Submission to the TGA public consultation:  
Regulation of autologous cell and tissue products and proposed consequential changes to the classification of biologicals

1 Introduction

Cell-Innovations welcome the opportunity to contribute to the TGA’s well-considered evidence-based consultation on the regulation of autologous cell and tissue products. Given the different pathways to medical innovation, we appreciate the challenges in consulting widely and ensuring that appropriate weighting is given to the voice of all key stakeholders. It is particularly important that biotech companies and medical practitioners are invited to collaborate fully as proposed changes to regulation will have significant impacts on clinical practice; cost of patient treatments; regulatory complexity and compliance costs; availability of investment for ongoing innovation; and the financial viability of the autologous cell therapy field of regenerative medicine.

Current TGA regulations have enabled an environment for Australia to become a leader in the research and clinical translation of autologous cell therapies, which offer great potential to reduce the health burden of chronic diseases in Australia. Proposed changes in regulation must be agile, and carefully balance patient safety and autonomy whilst continuing to foster innovation. There is a risk that increased regulation may stifle investment and innovation without measurably improving confidence in safety. We must be mindful to ensure Australia does not move towards more regulation when other countries have actioned risk-based strategic decisions to encourage innovation by moving towards less regulation.

Importance of Autologous Cell Therapy

The importance of autologous adult cell therapy in the current and future treatment of chronic diseases within Australia cannot be understated. One third of the Australian population (35% or 7 million) have reported having at least one chronic condition, with musculoskeletal conditions (12%) and injuries (9%). Almost 15% of the population have arthritis. In 2008–09, estimated health-care expenditure allocated to arthritis and other musculoskeletal conditions totalled $5,690 million – the 4th most expensive disease group, accounting for 8.7% of total health-care expenditure allocated to disease groups. It is clear that safe, innovative and evidence-based progress needs to be made in reducing this health burden.

Autologous adult cell therapy is a promising treatment that has already shown significant clinical benefits in peer-reviewed scientific literature, and in current medical practice, for osteoarthritis. Cell therapies are similar to ‘disruptive innovations’ that challenge the status quo, and may be unsettling to stakeholders comfortable with established practices. It is imperative to separate opinion and commentary from scientific fact in order to progress innovation in medical practice. Objective evidence should always be the primary consideration of regulatory decisions in this complex field.
Cell Innovations

Cell-Innovations (CI) is a private company (established in 2012) that licenses laboratory equipment to experienced clinicians who use it as one component of a regulated standard medical procedure to concentrate Stromal Vascular Fraction (SVF) from adipose tissue. The innovative process to mechanically concentrate SVF using ultrasonic extraction was developed in Australia and has a worldwide provisional patent. The CI process has been used safely and effectively in medical procedures in Australia for four years and the beneficial outcomes have been recorded, scrutinised and published.

CI is committed to providing patients with access to safe and effective treatments. Importantly, CI has actively promoted the: establishment of stricter standards by developing self-regulatory guidelines (Code of Practice: Australian Cell Therapy Society); sponsorship of scientific meetings and workshops on autologous cell therapy; publication of papers on cell therapy; and sponsorship of two ethics approved clinical trials.

Australian Cell Therapy Society (ACTS)

CI is on the committee of the Australian Cell Therapy Society (ACTS), and strongly supports the ACTS Code of Practice (http://acts.org.au/index.php/code-of-practice/) which was developed in collaboration with scientists and clinicians to consolidate, clarify and transparently document the rigour applied to the practice of autologous cell therapies in Australia. It is a significant code that applies to the practice of Autologous Cell Based Interventions (ACBIs) and use of human cell tissue (HCT) under item 4(q) and sets out: regulatory requirements, professional and ethical standards, advertising regulations; guidance on the translation of safe and effective therapies to improve patient lives; principles of evidence-based medicine and good clinical practice; and processes for patient informed consent, complaints and compliance. Extracts of the ACTS Code of Practice relevant to evidence-based medical practice; adverse events reporting; clinical registries; and advertising of regulated health services are included in Appendix D.

