materials of human origin?*

There are several materials of human origin that can be included in a medical device. These include:

- 'passive' biological scaffolds that provide bio-compatibility and/or bio-degradability, but no other functional benefits, and do not contain any allogenic components;
- 'active' components, including growth factors and other mediators. Examples are growth factors included in a biological or synthetic scaffold that effect better biocompatibility, active integration, and/or colonisation of an implanted medical device by cells; and,
- viable cells that mediate bio-compatibility and/or may provide additional functional features such as repair and integration.

Any active and viable cellular components have enhanced risk, as they have the potential to functionally modulate the human body and potentially could act outside of the initial side of implantation of a medical device. Especially cells, as prime example for a viable human origin component, can migrate and/or proliferate within the human body, and thus cause undesired effects.

Where such human origin components are derived in a non-personalised (heterologous) way, they also bear the risk of inducing immunologic rejection, due to potential display of allogenic immunogenic determinants to the host immune system.

Question16

- *If there are issues, can you provide suggestions for addressing them?*

We suggest that the TGA differentiates between

· viable vs non-viable;

· passive vs. active, viable or cellular; and,

· autologous vs. heterologous (syngeneic vs. allogenic)

human origin components.

Accordingly, we suggest that TGA only classifies medical devices that incorporate passive and non-viable human origin components, and which do not contain any heterologous (allogenic) components to the host immune system (viz. non-immunogenic), as Class III medical devices.

All other medical devices, which incorporate active, or viable or heterologous immunogenic human origin components, should continue to be classified as biologicals and regulated as such.

Question17

- *Do you have any other comments or suggestions for alternative or additional strategies?*

Question for consideration – General

- *Do you have any comments or suggestions for alternative or additional strategies regarding the regulatory framework as it applies to personalised medical devices or 3D printing in the medical device sector to ensure that it adequately addresses risks to patients?*

Regulatory Approval of Personalised Medical Devices

National medical drug and device regulatory body (FDA/TGA/EMEA) processes are undergoing a step change to deal with ***personalised medical devices***, and enabling technologies such as digital modelling and additive manufacturing that allow rapid development, evaluation and fabrication of ***personalised medical devices***.

For regulatory approval, ***mass produced medical devices*** (e.g. orthopaedic implants) must undergo extensive physical simulator testing, animal studies and clinical trials, which is a very time consuming and costly process. However, this extensive testing is not feasible for ***personalised medical devices***.

For this reason, fast tracking device approval via FDA 510(k), by demonstrating substantial similarity to previously approved implants, is a preferred and sought-after pathway to approval in the USA. The field is rapidly moving, and the FDA has approved personalised implants since 2013, including:

- Oxford Performance Materials, Inc.'s 3D printed "OsteoFab Patient-Specific Facial Device" for facial reconstruction surgery, made from a bio-compatible polymer (2013);
- MedShape's "FastForward™ Bone Tether Plate" for hallux valgus (bunion) deformities, 3D printed with medical grade titanium alloy (Ti-6AL-4V) (2015); and,
- SI-BONE's 3D printed titanium iFuse-3D Implant, for fusion of the sacroiliac (SI) joint (2017).

The FDA now have called for a new process for ***personalised medical devices*** that appears to be based on "product life cycle" and "digital engineering" encompassed e.g. in the Industry 4.0 concept. This process incorporates more extensive use of computer aided design woven with computer modelling and simulations to help rapid development and better evaluation of both devices and drugs. This is in addition to animal, bench and clinical trials.

Based on the proposed concept of ***medical device production systems***, the TGA could consider providing regulatory approval for any ***personalised medical devices*** that has been designed and manufactured with an approved / certified ***medical device production system***. That would require a regulatory approval process for ***medical device production systems*** and respective quality control standards for the application of the system, tiered to the classification of medical devices the system is capable of producing.

By doing so, the TGA would provide a framework for manufacturers to apply quality systems that will help ensure their products consistently meet applicable requirements and specifications. This would ensure that finished devices will be safe and effective and in compliance with the TGA requirements.

It also would enable point-of-care production of personalised medical devices, with associated potentials benefits for the health system and support the emerging additive manufacturing industry in Australia.

As a key enabler for development of ***medical device production systems***, the TGA should also consider approving / certifying:

- raw materials for additive manufacturing of medical devices;
- digital modelling, design and 3D printing software tools, including functional models and their utilisation for diagnostic and rehabilitation services; and,
- 3D printers and the respective finishing devices.

The TGA should aim at establishing regulation and standards in collaboration with the FDA and EMEA to enable the domestic industry to access the world-wide market and domestic patients to benefit from products developed overseas.

Computer Modelling and Simulation is a Key Enabler

It is suggested that, in addition to animal, bench and clinical trials, computer modelling and simulation (CM&S) is adopted as part of the digitally enabled product life cycle, which is strongly aligns with the paradigm set by the Industry 4.0 concept and its adaptation in Europe.

There is the opportunity to accompany the entire product life cycle of a medical device with a functional "digital twin", which is based on innovative and high-quality design, testing and evaluation, incorporates compliance enforcement and enables continuous product improvement through data obtained from the product.

This seems to be aligned with the direction of the USF DA, which is working towards integrating CM&S ("CM&S" is the respective US FDA terminology) into the regulatory approval process. The US FDA intends to use CM&S as a core evaluation tech ology for device and drug design, regulation and approval, for which they propose CM&S

as the 4th method, complementing the three current methods employed, laboratory testing, animal testing, and clinical trials.

We strongly believe that the design, evaluation and manufacturing processes to create a ***patient-specific medical device*** must be capable of being validated. To this end, CM&S needs to incorporate tuning to the patient's data and benchmarking, against *in vitro*, *in vivo* and *ex vivo* data.

Griffith University has strong capability, track-record and networks in the field of orthopaedic and neuro-musculoskeletal conditions. Led by Professor David Lloyd and Professor Randy Bindra, the Gold Coast Orthopaedic Research and Education alliance ("GCORE"), located at Griffith University's Menzies Health Institute Queensland (MHIQ) and the Gold Coast University Hospital, represents researchers and clinicians from Griffith University, the Gold Coast University Hospital, and other selected hospitals on the Gold Coast and in Brisbane.

Griffith University also can tap into a large network of researchers and clinicians spanning Australia and New Zealand, to provide expert advice specifically in the field of CM&S, particularly functional neuro-musculoskeletal models and simulation tools, as well as their application for diagnosis, design of medical devices and rehabilitation.