[redacted]
Biological Science Section
Office of Scientific Evaluation
Therapeutic Goods Administration
bloodandtissues@tga.gov.au
[redacted]

02/03/2015

Australian Cell Therapy Society (ACTS): Consultation submission on Regulation of Autologous Stem Cell Therapies

Autologous cell-based interventions (ACBIs) which involve the collection, ex vivo manipulation and administration of a patient's own cells, offer promise and great potential for treating a striking breadth of injury and disease.

In Australia, the TGA regulates the importation, manufacture and supply of human cell or tissue-based products (HCT/Ps) under the regulatory framework for biologicals. However, the Therapeutic (Excluded Goods) Order No.1 of 2011 (the EGO) provides broad exemptions for the use of autologous human cells and tissue (HCT) in the context of individualised medical care.

The EGO reflects the Australian Health Ministers' Conference (AHMC) agreement that single surgical procedures and medical practice should not be regulated by the TGA.[1]

The framework within which the safety and effectiveness of exempt ACBIs is regulated around Australia is complex and consists of a combination of common law obligations,[2] medical practitioner registration, professional codes and guidelines, public health legislation and infection control standards, [3] private health facility licensing (some jurisdictions), regulation of some of the devices and reagents used in processing the HCT, independent health complaints mechanisms and more general consumer and privacy legislation.

Critically, the exclusion from the operation of the Therapeutic Goods Act 1989 (TGAct) and Regulations of HCT under the EGO ***has no effect on the professional obligations of doctors*** to maintain high standards of practice that are appropriate to their profession and regulated under provisions of the Health Practitioner Regulation National Law Act (The National Law).

This includes adherence to professional standards, and particularly, principles of evidence-based medicine when providing ACBIs that have not been evaluated for safety and efficacy by the TGA. Medical practitioners must consider whether the ACBI is necessary and safe and whether its efficacy is supported by credible scientific and clinical evidence.

The Australian Cell Therapy Society has developed a Code of Practice for the use of autologous cell therapies in Australia. The code has been developed following a meeting hosted by the NSW Stem Cell Network in 2012. This meeting brought together a group of medical practitioners and research

scientists from multiple disciplines, with a common interest in Autologous Cell-Based Interventions (ACBIs). From this, the Australian Autologous Cell Therapy consortium was formed.

The aim of the consortium was to establish a professional organisation (the Australian Cell Therapy Society - ACTS) and fund the development of a Code of Practice.

The Code of Practice has been written incorporating existing regulatory frameworks. It aims to support the ongoing growth and development of a strong, ethical cell therapy industry in Australia.

This submission proposes maintenance of the current exclusion and industry regulation via the ACTS Code of Practice.

This proposal addresses the issues highlighted by the TGA and directly references the ACTS Code of Practice in response to those issues. The attached excerpts from the Code include direct links to all legislation, guidelines and codes of practice to which they refer. The ACTS Code of Practice provides a way of delivering an appropriately strong regulatory environment for an emerging technology while also supporting the development of a viable research based industry.

SUBMISSION STRUCTURE:

1. Proposal
2. Effect of the option
3. Advertising
4. Act Standards
5. Adverse effect reporting
6. Evidence to support the safety and efficacy of the product
7. Manufacturing
8. Patient Access

1. PROPOSAL

Maintenance of the current EGO and industry regulation via the ACTS Code of Practice.

2. EFFECT OF THE OPTION

Currently, there are no ***active*** means of monitoring the autologous cell based industry as all current systems require notification. Implementation of the ACTS Code of Practice will provide a mechanism for monitoring compliance and behaviour via an Accreditation Scheme administered by ACTS. Failure to comply will result in Reporting to and Sanctions by ACCC, AHPRA and Medical Board.

ACTS CODE OF PRACTICE EXCERPT
Section 8 – Code Administration:

MONITORING COMPLIANCE

8.27 To support compliance with the Code and In addition to a formal Accreditation Scheme and Member Reporting Requirements, the Code Committee will determine selected actions/issues each calendar year for monitoring. Members will be informed of this proactive monitoring by way of a newsletter, publication on the website, and/or notification in writing.

8.28 Monitoring could take the form of broad review of advertising practices or patient information sheets/informed consent forms used by members or spot audits of member laboratory practices.

8.29 Monitoring will be undertaken by the Code Committee or may be undertaken by an independent person whom shall report back to the Code Committee.

