PROPOSED REGULATORY CHANGES RELATED TO PERSONALISED AND 3-D MEDICAL DEVICES – A CONSULTATION PAPER

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SUGGESTED RESPONSE: FROM PLAC TO THE TGA

[redacted]

PREAMBLE

The PLAC membership is grateful to the TGA for the opportunity to contribute to the proposed changes in regulation of medical devices which have special capacities to subserve the needs of patients at an individual level.

The white paper produced by TGA in November 2017 followed the Melbourne workshop earlier in the year and provides a basis for the discussion.

The TGA document has been superbly prepared and presented. The author/s is/are to be congratulated. The issues have been clearly enunciated, the proposals that have been offered are wide ranging and all-encompassing and the appendices provide more than just a skeleton for understanding.

This PLAC response comes in three separate sections.

Section 1 – General Observations

1. Concept of a Definition

A definition is a concise description (of anything) that is singular, unambiguous and understandable.

Not all definitions in the document are so structured. For example, in Proposal 1 of that white paper on page 9 of 34, under the definition "Personal Medical Device", the definition could be viewed as describing a custom-made device, a customised device or a patient-specific medical device. All three are different. The definition fails the principal test.

It is imperative therefore that the definitions chosen are precise, concise, descriptive, singular, unambiguous and capable of being understood by the average reader.

2. Issues for Regulation

There are four separate areas for the Regulator to consider:

- Materiels

  All goods used in the manufacture of devices must conform to ISO standards, and be seen to do so. This already forms part of the TGA purview.

- Processes (for both design and manufacture)

  The processes will include data acquisition, the interpretation of those data, the subsequent utilisation of those data and the eventual manufacture of a device. The process will also include assembly, packaging, distribution and proper labelling. The acquisition of the data may include, but will definitely not be limited to, 3-D printing.
  The TGA could consider mandating that manufacturers specify boundaries within which the new design will conform. This would allow for more routine testing of performance at the extremities of this envelope in every permutation.

- Tools

  Instruments and other such tools may be specially manufactured for the insertion of devices, whether they are of a generic, customised or custom type. The production of these tools should also be subject to regulatory constraints and capable of validation.

- The Devices Themselves

  It is difficult to imagine that any medical device of Class II-b, or higher on the risk spectrum, could be used *sans* regulation.

Of these four categories, the first three appear to be relatively easily achieved by current TGA functions. It is the subset of the fourth element (custom devices), which is creating such concern.

3. Device Groups and their Definitions

It is suggested that there be three groups subject to regulation:

- Generic devices

  These are devices that can be manufactured in groups, in bundles or *en masse* and are available for general use. In this circumstance, the patient is modified to adapt to the shortcomings of the generic nature of the implant. For example, during the course of a total hip replacement, a femoral component (a metal device) is inserted in the upper end of the thigh bone. Whilst most systems will have as many as 10 or 12 options available to the implanting surgeon, not every patient will conform exactly to the sizes on offer. Diameters of the device typically vary in 2mm increments. Whether the principal number is odd or even is irrelevant. The patient may fall between those 2mm limits. In that situation, a slightly smaller device may be used or alternatively, the medullary canal of the recipient is enlarged slightly to accommodate the next larger size.

- Customised devices

  These are devices which typically have a generic origin but can be modified in some way post-manufacture but prior to insertion. An intramedullary nail may be bent, a spring may be stretched, a tube may be shortened. The process of alteration renders what was a previously generic device closer to the precise needs of the individual patient. Rather than being for *en masse* use, these customised devices may subserve the needs of a smaller subgroup of patients.

- Custom devices

  This is the device which is made specifically for an individual patient. It is personalised and single patient specific. Using the orthopaedic model of the hip, a useful example may be the manufacture of a specific femoral component for a patient who has suffered with congenital dislocation of the joint. A tiny implant may be required with a unique configuration derived from the templating of plane radiographs, of a CT scan or even some 3 dimensionally created image. So-called “3-D printing” is just one of the measurement tools available. The tool used for the acquisition of the data is not the issue. It is the device itself.

  Design modifications will be guided by both manufacturing principles and purpose. The former are already on the TGA agenda. It is the latter that requires ongoing surveillance. This can be referred to as "tracking the principle" as opposed to simply tracking the device. Both are important but the principle is essential. We should also differentiate between "tracking" a device to a specific patient and "tracing" the patient/device in perpetuity thereafter. Both are necessary.

