03 March 2015

Biological Science Section
Scientific Evaluation and Special Product Access Branch
Therapeutic Goods Administration
136 Narrabundah Lane
Symonston ACT 2609

Re: Submission on Consultation: Regulation of Autologous Stem Cell Therapies

To Whom It May Concern:

ERA Consulting (Australia) Pty Ltd hereby submits comments on the *Regulation of autologous stem cell therapies - Discussion paper for consultation* released by TGA for consultation on 06 January 2015.

We appreciate the opportunity to contribute to the ongoing considerations and discussions on this important topic regarding autologous stem cell treatments.

If there are any questions regarding this submission, please do not hesitate to contact me by phone on [redacted], or by fax on [redacted], or by email: [redacted].

Sincerely,

[redacted]

ERA Consulting (Australia) Pty Ltd
Level 3, 88 Jephson Street
Toowong, QLD 4066

Enclosures:

TGA Submission Cover Sheet

This Submission with ERA Comments on the TGA Public Consultation: Regulation of Autologous Stem Cell Therapies

COMMENTS ON TGA PUBLIC CONSULTATION: REGULATION OF AUTOLOGOUS STEM CELL THERAPIES

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Discussion Questions in the Background Section		
Background Pages 10-12	The potential public health risks of autologous stem cell treatment were posed as: • Safety of the product, including issues related to any processing of the product • Lack of evidence to support the efficacy of the product and the large sums of money being charged for unproven treatments • Lack of reporting adverse effects of the product • Inappropriate advertising the product	*ERA agrees that the list captures the key elements of risk pertaining in this scenario and that these should therefore be the risks (at minimum) subject to assessment in this TGA consultation.* *Due to our role as a consultancy, our comments will generally focus on regulatory rather than commercial aspects.*
Page 13	**What are the public health risks of 'autologous stem cells' in your view?**	*ERA considers a major public health risk issue is the lack of a process for reporting potential adverse events associated with autologous stem cell treatments being provided under the exclusion. The lack of safety reporting and safety data analysis together constitute a major gap in knowledge affecting the ability of relevant authorities to protect the public health, and the ability of the clinician to advise and treat patients under continuing best practice.*

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		We consider this is the first issue to be addressed in any new scheme, requiring a procedure that can be adopted by end-users who are unlikely to be part of a "pharma" environment accustomed to safety reporting and pharmacovigilance processes. Clearly stakeholder input from this consultation, and possibly through future interactions, would support implementation of the most feasible system for such reporting and for enabling assessment of such information from a secure database. *An equally important issue is that these autologous stem cell treatments being provided under the exemption in general have, and will continue to have, unproven efficacy in humans. In some cases, no evidence of nonclinical efficacy will have been demonstrated either. The need to understand the safety side of the benefit:risk ratio is thus reinforced.* *Given that these autologous stem cell treatments being provided under the exclusion may have "undocumented" safety and efficacy from the regulatory perspective, and may be administered based on information from unpublished sources or from publications not peer-reviewed, lack of control of promotional materials/advertising must be considered another serious risk.*
	What is the evidence for these risks?	*The lack of a framework for collecting adverse events outside clinical trials leads to the likely under-reporting of adverse events. But it is possible that concerns over safety may be more theoretical than based on real evidence at this time.* *We consider implementation of a safety reporting system a viable option to determine whether there are indeed few adverse effects, or if there is evidence of safety issues that is not being captured. The safety information should be collected from the relevant practitioners and authoritative bodies in a position to receive complaints, and from patients and the general public.*
	What identified risks should have the highest priority for resolving?	*ERA considers that in the current environment, the lack of reporting adverse effects may be considered the highest priority to address.*

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	Are there public health benefits, such as patient access to new and novel treatments, to consider?	*ERA endorses the need for patient access to treatments that may offer hope of benefit without high risk of harm – this may be considered the current status quo. ERA also endorses that physician discretion should be respected as long as the applicable regulatory and legal processes are followed.* *While the efficacy of certain treatments may not have been demonstrated e.g. via clinical trials, benefits to patients cannot be excluded on those grounds alone. A treatment that is of apparent low risk but possibly ineffective, per se, may still be a desirable alternative to a patient in need.* *The possibility that the indication for an autologous stem cell product might be considered as a specific factor in determining public health benefit (and risk) has not been highlighted in this review. However, ERA suggests that the intended use of these products, and the severity of the condition being treated, could influence the "regulatory" approach versus physician discretion.*
Discussion Questions: Option 1 - Continue to exclude autologous [stem] cells from regulation under the Act		
Option 1 Page 18	**Is there an argument that autologous stem cells are not therapeutic goods and, therefore, should remain under the current Section 7 declaration?**	*Yes, ERA considers there is an argument for autologous stem cell products to not be regulated as therapeutic goods.* *As mentioned in the discussion paper, under the current Therapeutic Goods (Excluded Goods) Order No. 1 of 2011 regarding HCT, autologous stem cells treated in such a way that they fall under Item 4(q) of this order are considered part of medical practice and therefore not regulated by the TGA. The guideline covering product under Items 4(o), 4(p), 4(q) and 4(r) from March 2013 outlines the circumstances in which 4(q) products would not be regulated by the TGA. The principles behind this reasoning appear sound. As long as these conditions are met, use of autologous stem cells may be considered part of medical practice.*

