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**Submission to the Therapeutic Goods Administration in response to "Discussion paper: Regulation of Autologous Stem Cell Therapies v1.0 January 2015".**

**Submitted 3 March 2015.**

This submission represents the views of the Biotherapeutics Association of Australasia (BAA), formerly the Australasian Tissue and Biotherapeutics Forum Inc, the peak body representing cellular therapy and tissue bankers in Australia and New Zealand.
We represent our membership's perspective to regulatory agencies and regularly engage with the Therapeutic Goods Administration regarding regulation of the tissue banking sector in particular. We welcome the opportunity to contribute to the TGA 2015 public consultation on the regulation of autologous stem cell therapies and note in paragraph 2 of the overview the request for input on five potential options for regulation of 'autologous stem cells', and to inform an appropriate regulatory path.

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;
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> 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.

**General comments on scope of the discussion paper**

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 believes that the breadth of the medical exemption in **Therapeutic Goods (Excluded Goods) Order No. 1 of 2011 (**TG1/2011) Item 4(q),

> *q. human tissue and cells that are:*
>
> *i. collected from a patient who is under the clinical care and treatment of a medical practitioner registered under a law of a State or an internal Territory; and*
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> *ii. manufactured by that medical practitioner, or by a person or persons under the professional supervision of that 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, or by a person or persons under the professional supervision of the same medical practitioner;*

which is unqualified for homologous or non-homologous use, or level of manipulation and does not impose any manufacturing controls, poses a significant risk to the biotherapeutics industry. As such, we feel it is important to ensure that all products derived from human tissues and cells are produced in such a way to ensure safety and clinical benefit to our patients. The **TGA Excluded Goods Order No.1 of 2011 Guideline for Items 4(o), 4(p), 4(q) and 4(r)** Version 1.1, March 2013 states that this provision reflects the Australian Health Ministers' Conference (AHMC) agreement that single surgical procedures and medical practice should not be regulated by the TGA. BAA does not accept that the introduction to medicine of autologous stem cells or stromal vascular fraction derived from adipose tissue should be considered to fall within this meaning.

The Australian Health Practitioner Regulatory Agency (AHPRA) does not appear to be in a position to determine the risk of non-homologous, highly manipulated cells, nor to limit the advertising and marketing to patients by commercial ventures operating under the medical practice exemption. We are aware of steps to draft a code of practice for the emerging autologous stem cell industry, but remain sceptical that there is sufficient understanding of the true risks of the products for this group to self-regulate.

Currently in Australia the regulatory framework with exclusions under 4q freely allows the provision of unproven products, without the requirement for manufacturing control, and yet poses a considerable regulatory burden on the manufacturers of products such as milled bone that have been safely and efficaciously used in surgical practice in this country for over 30 years.

In the United States of America, the FDA's framework segregates low risk products from full GMP and premarket authorisation requirements of section 351 of the PHS Act by means of GTP requirements under section 361 of the PHS Act and the regulations in 21 CFR Part 1271. Similarly in Europe under Article 28 of Regulation EC No. 1394/2007 (the 'ATMP Regulation') advanced therapy medicinal products prepared on a non-routine basis can be made and used under the responsibility of a medical practioner provided certain other requirements are met. The hospital supplier is still fully bound by product quality requirements. Furthermore, the European tissue directive (Directive 20004/23/EC Para 8) allows a medical exemption for products that have not been subjected to higher levels of manipulation, provided they are used in an autologous and homologous manner under medical supervision within a single procedure without storage or banking

The current Australian exemption is not framed around supply being based in a hospital, or on a non-routine basis, and has allowed the proliferation of commercial organisations that supply autologous products for a very broad range of indications and on a what may be perceived as a routine basis.

Unfortunately, the evidence provided in Appendix 2 could be misleading. Much of the data pertains to mesenchymal stromal or stem cells which, by definition, have been culture expanded and are thus not minimally manipulated. Futhermore, in many instances they are used in a manner that would not be considered homologous. This ambiguous nomenclature will contribute to difficulty in accurate classification of products. It should also be noted that the published literature is dominated by findings from established cell therapy laboratories in large academic institutions in USA and Europe where compliance with the local regulatory framework is in place. Medical practice based operations often rely on the published literature to support the use of their product without any evidence that they are actually manufacturing the same thing.

The Australian regulatory framework already provides for access to unapproved therapeutic products via multiple mechanisms. We have one of the most permissive schemes for clinical trials through the Clinical Trials Notification (CTN) route, as well as having an exceptionally rapid and broad exemption available to patients and clinicians under Special Access Scheme (SAS) and individual patient import. BAA believes that there is no clinical or patient justification for the current breadth of the 4(q) mediated exemptions.

