Submission to the Therapeutic Goods Administration in response to “Consultation: Regulation of autologous cell and tissue products and proposed consequential changes to the classification of biologicals” Version 3.0, August 2016

Submitted 6 October 2016.

This submission represents the views of the Biotherapeutics Association of Australasia (BAA), formerly the Australasian Tissue and Biotherapeutics Forum Inc. BAA, as the peak industry body representing tissue banks and allograft manufacturers in Australia as well as cell therapy manufacturers, is concerned about equitable regulatory oversight and access to safe and effective biotherapeutic products produced in Australia. We represent our membership’s perspective and regularly engage with the Therapeutic Goods Administration regarding regulation of the tissue banking sector and welcome the opportunity to contribute to the TGA 2016 public consultation on the regulation of autologous cell and tissue products.

One of the stated purposes of BAA is:
“Within the context of knowledge development and sharing, to act as an information conduit between members and regulatory bodies in order to;
1. Foster and promote best practice in the retrieval, preparation, storage and distribution of human biotherapeutic products for purposes of transplantation, diagnosis, teaching and research in Australasia.
2. To foster and promote best practice in the development, preparation/manufacture and distribution of biotherapeutics, including (but not limited to) cellular therapies (e.g. haematopoietic stem cells, mesenchymal stromal cells), scaffolds and breast milk.
3. Provide expert advice and guidance to those public authorities responsible for controlling and licensing Tissue Banks and manufacturers of biotherapeutics.”

The BAA Council and general membership represents a range of interests including both independent and hospital-based tissue banks and cell therapy manufacturers responsible for the provision of allogeneic tissue products (from both live and deceased donors) and both autologous and allogeneic cell products. BAA members represent TGA-licensed manufacturers.

Our Views
1. The description of the problems adequately reflects the potential problems associated with the existing regulation of autologous cells and tissue. The following examples of risk to patient health have been discussed at scientific and clinical meetings and biotherapeutics sector workshops:
   - Lack of secure & monitored storage of products (e.g. skull flaps),
   - Incomplete labelling of stored products,
   - Lack of product information on the product itself (e.g. patient identifiers, type & date of procedure, type of packaging, expiry date (if any), department/surgeon’s name & department);
   - Lack of material tracing and tracking (e.g. source, batch number, expiry, intended use) & product traceability from collection to re-insertion/implantation into the autologous patient,
   - Lack of demonstrated efficacy, lack of outcomes & lack of adverse event reporting.

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2. BAA supports the proposed approach. Clarifying that the proposed options apply to all autologous human cells and tissue products, not just "stem cells", will make it more straightforward to define the scope of the biological framework and how it applies to current and future cell and tissue products and procedures.

3. BAA agrees that the proposed options should also apply to registered dental practitioners supervising the autologous use of human cell and tissue products as part of a single course of treatment. The use of autologous (as well as allogeneic) cells and tissue products in dental procedures is becoming commonplace. Given the potentially invasive nature of some of these procedures, a framework regulating the safety, quality, reproducibility & benefit of these activities and the products being used is required.

4. BAA considers the storage of autologous cells and tissues as part of a single course of treatment carrying risks of such a nature that should require TGA regulatory oversight. Where a 'single course of treatment' involves storage and other steps considered within the biological framework as 'manufacturing', and/or increased complexity in processing, there will be inherent risks that should require control and TGA regulatory oversight. Appropriate processing, packaging, and control of the storage of any product are essential to ensure safety & efficacy is maintained. This includes ensuring:
   - Appropriate and controlled processing of the product is performed for storage.
   - Product is appropriately packaged and labelled, including chain of identity.
   - The storage conditions and duration are appropriate for the product.
   - Both the packaging and the labelling are suitable for the storage conditions.
   - The storage area is secure & monitored.
   - Records are maintained which provide the tracing and tracking of materials & product from collection to clinical utilisation of the product, including the identity of both the donor and recipient.
   - Product viability, consistency and potency are controlled.

