Regulation of Autologous Stem Cell Therapies Comments- Discussion paper v1.0
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1.0 Who we represent:

This submission represents the views of the Legal and Regulatory Affairs (LRA) Sub-committee of the International Society for Cell Therapy (ISCT) - Australia & New Zealand (ISCT). We represent our membership's perspective to regulatory agencies.

ISCT is a global society of clinicians, regulators, technologists, and industry partners with a shared vision to translate cellular therapy into safe and effective therapies to improve patients' lives. There is an Australian and New Zealand representative group with its own elected Vice-President, Secretary, Treasurer and subcommittees. The current membership of the ISCT ANZ LRA is as follows:

Rosemarie Bell, B.App.Sc Micro/Biochem MA SM
Queensland Institute of Medical Research
Herston, QLD
Australia

Michelle Coffey, MSc, BSc
Mesoblast
Melbourne, VIC
Australia

Craig Wright, MSc
Royal Prince Alfred Hospital
Sydney, NSW
Australia

Paula Stoddart BSc
Miltenyi Biotech Australia
North Ryde, NSW
Australia

Dominic Wall, PhD, FFSc (RCPA)
(Chair)
Peter MacCallum Cancer Center
East Melbourne, VIC
Australia

Sharon Bryce, BHSc
Australian Biotechnologies
French Forest, NSW
Australia

Ngaire Elwood, BSc (Hons), PhD
BMDI Cord Blood Bank,
Royal Children's Hospital / Murdoch Childrens Research Institute
Parkville, VIC
Australia
Also: Member, Board of Directors,
Foundation for the Accreditation of Cellular Therapies (FACT)

Gabrielle O'Sullivan, PhD
Royal Prince Alfred Hospital
Sydney, NSW
Australia

Annette Trickett, PhD, MappSc, FIBMS
Prince of Wales Hospital
Randwick, NSW
Australia

Our committee represents a diverse range of interests- commercial sponsors, devices manufacturers, academic and policy specialists with interests in ethics, gene technology and biologicals, as well as conventional hospital-based cell therapy providers.

2.0 Scope of the discussion paper

ISCT strongly endorses the concerns expressed in the discussion paper and considers the current excluded goods to be wholly unsuitable for ensuring safe supply of cell therapies to the Australian market. Due to our concerns about the availability of potentially unethical and dangerous unproven cell therapy treatments, ISCT requires its members to endorse the ISCT White Paper (Cell therapy medical tourism: Time for action *Cytotherapy,* 2010; 12:965-968.) as a precondition to society membership.

It was always evident to our membership, that the exceptional breadth of the medical exemption in Order Item 4(q), which was unqualified for either the homologous use, or levels of manipulation, let alone any form of manufacturing controls, would result in significant market and clinical risk; it is absolutely beyond the Australian Health Practitioner Regulatory Agency's (AHPRA) capabilities to assess the risk of non-homologous, highly manipulated cells marketed and advertised to patients by commercial interests operating under the guise of the medical practice exemption.

This has placed Australia in a unique global situation among developed markets, having an exemption framework that is unqualified by the homologous use or levels of manipulation. The FDA's framework segregates low risk products from full GMP and premarket authorisation requirements by means of being regulated solely under GTP requirements under section 361 of the PHS Act and the regulations in 21 CFR Part 1271.
Likewise in Europe under Article 28 of Regulation EC No. 1394/2007 (the 'ATMP Regulation')

> *Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.*

this current Australian exemption is **not** carefully framed around supply being based in a hospital, or being supplied on a **non-routine** basis. Furthermore, whilst the European exemption allows for use of these cells without a market authorisation, the hospital supplier is still **fully** bound by product quality requirements. The European tissue directive (Directive 20004/23/EC Para 8) also 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**.

We fully endorse the concerns expressed by the discussion paper, and note without the exemption Australia already has one of the most permissive schemes for clinical trials through the exempt goods pathway available under the Clinical Trials Notification (CTN) pathway for clinical trials, as well as having an exceptionally rapid and broad exemption available to patients and clinicians under Special Access Scheme (SAS). Thus there is no clinical or patient justification for the current breadth of the 4(q) mediated exemptions..

3.0 **Discussion questions**

Public health risks of autologous stem cells?