CI supports mandatory reporting of serious adverse events, and is working with ACTS in the development of policies and detailed requirements for data registries and adverse event reporting to improve the transparency of the safety record of autologous cell therapies. Consistent with national registries maintained in other fields of medicine, CI believes it is essential that serious adverse events are recorded in a confidential manner to facilitate complete and timely reporting; and that there is a rigorous investigation of causality (i.e. to distinguish events causally linked to surgical or medical practice from events that may possibly be related to autologous cells). A serious adverse events register will enable the appropriate comparison of the safety of autologous processes with the safety data of standard medical practice for the same disease. All medical procedures have risks, and safety evaluations must be made in context.

CI believes that a communication strategy to explain the ACTS Code of Practice, and proposals for data registries and adverse events reporting, will address many of the issues raised by the TGA.
Context

There is a clear difference between medical practice and therapeutic goods regulated by the TGA. Autologous cell concentration is an established medical practice providing cell therapy to patients in Australia for osteoarthritis. Medical practitioners are regulated by bodies including medical boards, AHPRA (Australian Health Practitioner Regulation Agency), ACCC (Australian Competition and Consumer Commission) and HCCC (Health Care Complaints Commission). In addition, the ACTS Code of Practice (explained above) sets standards for evidence-based practice and advertising of regulated health services. The recent action by AHPRA, Medical Council of NSW, HCCC and ACCC against medical practitioners is evidence of the effectiveness of regulatory agencies.

Proposed changes to regulation must be reviewed in context. CI appreciate the challenges in collating data to quantify the issues raised, and to assess the cost-benefit of proposed changes to regulations that may increase the cost of compliance and cost of patient treatments, and stifle investment and innovation, without measurably improving confidence in safety. CI believes the absence of data to contextualise issues is a weakness in this consultation process (although this will be addressed by the implementation of data registries and adverse event reporting in the future).

Medical therapeutic innovation is achieved via two pathways; the slower ‘big pharma’ drug pathway, and the substantially faster physician practice/discovery pathway. Neither system is perfect:

- The pharmaceutical pathway has the advantage of producing high quality data from randomized controlled trials in support of a new therapy, but the disadvantages of inflexibility, exorbitant costs and slow laboratory to clinical translation;
- In comparison, the medical practice pathway has the disadvantage of reliance on lower quality data (beginning, in all cases, with anecdotal experience), but the advantages of flexibility and a shorter timeline from discovery to clinical implementation. Physicians typically publish smaller studies that are reactive to problems encountered in daily clinical practice, and result from the rapid adoption of new therapies that appear to be effective in a semi- or uncontrolled setting.

It has been reported that Government funded research organisations have been slow to translate research into medical practice, and clinical trials of cell therapies for particular conditions are going on, but not in Australia. We have an obligation to ensure that Australian patients, their families, carers and physicians are not left behind in the stem cell revolution. We must ensure that both stem cell innovation pathways continue to operate in Australia: the pharmaceutical pathway for high risk cell therapy (e.g. allogenic and embryonic manufacturing processes); and the medical practice pathway for low risk autologous therapies.

It is also important to differentiate speculative opinion from scientific and clinical evidence of achievement in order to keep the field moving forward. Scientists, as is their profession, are cautious and call for more research to understand the basic biology of the cells. At the same time clinicians attending patients, look to new therapies that offer promise even though the scientific rationale has not been fully established. In our opinion, the resulting difference is unlikely to be resolved soon. We suggest that important lessons can be gleaned from the tangled path that was followed ahead of the science to develop the first successful stem cell therapies: hematopoietic stem cell transplants (HSCT). Therapies with HSCT are now successfully performed in over 50,000 patients per year worldwide.
There have been misstatements in the media regarding ‘loopholes’, and speculative commentary regarding safety and efficacy. It appears to CI that a primary issue to be addressed by changes to regulation is increased transparency, and evidence-based communication of safety and efficacy data to restore confidence in the highly regulated Australian medical environment. This will be achieved by the ACTS implementation of data registries and serious adverse event reporting. Efficacy data has already been collated by ACTS. Given the lack of credible evidence of a pattern of harm to patients, it would be a significant concern if it was proposed to significantly increase regulatory complexity, documentation, compliance costs, timelines and patient cost. To protect the interests of patients and industry investors in innovation, CI believe any variations in regulation must be defensible with evidence-based arguments of sufficient merit, or readily identifiable public health risk rationale, to justify the change.