5. BAA considers it important to distinguish between homologous and non-homologous use unless there is irrevocable evidence of safety and clinical benefit, but acknowledges that the understanding of what is homologous use will change over time based on scientific and clinical data. Non-homologous use may be associated with higher risks and adverse events as a result of such use. Reporting of adverse events associated with the use of any autologous product (homologous or non-homologous), should be a requirement. Failure to differentiate non-homologous use from homologous use could allow the use of risky procedures such as liposuction aspirate being injected into the spinal column.

6. We are aware of the use of autologous islets, and cultured skin, lymphocytes and mesenchymal stromal cells that may be impacted by the proposed changes. Unnecessary additional regulation of existing, established medical procedures is to be avoided, but an audit or review to formally establish the safety, efficacy & currency of these procedures is warranted. This should address safety and "duty of care" responsibilities. The TG Order exemption qualifications do not ensure product safety & efficacy. For example: Skin or adipose tissue collected and subjected to enzymatic digestion in the clinic/theatre, and reapplied to the patient within a single course of treatment should be regulated given enzymatic digestion of a product where the intended use is for repair/reconstruction is "more than minimal manipulation" by either the current or proposed definition. The current lack of clinical trial data for these procedures, even though they are considered "established medical practice", further supports the need for regulatory oversight.
7. Option 1. We do not support maintaining the current system. The fact that cell or tissue products are being used for autologous application under the supervision of a single medical/dental practitioner, and as part of a single course of treatment has little to no bearing on product safety or efficacy, particularly if more than minimal manipulation is involved. There should be regulatory oversight to establish minimum safety & efficacy criteria for any cell or tissue product (autologous or allogeneic) applied to a patient regardless of whether the procedure is part of a "service", a clinical trial or established medical/dental practice.

8. Option 2. It would be very difficult to effectively monitor & control the advertising of practitioner's "services" based on whether those services do or do not use cell or tissue products. In addition, a legal and detailed definition for "advertising directly to consumers" would be essential. If, for example, arranging for a celebrity or professional to promote the use of cell & tissue products in a medical or dental procedure is not considered "direct" advertising, then restricting the practitioners themselves from directly advertising services utilising these products would be irrelevant. In addition, informal and social media networks are highly developed as communicators of 'treatment options.' It would be more practical, and more effective in terms of ensuring the safe and efficacious use of cell and tissue products, to allow practitioners to advertise procedures which utilise cell or tissue products provided both the products and the procedures meet specified regulatory requirements (as evidence by licensing or accreditation) including the requirement to report adverse events related to the use of these products. Regulatory compliance to allow advertising of cell & tissue products would be in addition to compliance with relevant AHPRA and ACCC legislation and should be directly linked to the practitioner's on-going registration.

This option does not address the issues presented in this paper. The primary issues are to ensure the safety & quality of the products being used and the safety and benefits of the procedures themselves. Restricting direct advertising to consumers does not address these issues.

9. Option 3. This option is unnecessarily complex and would impact on practitioners currently manufacturing & using these cells and tissues, both financially and in terms of increased record keeping and reporting requirements. This would be comparable to or lower than the burden on manufacturers of products (autologous & allogeneic) currently regulated. More importantly, the proposed requirements in this option would provide a mechanism by which the safety and suitability of products and procedures that are currently exempt from regulatory oversight, can at least be partially monitored and controlled.

Currently, the manufacture and use of these products does not comply with the basic safety requirements of TGO88 and TGO87. A requirement to comply with these standards would 'add value' in terms of addressing the risks and issues such as infectious disease reporting, sample collection & storage requirements, product traceability (e.g. labelling requirements) and adverse events reporting all of which help to ensure the safety of these products. It is doubtful that a once-off notification would be useful in terms of ensuring the safety of the products and/or the procedures, particularly if the TGA will have no authority to enforce recommendations or to stop a practice or a proposed change to practice for which there was minimal to no evidence of efficacy, or which was no longer “best practice”. It is unclear how compliance will be monitored. The risks of this option outweigh any potential benefits and we do not support this option.
10. Option 4. The impact would be similar to that on manufacturers and practitioners currently manufacturing and/or using cell and tissue products (both autologous and allogeneic) which are not exempt from the TGA regulations (e.g. MSC, chondrocytes, keratinocytes). It will have both financial and operational impact, but is appropriate to ensure product & procedural safety for the patient.

