

Biological Science Section
Office of Scientific Evaluation
Therapeutic Goods Administration
PO Box 100
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Friday, 27 February 2015

To Whom it May Concern

Re: Public Consultation on the Regulation of Autologous Stem Cells

Thank you for this opportunity to comment on the discussion paper released 6 January, 2015 on the regulation of autologous stem cell therapies in Australia. The Centre for Biomedical Ethics was established in the Yong Loo Lin School of Medicine at the National University of Singapore in September 2006. It is South East Asia's first academic centre for biomedical ethics in a medical school, with a dedicated professor supported by a team of academic and research staff. We have established multi-disciplinary research programmes in biomedical ethics and international collaborative links with centres in Asia, the USA, Australasia and Europe. We are also independent and receive no funding from the pharmaceutical or biotechnology industries.

CBmE faculty have published widely on the ethics and regulation of stem cell science, biomedicine and cellular therapies. In particular, Assistant Professor Tamra Lysaght has published specifically on international regulatory issues concerning autologous 'adult' stem cells and currently holds competitive research grants to examine the clinical translation of stem cell-based technologies in Asia and Australasia. As international observers with expertise in this area, we are pleased to submit our response to just one question raised in the discussion paper:

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

We believe there are a number of substantive issues that have not been raised in the discussion paper and are worthy of consideration in addressing the way autologous stem cells are currently regulated in Australia. We will narrow our comments to emergent global practices and the regulation of autologous stem cell therapies from an international perspective.

Yours respectfully,



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Submission: Public Consultation on the Regulation of Autologous Stem Cells

For the purposes of the public consultation, this submission supports Option 4 as outlined in discussion paper with an additional provision for independent oversight, as well as an immediate amendment that limits the application of the Exclusion Order to minimally manipulated autologous stem cells that are intended for homologous use only. Our position is based primarily in response to the emergence of global networks of commercial providers of stem cells, private clinics, and medical practitioners who are exploiting weaknesses in Australia's regulatory framework by offering autologous cell-based therapies that they have not been demonstrated as safe and effective in formal clinical trials. We also base our position on how autologous stem cells are regulated in other comparable jurisdictions and international standards for the clinical translation of stem cell research. We begin with our justification of the latter issue.

International regulation of autologous stem cells

As noted in the discussion paper, there are variations in how stem cells are regulated across different jurisdictions. In particular, there are many technical differences in the nomenclature used to define concepts such as minimal manipulation and homologous use. Yet, as shown in a recent review of international regulations, there are also many similarities in the approach used across major jurisdictions.¹ Like Australia, many countries have adopted a risk-based approach to the regulation of stem cells and most have exemptions or exclusions for autologous cells that have been minimally manipulated and are intended for homologous use in a single procedure. Thus, any option that exempts from regulation stem cells *solely* on the basis of autologous use would, in fact, fall below international standards. In line with these standards, that are explicated in "Guidelines for the Clinical Translation of Stem Cells",² interventions involving stem cells that are more than minimally manipulated, *and for non-homologous uses*, should be supported with clinical evidence that demonstrates safety and efficacy regardless of whether they are autologous or allogenic.

For these reasons, we do not support Option 1, where all applications of autologous stem cells are exempted from complying with even basic manufacturing standards and demonstrating evidence that they are, in fact, safe for their intended use. At the very least, providers of autologous stem cells that are minimally manipulated and intended for homologous use should be required to demonstrate a satisfactory level of safety and report any adverse effects to the regulator, and recalled from the market if evidence emerges that they pose a serious risk to human health. Thus, we do not support Options 2 and 3, where sponsors are not required to demonstrate basic standards of safety. However, we would not support Option 5 either because an acceptable risk-based framework need not mandate the same requirements of clinical evidence that demonstrates efficacy for autologous stem cells that are minimally manipulated and for homologous use as those that are not. Therefore, we support Option 4 as this approach will require sponsors to submit safety data and report adverse effects for these lower risk products that may be regulated as Class 1 biologicals, while any type of stem cell that is more than minimally manipulated and/or for non-homologous uses be regulated according to the applicable Class of biologicals (Class 2, 3 or 4).

In addition to the regulations, there are internationally-accepted norms of clinical practice and research that prioritize the autonomy of patients to make informed decisions about their medical care. These norms are encapsulated in ethical guidelines and professional standards of the World Medical Association and the Congress of the Council for International Organizations of Medical Sciences, and

¹ Lysaght, T., Kerridge, I., Sipp, D., Porter, G., and Capps, B.J. (2013b). Oversight for Clinical Uses of Autologous Adult Stem Cells: Lessons from International Regulations. *Cell Stem Cell* 13, 647-651.

² International Society for Stem Cell Research (2008). Guidelines for the Clinical Translation of Stem Cells (International Society for Stem Cell Research).

which have been adopted by the Australian Medical Association and the National Health and Medical Research Council. Access to information is a necessary condition to make informed, autonomous decisions in clinical contexts. This condition applies not only to treatment options that are accepted as the standard of care but also, and perhaps especially, to unproven experimental interventions that lack evidence of safety and efficacy. Thus, to ensure greater transparency in the reporting of adverse effects, and promote patient autonomy, independent oversight of the collection, validation and dissemination of safety data should be added to Option 4.

