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Box Hill Stem Cell Centre Pty Ltd ABN 35 160 608 337
Trading as Melbourne Stem Cell Centre

To whom it may concern,

***RE: Regulation** of Autologous Stem Cell Therapies – Discussion Paper for Consultation*

I write this submission with reference to my role as [redacted] of Box Hill Stem Cell Centre Pty/Ltd (ABN 35160608337) trading as Melbourne Stem Cell Centre (MSCC). My fellow [redacted] have made a commitment with others to establish a state-of-the-art medical centre in Box Hill, Victoria, to research the efficacy of stem cell treatments in an ethical and scientific environment where we provide consulting rooms, a theatre and laboratory (at an establishment cost of circa $550,000) so that the harvested cells do not need to leave the facility and can remain under the direct supervision of the centre's clinicians.

I welcome the opportunity to provide input to the TGA's Consultation regarding the regulation of autologous stem cells.

MSCC aims to ensure that all patients are treated within either funded or self-funded approved trials/protocols where a commitment is made to record and publish our outcomes. Currently our research is focused on osteoarthritis. This debilitating disease affects many millions of Australians.

Importantly these research projects, which are of international significance, are being conducted under the Therapeutic Goods (Excluded Goods) Order No. 1. The ability to complete this research depends upon the current legislation being maintained.

MSCC and its clinicians - in acceptance of the Excluded Goods Order –acknowledge and require that all autologous therapies be used only under the formal `supervision of a medical practitioner who is caring for that patient'.

Any processing done by suitability accredited laboratory staff is done under direct supervision of the clinician and only when it has been thoroughly shown and documented that techniques used meet the required level of safety. Cells are harvested by a limited liposuction procedure and then transferred directly to our on-site laboratory via an air lock where they are assessed and stored under strict infection control processes. A sample of the cell population is sent to an independent laboratory at Monash University where they are further assessed to ensure their viability. MSCC ensures that cells are assessed for infection, evaluates the cell populations to ensure we have a defined number of pure stem cells and we then treat with pure stem cells only. We ensure that the cells are free of infection before they are administered. Although this adds time to the treatment process we believe these important testing procedures are required for patient safety. Such a step if adopted in the sector would not allow for same day treatment using stem cells.

Clinicians at MSCC recognize the responsibilities under clinician regulatory bodies (i.e. AHPRA, Medical Board of Australia and Specialty Colleges) to maintain professional standards of practice as per the Health Practitioner Regulation National Law Act. MSCC expects and formally requires that clinicians only practice within their area of expertise/specialization.

The [redacted] of MSCC maintain that the clinical approach used to evaluate the patient regarding suitability for the trials mentioned above, the harvesting of cells and the applied treatment utilized the cells, is done under the complete clinical sovereignty of the clinician.

MSCC believes Australia is well placed to become a leader and this in this area of medical research and it should be noted that this type of treatment can only be done in a small number of countries around the world. This type of treatment cannot be performed in China or the United States of America. This current situation creates a unique opportunity for Australia to achieve the status as a world leader in stem cell research and therapy. It is entirely feasible also that Australia may be able to develop as a destination for medical tourism, which would create a further opportunity to increase job opportunities and wealth for our country. Indeed we have already had expressions of interest from potential patients suffering from Osteoarthritis from the USA and China who wish to visit Australia for treatment of their arthritis condition. Such activity would mirror our national successes in other areas of medical science such as IVF, the Cochlear implant and immunology.

Melbourne Stem Cell Centre has invested $550,000 in 2014 to create a state-of-the art practice and laboratory.

The ongoing financial commitments per annum of Melbourne Stem Cell Centre include:

- Rent and property outgoings $200,000
- Leasing costs $124,000
- Nursing and administration salaries $120,000
- Clinician fees $220,000
- and other operating overhead costs $136,000
- Total $800,000

Funding into this area is also supporting two of the world's largest internationally registered randomized clinical trials into the use of autologous stem cells for the treatment of knee osteoarthritis and isolated knee cartilage lesions.
These trials have prospective Ethics Committee approval via Monash University and Latrobe University respectively. These trials are funded by both MSCC and Magellan Stem Cells.