**Specific Discussion questions**
**Public health risks of 'autologous stem cells'?**
The current situation means that manufacturing control, product characterisation, and clinical outcomes are not consistently monitored. There is no adverse event reporting, or outcomes which can be attributed to specific products. The absence of manufacturing control and lack of product characterisation information about what cells are being applied exposes patients to risks comparable to those associated with exemption frameworks such as compounded medicines. Globally there is a growing body of evidence to suggest that many of the products that are widely called stem cells vary considerably in composition, safety and potency. Furthermore, the ready availability of these 'autologous stem cells' with the promise of efficacy undermines the development of real therapeutic products via the traditional clinical trials route.

NHMRC has stated “Unproven stem cell treatments can result in serious health complications such as infection, allergic reaction or immune system rejection and in some cases, the development of cancer. In addition to the health and safety risks, these treatments often involve significant financial costs. Undergoing unproven treatments may also interfere with or delay a patient accessing proven and potentially beneficial therapies or treatment plans.” In addition to this, patients who seek such treatments may return to mainstream care requiring additional sometimes complex and costly interventions as a result of the unproven treatment.

**Evidence for these risks**

Without product registration and mandated adverse event reporting it is difficult to know the true extent of the public health risks. It is likely that the number of adverse events that come to the attention of the public is only a small proportion of the true problem.

The TGA took risk into consideration in the biological framework; risk increases with the degree of manipulation and alteration in intended use away from original properties of the cells and tissues. Indeed the FDA has recently published 2 guidance documents “Minimal manipulation of human cells, tissues, and cellular and tissue-based products - December 2014” and “Human cells, tissues, and cellular tissue-based products (HCT/Ps) from adipose tissue: regulatory considerations – December 2014” which outline these principles. Of particular note is the reiteration of the requirements in order to be classed solely as low risk 361 products. In these discussion papers, the onus is placed on the manufacturer to demonstrate that the minimal manipulation requirement is met (via request for designation)or the product is deemed to be more than minimally manipulated. The guidance provides details on the distinction between structural and non-structural tissue. In the interest of regulatory convergence we urge the TGA to clarify what homologous use is, particularly for fat tissue. The FDA states that adipose tissue provides padding and cushioning against shocks and stores fat, and that when the structural tissue is processed into components the characteristics relevant to reconstruction, repair or replacement are lost. Under the FDA, the tissue and cells product characteristics must remain unchanged. In this same guidance document the specific example of stromal vascular fraction (SVF) is provided as example 10-1 with the reason why such manipulation renders SVF as more than minimally manipulated fat tissue. Furthermore in example 12-1a) cell selection of a mobilized peripheral blood apheresis product, to obtain a higher concentration of hematopoietic stem/progenitor cells for transplantation, is considered minimal manipulation. We urge the TGA to consider these important precedents based on a large amount of data and to provide some consistency for our emerging industry.

**Risk with the highest priority for resolving**

The highest priority for resolution is to establish a risk scale for ‘autologous stem cells’. A stringent and robust mechanism for the independent determination of risk along the lines of minimal manipulation and homologous use is essential.

The risks that should be resolved in association with the establishment of a stratified risk-based approach are to address the lack of both manufacturing safety and adverse event reporting, and to prevent direct to consumer advertising. In a recent publication it was reported that the outcomes of cord blood transplant are better when the cord blood units are sourced from FACT accredited facilities. While this is not about autologous products, it does provide evidence that the requirements of

accreditation or other independent oversight lead to the manufacture of higher quality cell therapy products.

**Public health benefits**
BAA supports the continued availability of potential new cell therapy treatment options to patients on expedited and compassionate patient access. However, we believe that medical practitioners already have access to unproven and novel treatment options via the SAS scheme, and the CTN clinical trial route.
Contrary to the idea that access to such treatments might provide public health benefits, we are concerned that there may be at times an impost on the public health system as a result of patients who develop complications as a result of delaying conventional therapy or as a direct result of the novel intervention. We endorse the use of clinical trials to demonstrate a clinical benefit in a specific patient population, and support evidence based introduction of novel cell therapy products to the market.

**Discussion questions for each option.**
**Option 1**
There is no credible justification for the issuing of a legislative instrument under Section 7AA(1) of the Act. It is difficult to understand how the Minister could propose that manipulated cells used to treat a wide range of debilitating clinical indications should not be intended to be therapeutic, are to be excluded from regulation in the same way as sunscreen and magnetic mattresses. In terms of the regard the minister must have, we consider that there is at least anecdotal evidence of harm to health of members of the public, it is not appropriate in all cases, specifically for highly manipulated cells, and the current discussion paper sets out to determine an appropriate regulatory path. In the absence of any regulation, data about the true safety of these products will never be available. Option 1 is not acceptable.

**Options 2 - 5**
We welcome the proposal to apply a risk-based approach to 'autologous stem cells'. Higher levels of manipulation and non-homologous use of cells are associated with greatest risk. There can be no justification for excluding these products from regulation as therapeutic goods.