A Possible Way Forward

- As the ACTS Code of Practice applies to the practice of Autologous Cell Based Interventions (ACBIs) and use of human cell tissue (HCT) and is comprehensive (e.g. regulatory requirements, professional and ethical standards, advertising regulations; guidance on the translation of safe and effective therapies to improve patient lives; principles of evidence-based medicine and good clinical practice; and processes for patient informed consent, complaints and compliance), CI suggest that the TGA collaborate more closely with ACTS to consider the extent to which the ACTS Code of Practice addresses issues of concern.

- CI proposes that the TGA consult with ACTS to provide input into the requirements for data registries and serious adverse events reporting.

- CI propose further consultation is required to discuss the definition and proposed guidelines; real world examples of minimal manipulation; process flowcharts of proposed changes; and compliance costs.

Given the Australian context of fewer than 20 clinics (informal investigation based on Yahoo searches) engaged in direct-to-consumer marketing of stem cell interventions, with no demonstrated evidence of any pattern of harm to patients over a period of 14 years internationally with autologous cell concentrate treatments (i.e. stromal vascular fraction and bone marrow concentrate), CI believes there is time for collaboration and careful consideration of proposed changes.

2 Summary of Key Points

- Cell-Innovations support the implementation of data registries and mandatory reporting of serious adverse events. This will increase transparency. Evidence-based communication of safety data will restore confidence in autologous cell therapies. It is essential that serious adverse events are recorded in a confidential manner to facilitate complete and timely reporting; and that there is a rigorous investigation of causality (i.e. to distinguish events causally linked to surgical or medical practice from events that may possibly be related to autologous cells). Cell-Innovations support ACTS as a suitable national body to operate a detailed registry of minimally manipulated autologous procedures in Australia. This would include serious adverse event reporting (as set out in the ACTS Code of Conduct Section 3).
Cell-Innovations believe that to support the best interests of patients to have access to information on the risks and efficacies of treatments for informed consent, advertising regulations should remain unchanged (i.e. still subject to ACCC and AHPRA regulations and restrictions). In the context of evidence-based medical practice, and standards of conduct for advertising and informed consent (required by AHPRA and ACTS), there is no reason for the TGA to restrict direct-to-consumer advertising.

Cell-Innovations believe stromal vascular fraction (SVF) should be regarded as a standard medical practice based on current medical guidelines. When is enough evidence sufficient for the use of stromal vascular fraction (SVF) in the treatment of osteoarthritis? Stromal vascular fraction was first used as a cell therapy over 12 years ago in 2004 by Lendeckel et al. In Australia SVF therapy has been used over the past 6 years in medical practice in the treatment of osteoarthritis.

Cell-Innovations understands minimally manipulated autologous human cell and tissue products will continue to be treated as excluded from TGA regulation across all proposed options 1 – 4. We believe the following should be amended for Option 3:

- guidelines on the application of the minimal manipulation definition to include process actions in the EU definitions of ‘cell separation, concentration or purification’; with stromal vascular fraction as an example of minimal manipulation;

Cell-Innovations supports the proposed changes set out in Option 3 for higher risk autologous cell therapies that involve more complex manipulation of cells (i.e. cell culture and differentiation, and seeding on a medical device).

This provisional support is dependent on further consultation on the:

- proposed regulatory process and compliance costs for increasing levels of risk as it is neither cost-effective nor feasible to expect the same manufacturing quality controls for autologous therapies as those in place for mass-produced allogeneic therapies.

Cell-Innovations would not support significantly increased regulatory complexity or compliance costs for cell concentration processes where there is satisfactory safety and efficacy data and no pattern of harm to patients. We believe there is no credible evidence, in the context of the current highly regulated Australian medical environment, to justify significantly increase regulatory complexity, documentation, compliance costs, timelines and patient cost.

Safety and efficacy is well documented for minimally manipulated autologous cell therapies. Appendix A sets out a body of evidence in support of the use of stromal vascular fraction (SVF) cell concentrate for the treatment of osteoarthritis over 6 years. The safety of SVF compares favourably to the alternative surgical intervention for end-stage osteoarthritis, which has significantly higher mortality and serious complications.
In the context of evidence-based medical practice (as required by AHPRA and ACTS), autologous cell therapies are effectively regulated by agencies including AHPRA (Australian Health Practitioner Regulation Agency), ACCC (Australian Competition and Consumer Commission) and HCCC (Health Care Complaints Commission). In addition, the ACTS Code of Practice sets standards for practice. The recent action by AHPRA, Medical Councils, HCCC and ACCC against medical practitioners is evidence of the effectiveness of regulatory agencies.