8.30 The aims of monitoring are:

8.30.1 to encourage compliance with this Code

8.30.2 to provide an on-going mechanism for identification of compliance issues

8.30.3 to provide an on-going mechanism for identification of changes in the field, scientific advances or new technologies, which may indicate the potential need for Code amendments.

8.30.4 to provide and publish statistical data on the rate of compliance. (For example, participation rates for voluntary Accreditation once the Scheme is developed.

8.31 If the Code Committee considers there has been a failure to comply with the Code, the member in question will be advised in writing and asked to provide a response within 20 days of receipt of the request.

8.32 Member responses will be reviewed by the Code Committee, who will recommend;

8.32.1 no further action required; or

8.32.2 the apparent breaches of the Code so discovered will be handled according to Complaints and Inquiry Procedures, including Reporting the Member to AHPRA or ACCC.

3. ADVERTISING

The ACTS Code of Practice encompasses all requirements of the Medical Board and AHPRA for advertising. The above monitoring and reporting requirements in combination with this provide a strong means of regulation advertising in the industry.

ACTS CODE OF PRACTICE EXCERPT
Section 5 – Advertising:

5.1 Members must comply with advertising requirements of the Health Practitioner Regulation National Law Act – Section 133 and titles and practice provisions under Sections 113 – 120.

This includes compliance with the detailed requirements of the Medical Board of Australia's guidelines for advertising regulated health services ('Advertising Guidelines)', and 'Social Media Policy', based on provisions of the 'National Law'.

Members may also refer to a fact sheet and FAQ on advertising developed by AHPRA and the Australian Medical Association's position statements on advertising for additional guidance.

5.8 Members must comply with Australian Consumer Law (ACL), located in Schedule 2 of the Competition and Consumer Act 2010 in all commercial activities and in the provision and advertising of services and products to consumers.

Section 18 of the ACL requires that in operating a professional practice, medical practitioners, like all businesses, have an obligation not to make representations in advertising or promotion of services and goods that mislead or deceive consumers/patients. (This also applies to information provided in Patient Information Sheets, unlike the 'National Law' – which does not).

4. ACT STANDARDS

Compliance with the ACTS Code of Practice requires compliance with Good Clinical Practice (GCP) guidelines, and Principles of cGMP for more than minimal manipulation.

ACTS CODE OF PRACTICE EXCERPT
Section 6 – Safety and Quality Standards:

MORE THAN MINIMAL MANIPULATION

6.6 Although no reference is made to the level of manipulation in the EGO, depending on the circumstances under which HCT are manufactured and evaluation of the level of risk, compliance with the principles of 2013 cGMPs is recommended for ACBIs which involve 'more than minimal manipulation' of HCT.

Minimal manipulation, as defined in the ARGB, includes centrifugation, refrigeration, freezing, trimming, flushing, washing; processing steps related to preserving function or minimising contamination, including using additives such as cryopreservatives, anticoagulants, antimicrobial agents and irradiation; and freeze drying (of structural tissues only).

For the purposes of this Code, and as a point of difference from the TGAct and Regulations, minimal manipulation shall also include dissociation of mononuclear cells through enzymatic or mechanical means.

'More than minimal manipulation' includes complex methods of modification that are not listed under 'minimal manipulation', including cultured expansion of cells.

For example, cell culture techniques require stringent controls to avoid in-process contamination and patient-to-patient variation. Modifications may result from the culture, expansion, isolation or pharmacologic treatment of cells that alters their genotypic and phenotypic characteristics. Additional testing may be required prior to administration of the cells to assess bioburden and random genetic alterations.

Further consultation on appropriate standards of practice for 'more than minimal' manipulation is required and will be incorporated into guidelines developed by the Code Committee in the Accreditation Scheme.

5. ADVERSE EVENT REPORTING

Compliance with the ACTS Code of Practice will encompass mandatory reporting of all cases on a treatment registry including all adverse events.

ACTS CODE OF PRACTICE EXCERPT
Section 3 – Good Clinical Practice:

3.3 Members shall be open and honest in communications with patients when adverse, unplanned or untoward events occur, analyse causal factors, seek advice appropriately and implement changes to reduce the risk of recurrence.

Members shall establish and maintain policies and procedures that comply with ACSQHC's guideline for Open Disclosure in small practices, which provide a nationally consistent basis for communication when care does not go to plan. It is designed so that patients are treated respectfully after adverse events.

3.4 Members shall commit to routine follow-up and reporting of adverse events and outcomes to assist in the establishment of short and long term safety and efficacy of ACBIs.