This investment in medical research is only possible because stem cell research can be safely and appropriately undertaken in Australia under the current TGA exemption in line with good clinical practice, human ethics approval and other guidelines.

Changing the regulatory regime and imposing unnecessary restrictions would undermine this fledging sector and render it unviable. This would run counter to government policies and funding aimed at encouraging scientific research, such as the Medical Research Futures Fund, the National Statement on Ethical Conduct in Human Research and many others. This also runs counter to the current Liberal government plan to reduce Government legislation and regulation

The Consultation's outcomes should prioritize maintaining an environment conducive to growing this research industry in an appropriate manner with serious emphasis on patient safety and the sector seeks to work with the TGA to ensure these views are reflected.

Discussion Paper Review

The discussion paper has asked for feedback on a number of areas of concern -

1. Safety of the product, including issues related to any processing of the product

MSCC understands that concerns relating to the use of autologous stem cell therapies – particularly regarding safety – are dependent upon a number of factors including which patient is selected, the type of therapy and its dose and the variety of conditions being treated.

Due to the enormous potential variation in autologous cell based products it is understandable that not all cell therapies carry the same level of safety.

The clinician in all instances has primary responsibility in their duty of care to the patient to use and administer therapies with a proven level of safety. The current legislation also requires the clinician to also take primary responsibility for the `product'.

MSCC has taken the view that for new and emerging therapies it is essential to conduct research trials into the efficacy of stem cell treatment. To do that requires that such research have ethics approval. A significant aspect of gaining such approval is that the ethics committee is to understand and ensure that the treatment is safe to be administered to the patient

2. Lack of evidence to support the efficacy of the product and the large sums of money being charged for unproven treatments

Evidence of efficacy of these therapies and their safety is dependent upon type of stem cell therapy used and the condition being treated. Recent Level II and Phase II evidence of both safety and efficacy of intra-articular autologous isolated mesenchymal stem cell preparations in the treatment of knee osteoarthritis have been published (Saw et al 2013, Jo et al 2014). This proof of concept has been developed in Veterinary for over 10 years. This lack of evidence is precisely why trials such as ours are needed to continue.

As a commercial business working in this area we need to be comfortable that what is done within a clinic has had strenuous due diligence performed to ensure that the business model will be sustainable into the future. We are confident with the appropriate level, quality and strength of evidence regarding safety and efficacy.

Large sums of money being charged for unproven treatments

We agree with concerns regarding the expense of unproven therapies. MSCC are running two internally funded Randomized Controlled Trials on stem cell therapy for degenerative knee conditions at a cost of over $500,000 in year one of these trials. The operation of such a facility as ours requires extra expenditure in relation to air quality, protection and housing of cells in a specialized environment to ensure any risk of contamination or infection is virtually eliminated.

MSCC ensures that significant testing is performed on cells and even requires external assessment of cells to ensure their viability, vitality, number and quality. Such procedures are considerably expensive and add to the time taken to treat patients and process and store their cells but are the necessary steps our centre and clinicians take to ensure patient safety.

3. Lack of reporting of adverse effects of the products

It is apparent that adverse effects will be dependent upon the type of therapy, the patient and also protocols used and will not be consistent for all cell based therapies.

MSCC believe it is the responsibility of the clinician to document adverse events and publish this data on a recognized scientific platform or register. Involvement in registered clinical trials – which is encouraged by the current exemption – does promote documentation and adverse events and is a suitable platform.

4. Inappropriate advertising of the products

MSCC and its clinicians adhere to the legally enforceable Health Practitioner Regulations National Law and ensures that any advertising complies with both the National Law and AHPRA guidelines.

MSCC does not believe that further regulation re advertising is required.