3 Discussion

Section 4 sets out detailed responses to the specific issues for which views are sought from stakeholders. This section is a discussion of information we believe is relevant to the consultation.

Safety

Cell-Innovations believe that as minimally manipulated autologous cell concentrate (i.e. stromal vascular fraction) has a high safety record both internationally and in Australia (over 12 years and 6 years respectively), it should be regarded as a standard established medical practice (in particular, to reduce inflammation and pain in knee and hip osteoarthritis). As there has been no pattern of harm to patients, we believe there is no credible evidence to justify a significant increase in regulatory complexity, documentation, compliance costs, timelines and patient cost.

Cell-Innovations advocate evidence-based medical practice, and support the use of the CI SVF cell concentration process for the treatment of osteoarthritis only at this time. Peer-reviewed literature (over 20 publications – see Appendix A) on SVF evidences the treatment of over 1,600 patients for knee and hip disease, with two Level II studies and three Level III studies. Therefore, based on NH&MRC guidelines Levels of Evidence and Grade for Recommendations for Developers of Guidelines (and the ACTS Code of Practice), it is clear that there is sufficient evidence in the scientific literature, and Australian clinical practice data, to support the overall safety and efficacy of SVF in the treatment of osteoarthritis.

There is risk with all medical procedures. No pattern of harm is evident globally for stromal vascular fraction (SVF). Published clinical studies report a lack of serious adverse events with SVF cell concentrate (1,638 published osteoarthritis patients treated with SVF), although there were a few mild and transient peri-injection effects. Caplan et al reported that - from a review of all peer-reviewed literature that included safety assessments of clinical trials over the past 5 years - only 2% identified a safety issue for autologous and allogenic cell therapies.

In reviewing serious adverse events, it is critical to perform a rigorous investigation of causality (i.e. to distinguish events causally linked to surgical or medical practice from events that may possibly be related to autologous cells). In investigating the tragic death of Mrs Drysdale, the NSW Coroner found that the failure to cease anti-coagulant medications prior to the liposuction procedure was the reason for uncontrolled bleeding. A causal link was made to surgical practice, and not to cell therapy. This isolated event was attributed to a failure of medical practice; and appropriate action has since been taken by regulatory bodies.
It is appropriate to compare the safety of autologous cell therapies to standard conservative management of the disease being treated. SVF is used to treat knee and hip osteoarthritis, for which the end stage standard treatment is knee and hip replacement. In 2014, there were 76,357 primary, total knee and hip replacements performed in Australia, of which the primary diagnosis was knee (97.5%) and hip (88.5%) osteoarthritis. A study of Australian and Norwegian registries for 188,110 elective total knee and hip replacements concluded an excess mortality rate of 0.12% (1 in 833) over 26 days. This equates to an estimated 91 patient deaths in 2014 for an elective surgery (~1 death every 4 days in Australia from elective total knee and hip replacements).

The main risks associated with autologous cell separation are sterility and routes of administration. Doctors manage sterility risk every day by standard medical practice. Routes of administration beyond intra-articular joint injection introduce potentially higher risk to the patient (e.g. intravenous and intrathecal administration). We note that there is no evidence in the peer-reviewed literature of harm by intravenous infusion beyond that which is typical of bone marrow transplant, although caution should be applied. Cell-innovations do not support the use of any other route of administration except in a clinical trial with sufficient preclinical data. Medical practitioners have knowledge of the risks and practices for routes of administration. Inappropriate practice would be viewed seriously by medical regulatory bodies (e.g. AHPRA).

SVF cell concentrate therapy falls into the one-on-one delivery / non-magnified scale risk category. It has lower risk than the mass manufacture of drugs with the highly magnified risk to public health, or the risk associated with the implantation of cadaver-harvested transplant tissue into multiple recipients.

We agree with the TGA that it is difficult to quantify safety data for autologous cell therapies in Australia. Cell-Innovations support the implementation of data registries and mandatory reporting of serious adverse events.

**Efficacy**

Cell-Innovations believe minimally manipulated stromal vascular fraction SVF should be regarded as a standard medical practice when there is robust peer-reviewed evidence in-line with the medical guidelines of the NH&MRC Levels of Evidence and Grade for Recommendations for Developers of Guidelines. Stromal vascular fraction was first used as a cell therapy over 12 years ago in 2004 by Lendeckel et al. In Australia SVF therapy has been used over the past 6 years in medical practice in the treatment of osteoarthritis.