The main issue is that in the absence of any meaningful adverse event reporting, or manufacturing control, or product characterisation, there is no centralised gathering of adverse outcomes which can be allocated to known product types. The discussion paper itemises a number of reported outcomes which are only a subset of potential clinical outcomes. The absence of manufacturing control exposes patients to risks comparable to those associated with other exemption frameworks such as the ones associated with compounded medicines, and as seen in the recent issues noted by the FDA

> "*The fall 2012 outbreak of fungal meningitis has been linked to an injectable steroid medication that the Centers for Disease Control and Prevention says has infected hundreds of people across the country, with serious injuries and deaths reported. These infections have all been linked to a firm in Framingham, Mass."*

Furthermore the NHMRC has simply summarised the issues in its own policy statements:

> *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.*

Evidence for these risks

Not surprisingly, in the absence of any product registration, or recording of exempted treatments, and due to the potential conflict of interest for commercial providers making use of such exemptions for these treatments, there is no central record of the adverse consequences. Case studies and anecdotal observations are available, but in the absence of a centralised adverse event register we are only seeing a very limited perspective on the problem. More worryingly is the anecdotal evidence of the 4(q) exemption being applied to higher levels of cellular manipulation.

Highest priority for resolving?

The most straightforward solution would be to modify 4(q) and it is unclear why this has not been considered. We would endorse immediate application of a **risk adjusted** medical practitioner exemption as follows (changes in bold) :

> *4 (q) human tissue and cells that are:*
>
> *a) 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*
> *b) that are manufactured* ***with cells that are subject to no more than minimal manipulation*** *by that medical practitioner, or by a person or persons under the professional supervision of that medical practitioner, for* ***homologous use in*** *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;* ***or***
>
> ***c) utilised in one of the following recognised medical interventions:***
> ***d) skin grafts inclusive of sprayed and/or cultured skin;***
> ***e)skull flaps;***
> ***f)vascular conduits;***
> ***g) transplantation of pancreatic islet cells;***

h) bone grafts;
i) blood to seal CSF leaks and reinfused during surgery;
j) cosmetic/reconstructive procedures utilising skin, bone and fat transfer.

This would immediately address the risk of highly manipulated products being marketed to patients, whilst allowing a more considered risk-adapted framework to be evolved for these lower risk homologous and minimally manipulated products. There is little doubt that with higher levels of manipulation, and non-homologous use there is a considerably greater risk- addressing this risk should be the most urgent priority. This would allow, in the meantime, for a more considered approach for low risk product, given the extensive period of time required before the Act can be changed.

Public health benefits of patient access to new and novel treatments?
There should remain a number of avenues for expedited and compassionate patient access for unproven cell therapies- but this does not require an unrestricted medical practice exemption. If patients or medical practitioners require access, there are existing and well utilised pathways available for this. The SAS scheme is efficient and risk-adapted and the CTN clinical trial route remains one of the most permissive clinical trial schemes in developed markets.

As a general rule, it is desirable to demonstrate evidence for a claimed positive benefit, and we endorse the use of clinical trials to demonstrate a clinical benefit. Any changes to the scheme should encourage the use of clinical trials to build an evidence base for new uses of cell therapy.

Discussion question- Option 1
No developed market other than Australia exempts non-homologous, heavily manipulated autologous cells from some form of regulatory oversight under a medical practice exemption. There is no credible justification for considering manipulated cells as not being a therapeutic good. Option 1 is not acceptable.

Discussion question- Option 2
As higher levels of manipulation and non-homologous use of cells is associated with the greatest patient risk there can be no justification for excluding these from regulation.

Summary Review of Options 1 through to 5

Option 1 No change- unqualified exemption remains

Benefits- Ease of market access, increased patient availability, low potential cost
Risks- Substantial patient risk, patient exploitation, and market distortion discouraging legitimate product development, product safety issues, lack of either manufacturing or product control, no efficacy data

Option 2 Exemption retained only for minimal manipulation and homologous use (new s7AA)

- No advertising under any circumstances to patients
- Minimally manipulated and homologous use cells remains unregulated by TGA other than no patient advertising
  Benefits-Control of higher risk products, low risk products remain exempt with no oversight other than restricting advertising to patients
  Risks- some higher risk low manipulation products may still be harmful, loss of ease of market entry for complex /non-homologous cells, still discourages legitimate product development, very limited manufacturing or product quality oversight so a remaining substantial product risk.