Below I have responded to areas that The TGA Discussion Paper has further highlighted for discussion:

Discussion Questions :

- *What are the public health risks of `autologous stem cells' in your view?*

MSCC believes that the public health risk only exists where clinicians fail to fulfil an accepted level of `duty of care'. MSCC believe that suitable code of conduct be introduced to address such risks and concerns. MSCC has worked to mitigate any risks by providing an environment for patients where extensive information is provided, strict protocols regarding hygiene and infection risks are mitigated as much as possible and that the clinicians are well supported with appropriate staff to assist them.

- *What is the evidence of these public health risks?*

MSCC has no evidence of these risks where the services are being provided from, and considers that if current regulations encompassing clinical practice were appropriately enforced we do not believe that a level of `public risk' would exist. If however there are examples within the medical community where levels of efficacy and safety cannot be shown, nor can the clinician appreciably argue that they are practising within their area of expertise then these regulations should being enforced strongly.

- *What identified risks should have the highest priority for resolving?*

Enforcement of a level of care such that the public can trust that their clinician will need to meet the highest of ethical and clinical standards as required by professional bodies, APHRA etc. should be the already accepted standards of care which should be maintained thus allaying the need for special "priority"

- *Are there public health benefits, such as patient access to new and novel treatments, to consider?*

Current legislation encourages the translation of scientific research to the area of clinical development.

As outlined before, all practice of novel treatments should be undertaken within a registered and human research ethics committee trial (a primary aim of MSCC) – thus meeting requirements of adequate follow up, outcome and adverse event recording.

MSCC is a co-signatory to an industry driven `code of conduct' which has been developed by the "Australian Cell Therapy Society" (ACTS) and we refer you to that web site. (www.australiancelltherapysociety.com.au). Such industry code provides the accepted framework that all clinicians should operate within. MSCC very strongly supports such industry codes.

5 potential options are suggested within the paper with areas of discussion highlighted :

- *What do you see as the likely risks, benefits and costs of each option to you? If possible, please attempt to quantify these costs and benefits.*

Option 1. Continue to exclude autologous cells from regulation under act

Risks :

- The risk of maintaining the `status quo' will perhaps lead to continued confusion with both regulatory bodies and the medical profession as to who is responsible for regulation. The industry may also be left wondering if the exemption will be lifted in the future which provides uncertainty for an emerging industry and may stifle further investment.

Benefit :

- The above risk is addressed by the suggestion of the TGA to use the legislative instrument under subsection 7AA (1) of the Act which would specify that autologous cells are not covered by the Act. Rather than to have an exemption the onus would be on the clinicians to demonstrate to relevant regulatory bodies (i.e. AHPRA) that their use of stem cell therapies meets appropriate standards of accepted practice. While this remains the case under current legislation it is less clear. This may indeed provide greater certainty to an emerging sector but also keep the clinician as the key party in the intervention.

Costs :

- This would not place any further cost on our clinic. All of the steps to ensure safety and efficacy that we suggest within this response are already undertaken at MSCC as standard practice. Importantly it would allow us to continue current studies which our clinic has made a commitment to spend over $500,000 in clinical studies in our first year of operation.

Option 2. Relates to excluding autologous stem cells from regulation under the Act in defined circumstances.

Option 3. Is to regulate autologous stem cells under the act, but exempt from registration and manufacturing requirements

Option 4. Is to regulate under the Act as Class 1 biologicals

Options 2, 3 and 4 are discussed collectively below.

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Risks :

- The above options in part relate to the issue of safety. If Option 2-4 are to be introduced based on the notion that the criteria presented regarding autologous cells present the lowest risk then the logic is flawed. These options carry the same risk in that they encourage the continued practice of therapies with little or no proof of efficacy or safety. Importantly, however, Level II systematic review has concluded that isolated mesenchymal stem cells are relatively safe though this would mean greater than minimal manipulation as defined by the TGA.

MSCC has strict operating procedures that encompass testing and safety of cells both on and off site. MSCC ensures that cells are assessed for infection, evaluates the cell populations to ensure we have a defined number of pure stem cells and we then treat with pure stem cells only. We ensure that the cells are free of infection before they are administered. Although this adds time to the treatment process we believe these important testing procedures are required for patient safety. Such a step if adopted in the sector would not allow for same day treatment using stem cells.