For the safety of prospective patients, members shall ensure reporting of adverse events temporally associated with an innovative ACBI to relevant HRECs and/or Clinical Quality Registries, once established.

Likewise, it is incumbent on members to report the details of unexpected serious adverse reactions, as soon as possible, through case reports or conferences, or other mechanisms where such reporting may offer additional information to other medical practitioners of contraindications and risk factors, otherwise unknown or underestimated. This ensues that patients in other clinical settings can be fully informed of such risks and, where possible, protocols changed to avoid future occurrences.

This is especially important in relation to ACBIs not regulated by the TGA, as systems for expedited reporting of serious adverse reactions and systematic distribution of such information to other regulatory agencies and medical practitioners may not occur.

Mechanisms for reporting will be developed by the Code Committee and may include establishment of a National Clinical Quality Registry or collection and analysis of relevant data from members, with findings analysed and published in an Annual Report and/or presented at an Annual Conference.

6. SAFETY AND EFFICACY REQUIREMENTS

Compliance with the ACTS Code of Practice brings all treatment in line with NHMRC guidelines for "Additional levels of evidence and grades for recommendations for developers of guidelines" (2009) This Code mandates a minimum "satisfactory level" of evidence, as defined by the NHMRC, for all autologous cell based interventions. This brings ACBI's in line with all other therapies in Australia.

ACTS CODE OF PRACTICE EXCERPT
Section 3 – Good Clinical Practice:

3.3 An ACBI should meet the following minimum criteria prior to routine use outside the context of clinical trials, particularly when large numbers of patients are to be treated and charged for such services:

- *Safety* – is supported by 2-3 independent human safety studies, of an adequate number of patients.
- *Efficacy* – is supported by a 'satisfactory body of evidence' or better, demonstrating the effectiveness of the intervention in the disease area.

A 'satisfactory body of evidence' is defined in Table 1, NHMRC's "Additional levels of evidence and grades for recommendations for developers of guidelines".

- *Quality* – is supported by validated protocols and release specifications and compliance with recommended Safety and Quality Standards.

In all such cases *patients must be appropriately informed* about the ACBI, including the fact that it is innovative and that safety and efficacy has not be independently assessed by the TGA,

7. MANUFACTURING

The ACTS Code of Practice incorporates The Medical Board's Code of Conduct. This requires doctors to minimise risk (section 6.2). The ACTS Code expands on these requirements and will monitor and report to AHPRA doctors not actively engaging in activities to minimise risk, including compliance with an Accreditation Scheme as detailed below. Options for independent accreditation include NATA and JAS-ANZ Accreditation and will be established by the Code Committee in collaboration with these Accrediting Bodies.

ACTS CODE OF PRACTICE EXCERPT
Section 6 – Safety and Quality Standards:

ACCREDITATION SCHEME

Achieving independent accreditation against recognised industry standards is an effective driver for safety and quality improvements and shows patients that a practice is serious about providing high quality, safe and effective care to standards of excellence as determined by experts. Unless ACBIs can be reliably manufactured to high standards of quality, they can be ineffective or potentially cause harm to patients.

Accreditation offers assurance to patients that, whether ACBIs are provided in private office-based practices, day procedure centres or hospital settings, they can expect consistently high standards of care. Indeed, in the future, quality management standards and external audit procedures may be a requirement for access to the Medical Benefits Scheme and/or (for in-patients) private health fund rebates for such services.

In relation to clinical trials, adherence to recognised standards, demonstrated through accreditation, provides HRECs with evidence that patients will be treated in facilities equipped for specialised monitoring and a high degree of surveillance.

The Code Committee will coordinate the development of an **Accreditation Scheme**, including comprehensive guidelines for the adoption and, if required, development of safety and quality standards for specific ACBIs and associated independent accreditation, audit and reporting mechanisms to demonstrate compliance.

Once a member organisation and Accreditation Scheme is established, the accreditation status of members shall be published on the organisation's website to encourage participation and inform the public.

The recommendations herein represent a "work-in-progress" and aim to promote reflection and discussion during consultation on the draft Code of Practice. The subsequent Accreditation Scheme will be based on feedback received during consultation and developed in collaboration with members, and accrediting agencies.

The Code developers support a system of accreditation that is an educational and supportive process.

6.1 Members should participate in and contribute to the development of Safety and Quality Standards for ACBIs and an Accreditation Scheme to maintain and monitor compliance with high standards of practice.

Member may need to invest in their facilities, the training of personnel, and in the development and implementation of risk management and quality management systems to meet acceptable standards of practice. Such changes/ training/ investments would be deemed necessary for the practices to achieve a required and accepted level of care.