Option 3 No exclusion/exemption but provided that cells are not more than minimally manipulated or under homologous use only:

- No requirement for ARTG entry (saves fees, no dossiers)
- No manufacturing control other than a product standard (self disclosed)
- But retain adverse event reporting & advertising control

  Benefits- Control of higher risk products and reduction of risk to patients, low risk products remain exempt with limited oversight, adverse event reporting across all products would reduce undisclosed risk and adverse events, no advertising reduces patient exploitation, the use of a product standard would help educate all practitioners on minimum manufacturing benchmarks

  Risks – Self controlled manufacturing control of exempt products is one cause of product failure/risk as the manufacturing control is largely through self disclosure of meeting manufacturing standards of section 10 of the Act, some further loss of ease of market entry for lower risk autologous cells,

Option 4 Allows for "self regulation" of autologous cells provided these are not more than minimally manipulated or for homologous use only:

- Class 1 ARTG for minimally manipulated and homologous use cells
- Advertising control and adverse event reporting for all products
- Scope for self regulation similar to that accepted for IVF, HPCA
- Limited product safety self-certification

  Benefits- Improved control of higher risk products, low risk products lightly controlled with self certification (manufacturing, safety) retaining oversight for adverse event reporting & no advertising, product listed on ARTG allowing proper understanding of the products being manufactured and their intended uses

  Risks – Peer manufacturing control can be one cause of product failure/risk, further loss of ease of market entry for low risk autologous cells, potential expense for self regulation and Class 1ARTG listing

Option 5 Full regulation with no exemptions:

- Minimal manipulated cells used for homologous use only to be Class 2 Biologicals

  Benefits- full control, optimal product and patient safety with assured "real" manufacturing quality

  Risks – Major loss of ease of market entry for low risk autologous cells, much more expensive/slower process for all low risk products

Preferred Options

The ISCT LRA committee carefully considered each option.

We felt that Option 1 was unacceptable as this would retain the current unsatisfactory status quo with an ongoing risk to patient safety and potential patient exploitation. There would be a substantial disincentive to normal product development, and there would be a substantial risk of more credible technologies not entering the Australian market due to the unfettered nature of the medical exemption. The lack of advertising and adverse event recording is wholly unacceptable.

By contrast Option 5 seemed to lack the flexibility and desirability of allowing peer manufacturing for very low risk products (as per Option 4), and with the substantial existing dossier submission fees might discourage market entry to lower risk products.

Of all the options, Option 4 seems to be the most suitable. This allows for peer assessment to manufacturing standards for low risk products, a position that many in industry have already proposed (Self-regulation of autologous cell therapies Med J Aust 2014; 200 (4): 196). The

additional powers of recall available to TGA, as well as the benefits of listing all products on the ARTG seem to be highly desirable. It is also highly commendable, that this option would to some extent "line up" with the FDA GTP and GMP division between lightly regulated and fully regulated products. The absence of peer assessment and Class 1 ARTG listing makes Option 3 less desirable, whilst Option 2 is still attracts too much product and patient risk.

4.0 Other issues

4.1 Evidently some of the more highly manipulated products which are currently exempt such as cultured and manipulated skin cells (and which we initially propose be exempted through a revised 4q) would be captured under Option 4, this would seem acceptable under a presumption that there would be a substantial period of consultation, and to allow currently unregulated services to progress to licensure.

4.2 It is absolutely essential that the definition of products in Option 4 as being Class 1 or no more than minimally manipulated or homologous use only be objectively assessed, and not be through some form of self-assessment. Our preference would be for this to be initially determined by TGA, with a proviso that this does not cause lengthy delay or be overly costly to maintain ease of access to lower risk products. It is important that the TGA costs associated with ARTG listing do not detrimentally affect access for patients to low risk autologous cell product treatments.

4.3 Option 4 will require maturation of industry peer-assessment, however we do note the availability of FACT's cell therapy standards.

4.4 TGA's current definitions of minimally manipulated seems broadly acceptable.

4.5 FDA's definition of homologous use is used in conjunction with their more output-based definition of minimal manipulation. This has the desired effect of restricting GTP products (thus low risk products) to those where the cells have **NOT** been removed from their milieu to recapitulate their function in another organ. TGA's definitions of homology and minimal manipulation have to be read in conjunction, and as such do not preclude this undesirable use of cells isolated from one organ in another (ie a stem cell) where the sponsor may claim their biology is recapitulated, but where there is an elevated risk of undesirable effects. We would propose that homologous use should be restricted to use in the same organ system, or otherwise more stringently qualified to result in the same effect as the combined wording of the FDA. We propose wording to the effect of:

Current definition

The repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with a biological that performs the same basic function in the recipients as in the donor

Proposed definition

The repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with a biological cells or tissues that performs the same basic function in the recipients as in the donor from which the cells or tissues are obtained, and wherein the cells or tissues are implanted in the same organ system as that from which they were obtained,

Dr Dominic Wall PhD FFSc (RCPA)
On behalf of ISCT- Australia & New Zealand