- As the treatments with documented levels of efficacy and safety involve greater than minimal manipulation any further TGA involvement needs to be carefully considered so as to not inadvertently burden a developing and promising industry. The need to freely develop within safe and ethical guidelines without overt and over bearing government regulation is important.

- Options three and four would prevent the development of a research sector with enormous potential for Australia. Should such options have been considered for the IVF industry then Australia may not have become a world leader in that now significant industry.

- If under Option 4 stem cells become regulated as class I biological then we would need to certify the efficacy of the product. While we believe and studies show that the treatment is efficacious the onus would be there to prove this. Without appropriate long term government funding for larger scale research this would not be feasible and would stifle private funded research and development. We urge the TGA not to consider Option 4.

- The observation about the reporting of adverse events is of importance but as in other areas of Medicine such matters should be regulated by the industry and professional bodies and not the TGA. If, as in some of the options it was considered to have an option that included the mandatory reporting of adverse events then this would put an unnecessary burden on clinicians who are already regulated by their own professional standards etc.

Costs:

- Should manufacturing requirement be set at a higher level under options 3 and 4 then the costs would be overly prohibitive to developing this industry.

- If options 2, 3, or 4 were adopted we would no longer be able to complete our current ethics approved trials as they are being conducted under the `exemption'. The trials are expected to take 3 years to complete and a financial commitment of >$1,000,000.

- Trials in which enrolment and treatment has already commenced over the last 6 months would need to be ceased. A process of new trial submission would need to be undertaken and this may take >12months.

- Osteoarthritis is a degenerative condition. Under the TGA exemption the course of stem cell therapy for osteoarthritis in our clinic is often documented as 5 years. Use of Option 2, 3 or 4 would effectively prevent patients being treated within our clinic from having their complete course of treatment.

- Industry needs certainty to develop. When business makes investment of the sort of magnitude mentioned above there is a need to see how the investment can be repaid. If we were left with the option to treat trial patients only then the project viability becomes at risk. Under options 2 to 4 there may be risks that prevent the treatment of only trial patients. This means that those who do not meet the trial criteria but are keen to pursue treatment may be unable to do so. In such cases it would be necessary for MSCC to seek Government funding to continue whereas at present the funding is provided by private investors committed to making a difference and being pioneers in a potential billion dollar Australia industry. We urge to TGA to consider this.

Option 5. Regulate under the Act as Class 2, Class 3 or Class 4 biologicals

Risks :

- Option 5 would require that cell based therapies undergoing one or more action of minimal manipulation would be classified as Class 2 or greater Biologicals. This would mean TGA would need to be satisfied in regards to quality, safety and efficacy.
- It is important to recognise the enormous variability in processing methods, patient selection and treatment protocols such that all cell based therapies would need to be individually assessed by the TGA against their standards of quality, safety and efficacy.
- MSCC disagree with the TGA Discussion Paper in its assertion that this option offers the clearest incentive for gaining good quality clinical evidence. The cost would discourage Groups like MSCC from investing in ethics approved research and therefore would directly prevent the clinical development of cell based therapies within Australia. Given my comments re class I biological it would clearly be an even more difficult environment to operate with even more restrictions placed upon us should the stem cells be either class 2, 3, or 4 biologicals. Here the burden to be licensed, provide full clinical evidence, provide extensive and ongoing information to the TGA, as well as the fact that cells which have an inherent autologous variability would need to meet the requirements of applicable product standards, would be obstructive and near unachievable. In other words the ground rules being changed mid-game is not a workable way to grow a business or realise an opportunity that may build a viable sector that can assist Australia to be a leader in the world and develop many new jobs for Australians. We strongly urge the TGA to not consider option 5.

Costs :

- This option would lead to the immediate cessation of the sector's development in Australia.

The TGA discussion paper includes further questions for consideration:

Are there additional issues with the regulation of autologous stem cells that any changes should consider and/or address?