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		However, meeting only these conditions does not appear sufficient, in ERA's view, for autologous stem cell products to continue being used according to the status quo.
General questions Page 17	**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: Keeping the status quo would obviously not increase the regulatory burden on government agencies or on clinician end-users. However, the ongoing risk is that no robust knowledge about the safety of such products will be gained, and no according actions by health authorities or health professionals will be facilitated.* *As ERA is a consultancy, we do not have direct information on costs related to the options and practices being considered herein, and will therefore not offer comment on costs.*
	How do you think each option addresses the risks you identified in the earlier question?	*Option 1: While decisions under the current framework appropriately remain the responsibility of the treating physician, the gap with regards to learning about the safety (and efficacy) of the various treatments will not be addressed.* *Given the likely lack of proper evidence to determine safety and efficacy, the risk of continued use and advocacy/ advertising of products that are ineffective will continue unhindered.* *ERA therefore considers that Option 1 does not effectively address the identified risks.*
Discussion Questions: Option 2 - Exclude autologous stem cells from regulation under the Act in defined circumstances		
Option 2 Page 20	**Should autologous stem cells that are more than minimally manipulated and/or are not for homologous use continue to be excluded from regulation? Why or why not?**	*This discussion question is aimed at activities under the Excluded Goods Order wherein products are being subjected to processing by methods in addition to minimal manipulation and/or representing non-homologous use.* *Considering non-homologous use: ERA does not support the manipulation of autologous stem cell preparations provided under the exclusion such that their use will become non-homologous. These products belong in classes defined and regulated under the Act (i.e. Class 3 or 4 biologicals).*

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		More than minimal manipulation: The manufacture of autologous stem cell products under the direct medical supervision of the treating physician may quite feasibly include processing considered to be beyond minimal manipulation as strictly defined in the Regulations (e.g. through limited in vitro expansion, or selection through adherence, etc). The requirement for minimal manipulation (only) has not been explicitly stated in the Excluded Goods Order or the associated Guideline for Items 4(o), 4(p), 4(q) and 4(r) of the Excluded Goods Order No. 1 of 2011. As long as the inherent properties of the cells are not altered (and demonstrating this is true in a particular case may be recognised as a potential gap), then the responsibility for the use of these products in patients could reasonably continue to reside with the treating physician. *However, any autologous stem cell therapy that comprises cells intentionally (or unintentionally) altered to achieve a physiological function other than their normal one, would not be covered under the exclusion and should be subject to the Regulations as biologicals. Such products should be tested in humans within the clinical trial schemes, rather than under the exclusion.*
General questions Page 17	**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 2: ERA considers this option is potentially useful to allow some departure from the most narrow definitions of minimal manipulation. As an autologous stem cell therapy provided under the exclusion, such a product could be distinguished from an otherwise Class 2 biological.* *This option provides an opportunity for a potential benefit to patients who might receive a therapy that has been manipulated so as to comprise a more "defined" product (recognising that this does not necessarily imply more characterised).* *However, the risk is that unintended changes to the cells might result from those processing steps, and that such changes would probably not be detected.* *Importantly, Option 2 introduces restriction on advertising to the public.*