Autologous cell therapy tends to be investigator led (e.g. only 6% of autologous cell therapy clinical trials in the EU were company-led (2012)). Despite this lack of support by industry, there is a robust body of evidence for the safe and effective treatment of knee and hip disease with autologous cell concentrate (5,336 patients; 44 scientific publications over 12 years).

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1 An estimation of mortality is provided as we not have access to the Australian Orthopaedic Association registry.
Of the 44 peer-reviewed publications there are 6 Level II studies and 4 Level III studies which evidence over 20 publications with 1,628 patients for SVF-derived cells; and 22 publications with 3,708 patients for bone-marrow derived cells (Appendix A). By applying the NH&MRC guidelines on the interpretation of peer-reviewed data: *Levels of Evidence and Grade for Recommendations for Developers of Guidelines*, a rating of ‘C Satisfactory’ may be assigned to autologous cell concentrate for the treatment of osteoarthritis.

Contrary to mischievous generalised misstatements to the media implying *unproven procedures*, there is a significant body of evidence in support of the safety and efficacy of autologous cell therapies in the treatment of knee and hip osteoarthritis. Significantly, more than 10 stem cell-based products have been approved in some countries. Given the breadth and scope of peer-reviewed publications, clinical trials for autologous cell therapies and approved therapies, we have difficulty understanding how this could have been missed and misreported. We acknowledge that the evidence is not yet sufficient for the treatment of diseases other than osteoarthritis with SVF, but believe generalising SVF treatments for osteoarthritis with these other diseases to be inaccurate.

As previously discussed the medical practice pathway begins with anecdotal experience, case series and small clinical studies. Continual studies occur over time as protocols and treatment regimes are honed, and this leads to the adoption of new therapies that appear to be effective in a semi- or uncontrolled setting. A typical example is HSCT studies that occurred over a 60 year period, but did not prevent therapeutic treatment of patients. Protocols improve incrementally over long periods of time based on clinical results and observations. Furthermore, the clear majority of medical procedures (not drugs) are reviewed by comparison studies. Just over 1/3 (37.02%) of medical interventions are supported by randomised controlled trials (RCT).

The following is an example of unmet patient need, and the evidence for the treatment of osteoarthritis with stromal vascular fraction:

**The Issue**

Surgery has historically been considered the final solution for treatment of knee osteoarthritis, both by treating practitioners and by patients, with mortality a concern. However, most patients who suffer from end-stage knee osteoarthritis endure knee pain and dysfunction for years in an effort to delay surgery. In fact, only 20%–33% of patients with severe knee osteoarthritis are definitely or probably willing to consider knee arthroplasty, and within a 10 year period 22.6% of Australian patients will require a full revision to their knee joint replacement. Total knee arthroplasty (TKA) is recognised as a suboptimal treatment option in patients under 65 years since younger active and high demand patients are at greater risk for prosthesis failure secondary to aseptic loosening and, consequently, revision surgery versus their older counterparts. Lastly, there is a clear mismatch between patients expectations versus actual clinical outcomes following TKA, as 85% of patients expect to be completely pain-free after surgery when in fact only 43% report complete absence from pain.

Experts have identified the need for effective, minimally invasive osteoarthritis therapies that can prevent or delay joint-replacement surgery, especially as many patients with osteoarthritis are experiencing symptom onset at an earlier age due to active lifestyles (AHRQ Healthcare Horizon Scanning System (Priority Area 01: Arthritis and Non-traumatic Joint Disease)).
The Evidence

The objectives of osteoarthritis management, according to the Osteoarthritis Research Society International (OARSI), are to reduce pain and inflammation, slow cartilage degradation, improve function and reduce disability \(^{27-29}\) (Figure 1). Any of those potential outcomes would have a significant effect on delaying joint replacement therapy and result in savings of loss of life, surgical complications, and savings to the health system. Improvement in any of the above categories has to be the first in-line osteoarthritis treatment option.