Global networks of commercial stem cell providers

In recent years, there has been an increasing prevalence of autologous stem cell therapies being offered by clinicians without the support of published scientific evidence that demonstrates their safety and efficacy. These doctors often form part of loose collaborative networks that operate both domestically and across transnational boundaries. The operations of these so-called ‘bionetworks’ are well-documented as they work to exploit differences in the provision of healthcare, standards of evidence, and regulatory infrastructure across geographical contexts.³ They are most prominent in exploiting regulatory weaknesses and healthcare inequalities in low-to-middle incomes countries, such as India, China and Mexico, to attract patients from the wealthier countries of North America and the European Union. However, they are also emerging in more strongly regulated countries with internationally reputable healthcare systems, such as Japan, Australia and the United States.

An example of how these networks operate in these contexts was illustrated with the marketing of autologous cell processing technologies across borders between South Korea, Japan and the United States.⁴ The Seoul-based company that owned the technology had commercial relationships with medical practitioners in Japan where a Korean patient died after being administered with autologous stem cells.⁵ This procedure was (and still is) illegal in South Korea, but was allowed in Japan under certain circumstances under the *Practice Notice: Regarding the Practice of Regenerative and Cell Therapy with Autologous Cells and Tissue in Medical Institutions (2010)*. This notice, intended to provide guidance for medical practitioners administering autologous cells, was exploited as means of circumventing more restrictive regulations in one country and attracting patients to another with high medical standards for an intervention with autologous stem cell that lacked evidence of safety and efficacy.

The technology was introduced into the United States after an American orthopedic surgeon travelled to Japan for a similar procedure and administered it to the Governor of Texas in 2011. After passing a health care bill that authorized the banking of adult stem cells, the Texas Medical Board introduced rules that appear to allow the administration of human stem cells by registered practitioners without formal oversight by the Food and Drug Administration, even though federal manufacturing standards supersede state laws.⁶ A commercial biotechnology firm was established to license the technology from an American subsidiary of the Korean company, and market the stem cell banking services to physicians working in private practice who administer the cells to patients for a wide range of conditions that are not supported by the scientific literature, or approved for marketing by the

³ Patra, P.K., and Sleeboom-Faulkner, M. (2009). Bionetworking: experimental stem cell therapy and patient recruitment in India. *Anthropology & Medicine* 16, 147-163, Sleeboom-Faulkner, M., and Patra, P.K. (2011). Experimental stem cell therapy: Biohierarchies and bionetworking in Japan and India. *Social Studies of Science* 41, 645-666.

⁴ Lysaght, T., Kerridge, I., Sipp, D., Porter, G., and Capps, B.J. (2013a). Global bionetworks and challenges in regulating autologous adult stem cells. *American Journal of Medicine* 126, 941-943.

⁵ Cyranoski, D. (2010). Korean deaths spark inquiry. *Nature* 468, 485.

⁶ Texas Medical Board (2012). Texas Administrative Code, Title 22, Part 9... Levine, A.D. (2012). Improving oversight of innovative medical interventions in Texas, USA. *Regenerative Medicine* 7, 451-453.

regulator.⁷ This global network of commercial interests, political actors and medical practitioners continues to operate amidst ongoing legal disputes over the ownership of cells manufactured with the cell-processing technology, and without demonstrable scientific evidence that they are safe and efficacious.

Evidence has emerged of these types of networks operating in Australia. Prior to 2011, Australian patients needed to travel overseas to access stem cell-based therapies that were clinically unproven and not available domestically, in a phenomenon frequently referred to as ‘stem cell tourism’.⁸ However, since the Biologicals Regulatory Framework was introduced, many clinics are now offering previously unavailable interventions with autologous stem cells.⁹ These clinics are generally privately owned and operate within networks of medical practitioners and commercial manufacturers of autologous stem cells as permitted under the Exclusion Order.¹⁰ This development has not only reduced the need for patients to travel abroad for certain interventions with autologous cells, but has attracted interest from international biotechnology firms that have established cell manufacturing services in Australia that are marketed both directly to patients as well as medical practitioners.¹¹ Through their global networks of commercial companies, clinicians, patients and healthcare providers in other countries, the availability of autologous stem cell therapies may appeal to patients abroad attracted to the high quality of healthcare services in Australia and its perceived well-regulated market for therapeutic products.

For these added reasons, we do not support Option 1. This option places no restrictions on the direct-to-consumer advertising of stem cells for therapeutic purposes that would be required under the other options. Indeed, to reduce some of the more unethical and potentially dangerous practices, we support an immediate amendment to the Exclusion Order that limits its application to minimally manipulated autologous cells that are intended for homologous use pending further review of the regulations. This provision is not only to protect vulnerable patients populations in Australia and abroad who are being targeted by these networks, but to help ensure that Australian biomedical science and healthcare services retain their deserved international reputation of high quality standards of care.

⁷ Cyranoski, D. (2013). Cowboy Culture. *Nature* 494, 166-169.

⁸ Petersen, A., Seear, K., and Munsie, M. (2014). Therapeutic journeys: the hopeful travails of stem cell tourists. *Sociology of Health & Illness* 36, 670-685.

⁹ McLean, A.K., Stewart, C., and Kerridge, I. (2014). The emergence and popularisation of autologous somatic cellular therapies in Australia: therapeutic innovation or regulatory failure? *Journal of Law and Medicine* 22, 65-89.

¹⁰ Pera, M.F., and Munsie, M. (2012). Submission to the NHMRC Public Consultation - Stem Cell Treatments. In *A quick guide for medical practitioners and Frequently Asked Questions: A resource for patients* 31 August 2012.

¹¹ Lysaght, T., and Sipp, D. (2014). Dislodging the direct to consumer marketing of stem cell-based interventions from medical tourism. In *Bodies Across Borders: The global circulation of body parts, medical tourists and professionals*, B. Parry, B. Greenhough, T. Brown, and I. Dyck, eds. (Ashgate Press), p. in print.