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	How do you think each option addresses the risks you identified in the earlier question?	*Option 2: Since this option does not include requirements for safety reporting, ERA considers this approach alone to be insufficient to address the identified risks.*
Discussion Questions: Option 3 - Regulate autologous stem cells under Act, but exempt from registration and manufacturing requirements		
Option 3	*This option provides a different perspective – that of actual regulation – even though specific exemptions are included to avoid need for inclusion in the ARTG and for manufacturing licensure for persons and processes. ERA considers some useful additional requirements in Option 3 might complement Option 2 = "Option 2.5" as described below.*	
General questions Page 17	**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 3: The risk associated with lack of adverse effects reporting is addressed in this option, so ERA considers this a major benefit.* *A requirement for compliance with TGO 87 may have minimal impact on those practitioners/entities whose activities are currently covered by the Excluded Goods Order, and for whom it would be straightforward to justify departure from a particular requirement that would be recognised as not applicable. For example, compliance with the labelling requirements would be entirely appropriate in the case where a patient treatment comprised more than one dose of the cells, and where the additional doses are stored frozen until use. ERA views this as a benefit.* *ERA considers that requirement for compliance with TGO 88 may not be particularly useful in mitigating risk in all (or most) cases, and may be overly burdensome on many practitioners. So this might not be a beneficial step unless analysed in more detail for relevance to autologous stem cell treatments. An appropriate (less comprehensive) donor history might be envisaged (e.g. without need for the syphilis test). The physician should decide which infectious disease testing is relevant to the patient under his/her supervision. Nevertheless, for an autologous stem cell treatment involving multiple doses, where the product is stored frozen, the requirements in TGO 88 regarding testing for absence of microorganisms should be considered as this should be feasible time-wise*

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		and be risk-mitigating for the patient. *It is noted that consequent to the safety reporting requirements, and the introduction of TGA oversight of information to confirm the product eligibility for the exemptions, and compliance with TGOs as relevant, etc, there will clearly be a regulatory burden for the Agency and the practitioners.*
	How do you think each option addresses the risks you identified in the earlier question?	*Option 3: This has the advantage of being the first option to introduce the requirement for adverse effect reporting, and ERA considers this a pivotal step in addressing the identified risks.*
"Option 2.5"		*ERA suggests that aspects of Options 2 and 3 might be considered, since adoption of Option 3 may well be too burdensome and be a barrier to the development and use of novel autologous stem cell treatments.* *Proposal for introduction of steps above the status quo:* *i. From Option 2 consider the potential "widening" of minimal manipulation in specifically designated ways, while introducing a restriction on advertising to the public.* *ii. From Option 3 consider the products be regulated under the Act but with provisions for the cited exemptions from ARTG entry, manufacturing licensure, and compliance with applicable Orders unless otherwise justified. Introduce safety reporting and record-keeping requirements to ensure the availability of certain information on supply and handling.*
Discussion Questions: Option 4 - Regulate under the Act as Class 1 biologicals		
Option 4 Page 23	*ERA recognises that the introduction of autologous stem cells into the Class 1 biologicals category as described in the discussion paper has the advantage of logic and consistency within the framework.* *However, we perceive a potential drawback that may be cause for concern, perhaps more from the outside than inside the system.*	

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	For those autologous stem cell products that may fall under this option if adopted, the products would still be of effectively unproven safety and efficacy by normal therapeutic goods standards, but they would be "registered", with all the potential/claimed legitimacy of that designation. Such products could therefore be promoted as if they have been reviewed by the regulator, since this is a distinction that would likely be unobvious to the public. *ERA sees this as a substantial potential risk to patients and also a potential risk of misinterpretation of the value of the TGA imprimatur.*	
General questions Page 17	**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 4: ERA recognises this option carries some benefits (as for Option 3), but also carries the same burdens discussed under Option 3 particularly relating to compliance with standards under the Act, and increased oversight. There is the same concern that these requirements in full will be a barrier to potential treatments being available to patients.* *As noted, ERA considers this option carries additional risks relating to the potential for false appearance of credibility of a registered product that is not, nor will be, evaluated by the Agency.*
	How do you think each option addresses the risks you identified in the earlier question?	*Option 4: While this option does address identified risks, others are likely that could have a negative impact on the field in general.* *ERA does not favour this option.*
Discussion Questions: Option 5 - Regulate under the Act as Class 2, Class 3 or Class 4 biologicals		
Option 5 Page 26	*Option 5 appears overly restrictive and may indeed prevent patient access to treatments. Regulation at Class 2-4 'may limit innovative potential of individuals and smaller groupings of clinicians working in the autologous stem cell space.* *ERA does not favour this option.*	

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Discussion Questions: General		
Page 17	**Are there additional issues with the regulation of autologous stem cells that any changes should consider and/or address?**	*ERA suggests the following:* *a. If and when a new framework for autologous stem cell treatments is adopted, and particularly if that action results in the loss of coverage for certain therapies under the Excluded Goods Order, ERA recommends that a transition period should be implemented to allow these various practitioners/groups to make appropriate decisions and plans to adapt to the new requirements and support their patients.* *b. Consideration should be given to any aspects that might differ if an autologous stem cell therapy were sourced from inside Australia versus being imported, e.g. prolonged (unvalidated?) transportation.* *c. An intermediate option ("Option 2.5") as described above, that might embody advances in patient safety and the gathering of relevant safety information while still allowing low risk products to be innovated and made available under the responsibility of treating physicians as per medical practice.*