RISK MANAGEMENT AND QUALITY MANAGEMENT SYSTEMS

6.2 Members shall establish and maintain risk assessment and management plans and participate in strategies for continuing pharmacovigilance.

Risk is inherent in healthcare. However, minimising risk to patients is a critical component of good medical practice.

The diverse range of starting materials and manufacturing processes can lead to varied levels of risk. Risk evaluation and mitigation strategies shall be commensurate with the level of manipulation, intended application and current state of knowledge of the ACBI.

Members shall identify known and potential risks, as well as missing information and consider actions to minimise those risks (including further evaluation and clinical trials).

Risk factors that may be considered include:

- the ability of the cells to proliferate and/or differentiate
- the ability of the cells to initiate an immune response
- the level of cell manipulation
- the combination of cells with bioactive molecules or structural materials
- the nature of ACBI's involving gene therapy, including the extent of replication competence of viruses or microorganisms used *in vivo* and the level of integration of nucleic acids sequences or genes into the genome
- the long time functionality of cells
- the risk of oncogenecity
- the mode of administration or use

Also refer to the TGA's, Australian Regulatory Guidelines for Biologicals, Appendix 11 - Risk Management and the resources listed on the TGA's Pharmacovigilance Guidelines webpage.

6.3 Members shall demonstrate a professional commitment to quality and safety in the manufacture of HCT. The fundamental element to manage risk and achieve and maintain high standards of practice is a working Quality Management System.

All activities shall form part of a comprehensive Quality Management System, which includes the following elements:

- facility designed to control operations
- adequate documentation/records
- production and process controls
- quality control/assurance
- validation of critical procedures
- equipment calibrated/qualified
- personnel training & certification
- environmental monitoring
- regular periodic quality reviews, particularly in relation to changes to key materials, processes and equipment

6.4 All HCT, which require ex vivo manipulation steps prior to administration, shall be produced via a validated and well-defined manufacturing pathway governed by quality control sufficient to prevent the introduction of adventitious agents and reduce patient-to-patient variability in the quality of ACBIs.

Validation means establishing documented evidence that provides a high degree of assurance that a specific process, piece of equipment or environment will consistently produce a product meeting its predetermined specifications and quality attributes. A process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.

6.5 Collection, processing, storage and administration of HCT shall always be conducted using aseptic techniques and universal precautions to minimise the risks of infection and contamination. All aseptic and sterilisation procedures shall be validated and in accordance with:

- AS/NZS 4187:2003, Cleaning, disinfecting and sterilizing reusable medical and surgical instruments and equipment, and maintenance of associated environments in health care facilities
- AS/NZS 4815:2006, Office-based health care facilities—Reprocessing of reusable medical and surgical instruments and equipment, and maintenance of the associated environment
- and, the NHMRC's Australian Guidelines for the Prevention and Control of Infection in Healthcare (2010)

8. PATIENT ACCESS

With implementation of the ACTS Code of Practice patients will have access to treatments that meet with ACTS Code requirements for Safety, Efficacy & Quality. (Based on NHMRC and AHPRA requirements). This will prevent patients from travelling overseas to access treatment at far greater cost and risk. Implementation of the Code will also facilitate ongoing and future research in Australia.

CONCLUSION:

Australia is well placed to become a world leader in the area of stem cell research and therapy. This would mirror our national successes in other areas of medical science such as IVF, the Cochlear implant and immunology.

Codes of Practice are a proven way of delivering an appropriately strong regulatory environment for an emerging technology while also supporting the development of a viable research based industry.

The ACTS Code of Practice has been written incorporating existing regulatory frameworks. It aims to support the ongoing growth and development of a strong, ethical cell therapy industry in Australia.

A full copy of the ACTS Code is included in the submission. It is comprehensive and extends well beyond the above outlined areas. We hope that you will genuinely consider the Code of Practice as a viable solution for developing a safe and efficacious industry.

REFERENCES

[1] 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), Hyperlink

[2] The doctor-patient relationship is defined in the common law (made by the courts) in terms of the law of negligence, which imposes a duty of care on doctors to care for patients. (Rogers v Whittaker (1992) 175 CLR 479; Breen v Williams (1996 138 ALR 259)

[3] For example, as required by Health Practitioner Regulation (NSW) Regulation 2010 – Schedule 1, Hyperlink and Public Health Regulation (NSW) 2012 or corresponding State and Territory legislation.