In Australia SVF therapy has been used over the past 6 years in medical practice in the treatment of osteoarthritis successfully \(^{11}\). Appendix A presents a strong body of international evidence and Appendix C (commercial-in-confidence) further details pre-clinical and clinical evidence that demonstrates:

- Improvement in pain and inflammation
- Improved patient mobility
- Cartilage improvement with the potential for slowed cartilage degeneration

In addition, many hundreds of patients have been treated safely and effectively for osteoarthritis using stromal vascular fraction therapy in Australia (supplementing the global clinical experience where thousands of patients routinely receive guided injections of stromal vascular fraction each year with excellent safety and success).

Further good quality randomised controlled trials with long-term functional outcomes are still required to investigate sub-types of osteoarthritis, and improvements in protocols will lead to better outcomes. Cell-innovations is contributing to this evidence by sponsoring an HREC approved clinical trial on the treatment of focal chondral defects of the knee with SVF.
Autologous cell concentrate therapy compares favourably to orthopaedic treatments with key advantages of low toxicity and a high safety margin. An excess mortality rate of 0.12% has been observed for total knee and hip arthroplasty within 26 days of surgery\(^1\). We can estimate from this that 1 Australian patient dies every 4 days from total knee and hip arthroplasty (76,357 primary total knee and hip replacements were performed in Australia (2014))\(^2\). In contrast, 1 mortality has been reported in 6 years for the standard liposuction procedure required for autologous cell therapy, and appropriate medical regulatory action was taken in response.

Based on the safety and efficacy of autologous cell therapy in comparison to total knee and hip arthroplasty, we should be asking the question “\textbf{Why are we not doing this therapy?}”; rather than should we be stopping this therapy, or should we be increasing regulatory requirements?

The potential savings to healthcare have already been recognised in the animal sector with 12 veterinary insurers in the USA who cover SVF stem cell procedures for osteoarthritis: Pet Plan, Trupanion Pet Insurance, Veterinary Pet Insurance (a division of Nationwide), Embrace Pet Insurance Company, Healthy Paws Pet Insurance, Pet First Insurance, Pets Best and ASPCA Pet Insurance. Animal studies and veterinary practice often lead medical practice.

Based on NH&MRC guidelines, Cell-Innovations believe there is currently insufficient clinical evidence for the treatment of diseases other than osteoarthritis. Under these guidelines there would be insufficient evidence for the treatment of other diseases such as MS, Parkinson’s, Motor Neuron.

\textbf{Advertising}

We believe that to support the best interests of patients to have access to information on the risks and efficacies of treatments for informed consent, advertising regulations should remain unchanged (i.e. still subject to the ACCC and AHPRA regulations and restrictions). In the context of evidence-based medical practice and codes of practice for advertising (required by AHPRA and ACTS), we believe there is no reason for the TGA to restrict direct-to-consumer advertising. The recent action by AHPRA and ACCC against practitioners is evidence of the effectiveness of regulatory agencies in an environment where there are less than 20 clinics in Australia engaged in direct-to-consumer marketing.

We support the current restrictions on advertising overseen by AHPRA and ACCC, and the ACTS Code of Practice: Advertising a Regulated Health Service (as set out in Section 5, a subset of which is in Appendix D).

AHPRA regulations prohibit: false, misleading or deceptive claims; unreasonable expectations of beneficial treatment; or encouragement of unnecessary procedures. Medical practitioners are expected to comply with a code of conduct which includes providing fully informed consent. Concerns about the conduct of medical practitioners can be reported to AHPRA, HCCC and ACCC.

In the context of AHPRA and ACCC regulation, and evidence-based medical practice, we believe detailed information about autologous cell therapies is necessary for informed consent. It is in the best interests of patients to have the same access as doctors to information on treatments, risks and efficacies. It would be difficult to justify to patients that information should be filtered by doctors, without the patient having detailed information to compare treatment options. GPs are not well-informed about autologous cell therapies.
The Australian Competition and Consumer Commission (ACCC) expressed the view that patients should be able to receive accurate and relevant information in order to make informed decisions in their dealings with medical professionals. With the conflicting medical viewpoints on treatment options available it is important the patient is kept fully informed with knowledge of options and services available.

The continuing availability in Australia of effective low risk autologous cell therapies is important to patients. The financial model of autologous cell therapy clinics is dependent on stable operating revenues to finance continuing innovation, research and clinical trials. Small clinics do not have the substantial marketing budgets of pharmaceutical companies that sponsor conferences and deploy teams of medical reps to educate doctors. The proposed restriction on advertising would detrimentally impact operating revenues and discourage future investment. It is possible that small clinics would no longer be financially viable, or able to finance research and clinical trials.