**Option 2**
Under this option, exemption from TGA regulation under subsection 7AA(2) is retained only for products that have undergone minimal manipulation and are intended for homologous use, and there is restriction on advertising to patients. We fully support the risk-based distinction and proposal that 'autologous stem cells' that are more than minimally manipulated and/or are for non-homologous use should not continue to be excluded from regulation. BAA considers the collection of adverse event information fundamental to demonstrating the public health benefit of these novel products. Lack of incentive to collect evidence of efficacy and safety for the current proponents of exclusion of 'autologus stem cells' under 4(q) does not mean that similar products would not be developed by other parts of the sector, and could potentially become available to all patients not just those who are willing to pay.

**Option 3**
Under Option 3 there is no exclusion or exemption from the Act and all 'autologous stem cells' would be considered to fall within the definition of a biological. The removal of the requirement for ARTG listing and a manufacturing licence via an

exemption is contrary to the intent of the biologicals regulation which was introduced at least in part to remove the broad range of exemptions that had previously been introduced since 2000.
We support the requirement to comply with applicable standards although such standards do not currently exist, and it would appear that adverse event reporting is only required if the exemption is mediated via schedule 5A. Furthermore, we are concerned that not only is there no precedent for such an exemption but there is no information on the mechanism be which products would be classified i.e. is there an application process, how is this managed, and who would pay for this process? In addition, the TGA recall powers rely on reporting. And it is not clear to what extent non-compliance with an as yet undefined manufacturing standard would be reported.

**Option 4**
Option 4 allows for "self regulation" of 'autologous stem cells' as Class 1 biologicals provided these are not more than minimally manipulated and are for homologous use only; ARTG listing is required. The products would need to be declared as Class 1 biologicals and at this time it is not clear that there is sufficient product characterisation nor safety data available to allow this to occur in a rigorous manner. As a positive, this option provides advertising control and adverse event reporting for all products.
While there is scope under this option for self-regulation similar to that accepted for IVF and HPC-A, there does not appear to be the same body of data to support safety or clinical outcomes. Indeed HPC-A were excluded from the biological regulations as published but had previously been proposed to be included as Class 1, only if they have not been stored. If a product such as HPC-A were to become regulated under the Act would autologous and allogeneic products be regulated differently? In some cases, manufacturers of HPC-A have retained manufacturing licences and work to comply with the manufacturing and infectious diseases testing requirements of the regulations for all products.
Similarly, musculoskeletal products that are traditionally manufactured by tissue banks are highly reproducible products with a long history of safety and efficacy yet these and these are regulated as Class 2 products due to allogeneic origin, even though they often undergo irradiation.

**Option 5**
Option 5 provides for full regulation under the biological framework with no exemptions and would seemed to be most closely aligned with the regulatory controls in place in other aspects of the tissue sector. Minimal manipulated cells used for homologous use only would be Class 2. The benefits of this option are full control by TGA, optimal product and patient safety with true manufacturing oversight. The major risk is loss of products from the market immediately and longer time to market in the future and indeed some products may not continue along the development path. However, we believe that if there is no substantive data regarding the safety and efficacy of these products then failure to bring to market is not a loss for patients and our health care sector in the long-term.

## Preferred Options

BAA favours a stricter regulatory framework - in particular around manufacturing controls and clinical follow up. Our recommendation is that the TGA proceeds with further consultation as rapidly as possible and explores all avenues for rapid change to the current unacceptable situation.

Option 1 is unacceptable, but all other Options offer benefits of variable extent to the cell therapy sector as a whole. Option 5 is the most rigorous option, and does not allow any flexibility of self-regulated manufacturing for very low risk products that is available in Options 2, 3 and 4. However, even in these other options, the TGA cost recovery model provides somewhat of a barrier to the introduction to market of all low volume products irrespective of level of manipulation or intended use. Beyond increased costs in manufacturing quality, listing, dossier and audit, as well as biovigilance, our major concern if for the requirement for safety and efficacy to be demonstrated for new therapies before they are introduced to the market. Thus Option 4 would be acceptable. In the absence of exceptional access or orphan designation programs, the introduction of therapies for rare or uncommon diseases could be crippled.

BAA also represents skin banks and we are extremely conscious of the need to continue this life saving treatment option for patient with severe burns. In most instances we believe that this treatment would be classified as an exceptional need and not be captured, but we urge the TGA to ensure any change does not impact on this category of products and other well established medical and surgical practices.

It is essential that in all Options the classification of products as Class 1, or no more than minimally manipulated and for homologous use only, is objectively and independently assessed. As noted earlier, TGA's definition of minimally manipulated could be more aligned with other major jurisdictions such as the FDA. Peer assessment to manufacturing standards for low risk products, has already been proposed by some in the industry (Self-regulation of autologous cell therapies Med J Aust 2014; 200 (4): 196), although there is lack of agreement if this is aligned with option 4 or one of the other options. BAA considers this to be aligned with Option 4 where only Class 1 products could be self-regulated.

We support change to control the manufacture and clinical/safety reporting for cell products that are more than minimally manipulated and intended for non-homologous use. We support listing of all products on the ARTG using the current separate and distinct product criteria.