BAA considers that this option address the issues. A transition period would be appropriate for the two products identified, but the requirements of this option should apply to all autologous products which are more than minimally manipulated including those which are used under the supervision of a single practitioner and as part of a single course of therapy as well as those used as part of existing, established medical practice.

11. The proposed new definition of minimal manipulation is acceptable. However, even if representative ‘actions’ are listed, there is no doubt that determining whether the alterations are relevant to the intended use will be subject to debate, and will be difficult to standardise and justify.

12. BAA supports the proposed changes to the classification criteria as set out in the proposed new definitions (to rely on the new definition of minimal manipulation and, as a result, to redefine Classes 3 and 4), subject to the comments raised above pertaining to the new definition of minimal manipulation, and the requirement for a clear definition of homologous use. We do not consider that the proposed changes to the classification criteria will affect existing products or products currently under development by our members.

13. Clinical trials. The question of application (or not) of the requirements for CTX approval to the new redefined Class 3 generally or just to a subset is beyond the initial scope of this consultation. Indeed this proposal begins to blur the distinction between Class 3 and 4 products. BAA supports the requirement for an in depth review of clinical trial packages such as those required under CTX, or INQ or similar submissions. However such a requirement should be accompanied by increased resources for the review and a reduction in the statutory period to align with other jurisdictions. In addition, the OGTR licencing of gene therapy clinical trials should be integrated into the CTX process.

General comments
Exempting practices which utilise autologous cells & tissues from regulatory oversight simply because they are:
- seen as established medical practice (historical)
- collected/manufactured under the supervision of a single medical practitioner
- for therapeutic application in the treatment of a single indication and in a single course of treatment of that patient by the same medical practitioner,

is in itself a significant risk to patient health, particularly those practices that involve more than “minimal manipulation”. These exemption criteria do not ensure the procedures or products are safe, efficacious or current. Simply because it has “always been done that way” doesn’t mean it should be allowed to continue without objective review or oversight. The review need not be onerous, and many of these practices may meet identified safety & efficacy criteria, but in terms of “duty of care” as well as to maintain consumer confidence in the regulation of therapeutic goods, the safety and medical suitability of all procedures, old and new, autologous and allogeneic utilising autologous cells and tissues should be formally verified.
BAA notes a substantial gap between the potential risks associated with unregulated minimally manipulated autologous products (that are not to be restricted to homologous use) and minimal clinical data, and the minimally manipulated, allogeneic bone or connective products that are currently strictly regulated as class 2 biologicals but are supported by extensive history of clinical safety and efficacy.

A mechanism to reverse a Schedule 7AA declaration, on evidence of harm, is essential.

BAA strongly endorses the concerns about the increasing number of therapeutic applications of ‘autologous stem cells’ that are expressed in the discussion paper and considers the current practice of excluding goods to be unsuitable for ensuring the safe supply of all cell therapies in the Australian market. Our members have concerns about the advertising and availability of unproven and potentially dangerous cell therapy treatments. All members of BAA work in and/or fully endorse organisations that have embraced the regulatory requirements of the Biologics Framework.

BAA supports Option 4, to restrict the provision of more than minimally manipulated cell and tissue treatments made from autologous products, and prevent direct to consumer advertising of products although the advertising of services could continue. Under this option these cell products would be regulated as Biologicals class 2-4 and together with the proposed changes to the definition of minimally manipulated would provide a regulatory framework for autologous procedures and products that present a higher risk to patients. With improved adverse event reporting the safety profile of products may become established. We welcome further regulation and oversight by TGA to minimise risks to vulnerable patients both directly and financially, without detrimentally affecting access for patients to low risk autologous cell product treatments.

BAA gratefully acknowledges the contributions to this document from [redacted], Development Manager, Cell & Molecular Therapies Royal Price Alfred Hospital and [redacted], Managing Scientist – Research Centre Cell & Tissue Therapies WA.