**Minimal Manipulation**

We propose that guidelines on the application of the minimal manipulation definition include the EU definitions of ‘cell separation, concentration or purification’; with stromal vascular fraction an example of minimal manipulation.

1. The TGA propose that physical disruption of a tissue will lead to changes in their properties i.e. activation state or surface molecule expression, which may impact the cells characteristics or functions leading to more than minimal manipulation.

   We understand this but observe that other examples of minimal manipulation processes (e.g. centrifugation, washing, refrigeration and freezing) would all similarly impact the activation state and surface molecule expressions of the tissue or cells (e.g. cells and tissues react to environmental changes such as temperature, washing reagents used, and centrifugation). All of the current minimal manipulation definition process actions seek to modify the tissue or cells in some way for further use.

2. The TGA proposes that the following definition of minimal manipulation be applied:

   "Cells or tissue are subject to a process that is more than minimal manipulation if the process results in the alteration of any of the biological characteristics, physiological functions or structural properties that are relevant to the intended use of the cells or tissues."

   Autologous cell concentrates operate primarily by strong paracrine affects. The intended relevant therapeutic use is determined, not by a cell separation or concentration process, but by the host site (i.e. the molecular response is different in different environments). The therapeutic proteins are coming from the host site (e.g. there are over 90 different transcripts coming from injured tissue sitting next to a stromal cell).

   The paracrine affect of the cell concentrate is to positively impact the microenvironment. Complex numerous actions in response to the micro-environment are possible by the cell concentrates (e.g. modulation of local tissue levels of pro-inflammatory cytokines by anti-inflammatory paracrine factors; production of molecules that can sit on opioid receptors and reduce the perception of pain. No one yet understands the exact interactive process but...
there is already strong clinical evidence and outcomes to support the continued use in the clinical setting (e.g. orthopaedic actions).

Difficulties in applying the definition of minimal manipulation to simple proven cell concentration processes well-established in clinical practice, and for which there is satisfactory evidence supporting the safety and efficacy of the cells for the intended use (e.g. stromal vascular fraction to reduce inflammation and pain in knee and hip osteoarthritis), should be handled in the guidelines by including the processes as examples of minimal manipulation.

**Summary**

We understand the challenge in developing an agile and pragmatic regulatory framework that balances patient safety and autonomy whilst fostering continuing innovation.

**We interpret minimally manipulated Stromal Vascular Fraction (SVF) as continuing to be excluded from TGA regulations under Options 1-4.** We appreciate that the proposed Option 3 provides an alternative pathway based on risk and degree of manipulation of autologous cells and tissues. It provides a middle ground between the ‘status quo’ and the intense regulatory pathway of biologicals that is not financially viable for autologous cell therapies.

The TGA raised concerns in the consultation paper regarding communicating evidence of safety and efficacy; reporting data on therapies and adverse events; and direct-to-consumer advertising. The issues raised have been addressed, in part, by the initiatives of ACTS to: communicate peer-reviewed evidence of safety and efficacy for osteoarthritis (Appendix A); draft requirements for data registries and adverse event reporting; and implement a code of practice that documents safety standards and guides evidence-based practice to provide therapies for osteoarthritis only at this time.

The issues must be reviewed in context. Government funded research organisations have been slow to translate research into medical practice. The recent informal investigation based on Yahoo searches estimated that there are 19 clinics in Australia engaged in direct-to-consumer marketing of stem cell interventions. Over the last 6 years, there has been a slow but steady uptake of autologous cell procedures by medical practitioners as evidence accumulates in support of efficacy for osteoarthritis. There has been no demonstrated evidence of any pattern of harm to patients over a period of 14 years internationally with autologous cell concentrate treatments.

In the context of evidence-based medical practice, we cannot support significantly increased regulatory complexity or compliance costs for cell concentration processes where there is satisfactory safety and efficacy data and no pattern of harm to patients. We believe there is no credible evidence, in the context of the current highly regulated Australian medical environment, to justify increased regulation of stromal vascular fraction.

Thank you for the opportunity to provide feedback on regulations associated with cell therapies. We look forward to continued engagement with the TGA to support the regulations of cell therapies.