Section 2 – Constructive Criticisms

The TGA white paper relies upon a number of basic premises and refers to international comparators. The following observations may be of some assistance in formulating a safe and well-structured regulatory framework:

1, 3-D Printing is not the Issue

So-called three dimensional printing, regardless of the methodology used, it not the only tool available for the construction of a true custom device for an individual patient.

An example may be of a patient who has a serious hemi pelvic deficit following removal of a malignant bone tumour. A generically–shaped bioresorbable template, seeded with host or donor stem cells, can be inserted and moulded in situ to recreate a “skeletal frame” capable of osteogenesis and hemi pelvic regeneration. 3-D printing has nothing to do with the process.

2. International Comparators

The approach adopted by the Food and Drug Administration in the United States of America with custom-made devices being limited to five in number per year, with annual reporting and limited to the use in rare cases only, is unworkable. It can be safely assumed that the stimulus for the production of truly custom devices for individual use will continue to burgeon. The North American limitations will fail to keep pace.

3. Obligations Assumed by a Customiser

The white paper suggests that the customiser of a previously manufactured device should "assume" the obligations incumbent upon the manufacturer. This appears to be excessively Draconian. It would be more reasonable to assume that the "customiser" will "share" those obligations with the principal manufacturer. Separating those levels of responsibility may be difficult but the problem will have a solution.

4. Devices with Biological Capacities

The term "bioprinting" has been used. Biofabrication is an alternate word and possibly more accurate. These biofabricated devices usually have an absorbable framework which acts as a temporary scaffold for pluripotential cells capable of organ replacement. The scaffolds should be plastic, elastic and durable. They should also be capable of resorption by the host without mounting a locally destructive reaction. Once seeded with the requisite cells, the biofabrication frame can be customised in situ. External 3-D printing or other forms of data manipulation are not necessary. Whatever regulatory programme is inducted by TGA, it is imperative that the focus does not dwell solely upon "3-D printing".

Section 3 – Challenges

The Prosthesis Listing Advisory Committee recognises a number of pressing and inevitable challenges:

1. *The Testing of Safety, Efficacy and Cost Effectiveness*

As the number of custom devices increases, so does the opportunity for mass post-market surveillance diminish. Currently available registries do allow for the relatively prompt recognition of higher than expected failure rates of implanted devices. They rely upon prospective analyses of generic device performance. The power of the observations is increased by the implanted number. Greater comfort can be taken from the successful survivorship or otherwise of 1,000 devices of a generic kind (and the same kind) than from the observation of 1,000 completely different custom devices. No custom device has its own control group for comparison.

Manufacturers and sponsors of custom devices must therefore assume greater responsibility, undertake to participate in prospective registry analyses and be subject to close scrutiny from regulators armed with clinical advice.

Given the excellence of the Australian Orthopaedic Association National Joint Replacement Registry and its vast repository of hip and knee devices gathered over the last decade or more, this forum could provide an ideal pilot study for custom devices.

2. *ARTG Listing*

PLAC is limited in its administration of the Prosthesis List in that all devices worthy of a rebate must have an ARTG listing, subserve the needs of a Commonwealth Medical Benefits Schedule (CMBS) service and be seen to be safe, efficacious and cost effective. Custom devices in Australia currently do not have ARTG listing. They are currently excluded from the Prosthesis List. Funding sources for these often expensive devices are at the discretion of the private health insurance companies. This arrangement is anathema. It requires resolution.

3. *Emerging Technologies*

As timely and as important as this debate is, the horizon already heralds the imminent arrival of even more challenging advances in medical science. The greater use of robots with device implantation, remote surgeries and even the digitisation of memory are not so far away.

It would be prudent therefore not to focus simply upon "3-D printing" but instead, view the entire process from ore to functional device as a process that is both worthy of and capable of being regulated.

4. Determining "Value"

PLAC and its HESC must be able to place a monetary value on every custom device. This will require regulation and validation of every manufacturing/distribution step, ARTG listing, cross referencing and clinical advice.

In Conclusion

- PLAC supports the efforts expended by TGA in this challenging space.
- Precise definitions are required.
- Custom devices are likely to increase in number and importance.
- Appropriate funding will depend upon ARTG listing which in turn requires validation and regulation.