- MSCC was encouraged to develop their clinic because there was appropriate recognition (the biological exemption) that this was a developing industry and that over regulation would not enable the nimble and effective start-up of clinics that may be interested in working with clinicians to investigate, research, prepare an administer stem cell therapies within an ethical framework . The Exemption – if regulated correctly - remains a robust tool in that it stipulates that the clinician takes complete responsibility and therefore must show an accepted 'duty of care'.

Within the area of autologous therapy there is an accepted precedence of `self-regulation' – the Australian Health Minister Council ratified the self-regulation of Assisted Reproductive Therapy in 2008. MSCC is a co-signatory to an industry driven `code of conduct' which has been developed by the "Australian Cell Therapy Society" (ACTS) and we refer you to that web site. www.australiancelltherapysociety.com.au.Such industry code provides the accepted framework that all clinicians should operate within. MSCC very strongly supports such industry codes.

Further comments below will add to those already outlined above but to summarise the discussions points raised thus:

Discussion question for option 1

- *Is there an argument that autologous stem cells are not therapeutic goods and therefore, should remain under the current section 7 declaration?*

- No, there is not an argument that they are not. They fall within the definition of therapeutic goods. We welcome such regulation once adequate review of what we at MSCC are doing. Therefore use of section 7AA to enable the Minster to exclude them from the act is an appropriate step.

Discussion question for Option 2

- *Should autologous stem cells that are more than minimally manipulated and/or are not homologous use continue to be excluded from regulation? Why or why not?*

As indicated above, the accepted safety data for mesenchymal stem cells and also evidence of efficacy in the treatment of osteoarthritis is for isolated mesenchymal stem cells. We isolate and then treat with "pure" stem cells.

Summary

MSCC's welcome the formal TGA review of the regulation of autologous cell based therapies. We believe in a regulatory framework but think it should work in concert with business to allow the development of an exciting new sector. Over-regulation would stifle opportunities and should be considered very carefully and with appropriate consultation with the industry players including clinicians, business operators and industry bodies.

Importantly the current legislation both encourages and allows Australian clinicians and scientists to work together world leading clinical trials. Such trials need to be conducted in safe and appropriate environments and MSCC provides such an environment. Appropriate, safe and significant medical advancement under the current regulation can occur and an example of this is our two world leading randomized controlled trials of the use of stem cells in degenerative knee conditions.

Clinical sovereignty is the hallmark of good medicine and in no way does MSCC impose its view on clinicians in matters clinical. As the TGA exemption highlights, treatment remains the `responsibility' of the clinician. As mentioned before the recently constituted body Australian Cell Therapy Society has developed a further code that covers many of the aspects addressed in this paper. I urge the TGA to consider this code for the sector. As such clinicians should face investigation and prosecution by the appropriate regulatory authority should they transgress such codes. (I.e. AHPRA, Medical Board of Australia).

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We have outlined above that some alternatives suggested in place of the current legislation (Options 2, 3 and 4), rather than preventing poor medical practice, in fact encourage the continued use of unproven therapies (those with minimal manipulation). Option 5 is not conceivably unachievable given the infinite variability of cell therapies and will only serve to delay and prevent the development of cell based therapies within Australia.

MSCC believes that option 1 –with the addition clause of Section 7AA –more clearly defines the responsibility of the treating clinician. MSCC will continue to be vigilant and ensure that we also meet strenuous standards of hygiene and infection control within our clinic. We will continue to support appropriate clinical research (arguably an ethical requirement when working in this field) and will continue to be encouraged to invest in development of the industry within this framework – such that Australia, through the research and work of the clinicians we support, remains at the forefront of medical advancement.

MSCC believes that the most important consideration should be around safety. We have made sure that in the development of our clinic, in the clinicians we work with, the theatre environment we use and the laboratory that assesses and tests our harvested cells we have made sure that safety is our focus. We have avoided same-day treatment to allow our cells to be appropriately assessed for viability, contamination and cross-infection. By gaining ethics approval for our trials we are confident that such a rigorous approach demonstrates that the procedures we follow are safe and will be proved efficacious.

Yours sincerely,

[redacted]

[redacted]

[redacted]

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